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The Identification of Hepatic Injury and Hepatic Angiosarcoma Among Vinyl Chloride Workers - The Epidemiological Approach

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Introduction

Hepatitis-like liver changes in vinyl chloride polymerization workers were reported in 1949 by Tribukh et al. [1]. In 1967, Creech et al. reported the occurrence of occupational acro-osteolysis in vinyl chloride workers [2] and eight years later identified the first case of human liver angiosarcoma [3]. Although these occupationally-related diseases were observed by astute industrial physicians, the establishment of a causal-relationship between liver disease and occupational exposure to vinyl chloride took 25 years.

Industrialized societies throughout the world have become concerned over the potential health hazards of synthetic agents in the occupational environment. Screening programs have been instituted in work environments suspected or proven to have toxic or carcinogenic agents present; the primary objective is to reduce disability, morbidity and mortality in the workplace, especially as related to serious low-grade health hazards. Nearly all screening programs are started retrospectively and few have been instituted with any prior knowledge as to their effectiveness or capability of early detection and future prevention. These retrospective approaches invariably deal with occupationally-related disease after its clinical manifestation has become overt and the causative connection has been made. Establishing a connection between toxic injury and exposure, and especially cancer development in the work environment, has been difficult due to the slow development of injury, the long duration for malignancy to appear, the lack of uniform methods for monitoring the incidence and prevalence of medical disease, the limitations of devices for exposure monitoring, and the non-availability of a control population similarly monitored.

The discovery of hepatic angiosarcoma in vinyl chloride workers in the United States by Creech provided the impetus for the development of an

industrial prospective occupational health surveillance system [4]. Although this system was initially developed to identify occupationally-related cancers [5], it is equally capable of identifying other potential occupationally-related medical disorders. This system is not intended as a substitute for determining the safety of chemicals by chemical structural analysis, bacterial screening [6], tissue [7], or animal exposure studies [8] prior to their introduction into the industrial environment, but rather is a complementary, primarily preventive system directed at humans. Its structural development builds on already existing occupational, environmental, and medical data available or accessible through industrial and medical records. The development, implementation and evaluation of an operating prototype prospective occupational health surveillance system, begun in 1974, will be discussed herein.

Occupational Health Surveillance System

The occupational health surveillance system (OHS) can be applied retrospectively but is best instituted prospectively and consists of three programs or levels of complexity.

Level I: Epidemiological Surveillance Program (ESP)

Level II: Medical Surveillance Program (MSP)

Level III: Medical Disease Detection and Treatment Program (MDDTP)

The various levels of the OHS system are comparable to three major industrial environments [9]. Utilization of all levels of the OHS system constitutes a comprehensive medical surveillance program. However, all the various levels may not be needed in every industry nor at every plant of the same industry. It is necessary, therefore, to determine into which category an industry fits in order to assign the appropriate level(s) of surveillance.

Classification of Industrial Environments

All industrial or occupational environments, depending on their toxic or carcinogenic potential, fall into one of three major categories.

Category A includes all industries or occupations in which the industrial materials used have not yet been studied for toxic or carcinogenic capability.

Category B includes all those industries or occupations utilizing

materials suspected of being potentially toxic or carcinogenic from laboratory, animal or human studies.

Category C includes all industries or occupations utilizing agents known to be toxic or carcinogenic, especially to humans.

The OHS system's three major programs are appropriate to the different industrial categories listed. The OHS system's basic program, the ESP, is designed for industries or occupations in Category A. The next program level, the MSP, is appropriate for Category B industries. The MDDTP is the most complex and is designed for Category C industries or occupations.

Epidemiological Surveillance Program - Level I

The prospective epidemiological approach requires accurate and complete data. The data collected must identify and characterize all the agents that workers are exposed to, and also identify the medical illnesses and disorders within the worker cohort.

The ESP consists of four components.

1. A standard job classification code.
2. An employee work history record.
3. A rank ordered exposure rating system.
4. A medical illness and disease data base.

The standard job classification code identifies individual jobs based on their activities or function. An example of this is shown in Table 1.

Employee work history records should begin with first time employed, should be continuous, include all transfers from job to job, and should be carried from company to company. No employee activity or responsibility should be without a job classification code. The code should include a specific listing of all agents or potentially harmful activities involved with that job.

Table 1

GENERAL LISTING - WORK HISTORY CODING SYSTEM

WORK ASSIGNMENT	MOVE BASES	JOB CODES
POLYMERIZATION OPERATORS	ANY BUILDING EXCEPT AS LISTED BELOW	130
A. CHARGING OPERATOR - GEN.	4, 30, 131	131
B. CHARGING OPERATOR - PVC	1, 15, 111	132
C. CHARGING OPERATOR - P.A.	111	133
D. CHARGING OPERATOR - PASTE	121	134
E. CHARGING OPERATOR - LATEX	121	135
F. CHARGING OPERATOR - PLASTIC	121	136
G. BOARD/CONSOLE OPERATOR	1, 131, 149	137
H. BLOWDOWN OPERATOR	30, 131	138
I. PROCESS CONTROL OPERATOR	131	139

A rank ordered exposure rating system requires specific knowledge of all potentially hazardous agents or activities found within the occupational environment. The rank ordered approach to exposure is preferred because all agents are not always monitorable, nor is the monitoring of a few agents necessarily adequate in determining the overall occupational risks. Those agents which can be monitored provide additional data which can be incorporated within the rank ordering system, whether such monitoring is on an individual, job, or location basis. In this fashion, interactions between various agents and chemicals can be accounted for. An occupational health surveillance system utilizing a six-point rank ordered scale applied to 22 chemicals (selected for their hepatic toxicity and carcinogenicity) has been applied to a vinyl monomer and synthetic rubber monomer plant; it has been shown effective in identifying relationships between chemical exposure and cancer development [10].

A medical illness and disease data base requires systematic recording of all medical illnesses (i.e., greater than three days) and diseases which require medical attention or hospitalization. The medical data should be recorded using the international classification of disease code to allow agreement between companies and occupations regarding the description of diseases or illnesses which occur.

Medical Surveillance Program - Level II

The MSP incorporates all the components of the ESP in addition to a periodic medical examination and limited but specific laboratory screening studies. The medical examination includes a basic history and physical. There must be uniformity in the history and physical data collected if this information is to be effective in identifying developing illnesses. Studies

at the University of Louisville using different facilities and methods of examination (plant versus local hospital; licensed physicians versus trained paramedical personnel, etc.) indicate that examinations by paramedical staff can provide reproducible examinations of high quality, minimizing down-time, and examination and data collection costs without loss of effectiveness in identifying physical abnormalities [11].

Specific laboratory screening studies are divided into a) those selected for monitoring body systems most likely to be affected by the suspect agents, and b) the screening tests designed to monitor the functional capability of body systems independent of the agents or toxic substances being considered.

Medical Disease Detection and Treatment Program - Level III

The MDDTP contains all the components of ESP and MSP and has, in addition, a multi-system testing program, a diagnostic triage program, and a therapeutic management protocol for early treatment.

The MDDTP is needed for those environments which utilize agents or chemicals which are known toxins or carcinogens. In this circumstance the actual occupational risk to humans may or may not be known. It should be presumed that a toxic potential is present and needs to be monitored. This would be akin to industrial monitoring for leaks of explosive materials or the breakdown of a manufacturing process which could cause serious consequences. Because of the higher potential for injury at this level, the medical history and physical examinations are more specialized and tailored to deal with the known toxin or carcinogen. At this point, work exposure histories may be expanded to include individual or personal monitoring of the known toxic or carcinogenic agents. Additional screening studies may also include radiological and radioisotopic screening, such as chest x-rays for asbestos exposure, liver-spleen scan for vinyl monomer workers, bone x-rays for lead workers, etc. [12] Furthermore, screening tests are directed toward the assessment of overall organ function rather than solely to detect acute injury. Since most occupational disease that develops in industrial areas occurs from chronic low-level exposure, screening tests which identify acute or severe injury are usually incapable of detecting subclinical progressive damage to an organ. These latent developments go undetected because there are usually no symptoms or signs present during this early injury. Functional studies are far more sensitive indicators of small but progressive changes than simple biochemical

screening tests. Serial testing also provides evidence of progression long before there is clinical evidence of organ impairment.

Medical Evaluation - A Diagnostic Triage System

The systematic protocol used for liver injury in vinyl chloride environments can provide a model for other types of organ injury [13]. It includes:

1. Identification of persistent false-positive laboratory tests. These would include normal variations such as increased alkaline phosphatase in young adults, and the congential variations such as congenital indirect hyperbilirubinemia.
2. The elimination of common non-occupational cause of liver abnormalities. These would include viral hepatitis, alcoholic liver injury, drugs, diabetes, hyperlipidemia, obesity, etc.
3. Removal of the individual from the work environment if the organ system injury is considered to be occupationally related and monitoring of changes in that organ system.
4. The screening of other individuals with known similar exposures for similar abnormalities.
5. Upon identification of the causative agent, elimination or reduction of exposure to the lowest possible level and continued monitoring of the organ system for changes.
6. Return of workers to the work environment only after exposure to the causative agent has been eliminated or the job environment is shown to be safe. For further details regarding implementation of an OHS, see references 9, 13 and 14.

Results

In the eight years of application of the Occupational Health Surveillance System to an industrial cohort of approximately 1,200 employees, at least six major observations have been made regarding vinyl chloride-induced disease.

1. Verification of vinyl chloride and other vinyl monomers' role in induction of hepatic cancer [3, 10].
2. The characterization of chronic non-malignant subclinical liver disease [4, 11].

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3. The identification of early hepatic lesions characteristic of chemical injury [15, 16].
4. The inverse relationship between exposure and latency of vinyl chloride cancer induction [17].
5. The effectiveness of clinical screening tests in the detection of chemically-induced liver injury [18].
6. The separation of non-occupational versus occupational medical disease using dye clearance studies and serum bile acid levels [19, 20].

Additional findings include:

a) Assessment of Screening Tests in Asymptomatic Populations.

Few of the commonly available medical tests have been adequately evaluated for sensitivity (the ability to detect correctly all positive cases) and specificity (the ability to detect correctly all negative cases) in asymptomatic healthy populations. The majority of medical tests presently used for screening have been evaluated only in ill populations. It is necessary, therefore, that a medical surveillance program(s) contain within it control populations for comparison and subsequent test evaluations.

An example of this need is seen in the comparison of common "liver tests" in an asymptomatic worker cohort. Figure 1 illustrates the sensitivity of standard screening tests in an ill or hospitalized population.

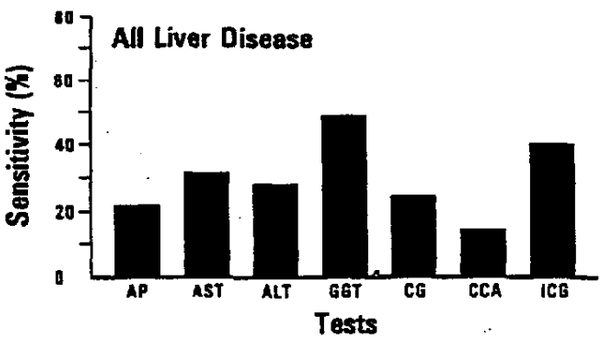

Fig. 1. The sensitivity of standard biochemical liver tests* in identifying liver disease in an asymptomatic population.

Figures 2, 3 a and b illustrate the same standard tests with regards to their sensitivity in detecting hepatic disease in an asymptomatic population with non-chemical liver disease and chemical liver injury proven by liver biopsy.

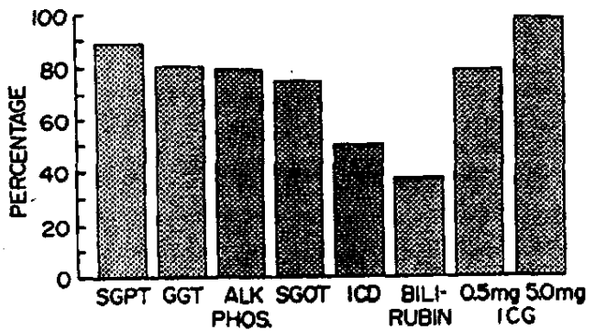

Fig. 2. The frequency of standard biochemical liver tests* reflect presence of hepatic disease in chemical workers suspected of having liver disease.

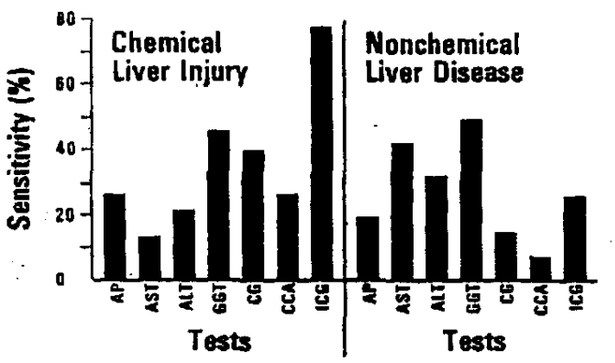

Fig. 3. The sensitivity of standard biochemical liver tests in identifying:
a) chemical liver injury in asymptomatic worker cohort.
b) nonchemical liver disease in asymptomatic worker cohort.

Clearly there is considerable difference regarding these various tests ability to detect liver disease in these populations. Similar type studies are needed

* (SGPT, ALT) alanine aminotransferase, (SGOT, AST) aspartic aminotransferase, (GGT or GGTP) gamma glutamyl transpeptidase, (AP, ALK PHOS) alkaline phosphatase, (ICG) indocyanine green clearance, 0.5 low, 2.5 medium, 5.0 mg/kg high dose, (SBA) serum bile acids, (ISD) isocitric dehygrogenase, (CG) choleglycine, (CCA) conjugates of cholic acid.

for all screening tests which are to be applied to an asymptomatic population. Otherwise, screening tests will provide little useful or additional information and incur excessive costs to the industry and ultimately to the public.

b) Assessment of Possible Vinyl Chloride Injury to the Pulmonary System

Forty-five individuals in the worker cohort were discovered to have bilateral midzonal pleural thickening on routine annual chest x-rays. Lung and pleural biopsies identified the thickening as fatty scar tissue without evidence of malignant change. No asbestos material was found in this tissue. The high incidence of smoking among these workers might have some relationship to the bilateral pleural thickening. The thickening, however, seems to have no relationship to the work exposure data and fails to correlate with any of the 22 chemicals studied [21].

c) Pulmonary Function Studies in Exposed Workers

Pulmonary function status was studied in 112 randomly selected workers: 63 smokers, 49 non-smokers. Participants were classified into four smoking groups: those who had never smoked (28), those who had smoked 14 or fewer cigarettes/day (11), those who smoked 15 to 25/day (52), and those who smoked 26 or more/day (31). Pulmonary function studies included mid-expiratory time (MET), forced expiratory volume (1 second - FEV), forced expiratory flow (FEF 75-85), maximum mid-flow rate (MMFR) and closing volume. The purpose was to determine whether the pulmonary function studies would differentiate between exposed and non-exposed workers. No significant differences were demonstrated. This preliminary data indicates that significant pulmonary disease is not associated with exposure to vinyl chloride.

d) Cardiac Studies in Exposed Workers

Fifty-two randomly selected participants were studied for evidences of cardiac conduction irregularities (arrhythmias) after Holt monitoring for a 48 hour period. Eleven had recordings with at least one irregularity. The distribution of these irregularities was studied with regard to the cumulative exposure indices for each of the 22 chemicals. The median cumulative exposure of the subjects with conduction irregularities was the same as those without irregularities. This study had a P value of 0.65. A second analysis was

performed in the same manner, but instead of using total cumulative exposure index, an index for the most recent period of exposure (the prior year) was used. Analysis by the Mann-Whitney-Wilcoxon Test provided a P value of 0.57. Both studies again demonstrated no statistical significant relationship between total cumulative exposure ranking and the most recent exposure ranking with regards to the frequency of cardiac abnormalities.

e) Program Costs

The ESP can be provided for industry by university health science centers at an approximate initial cost of $40 - $50 per worker and maintenance cost of $5 - $7 per year. Although the higher level programs are more expensive, the cost can be controlled for maximum effectiveness by the regular epidemiological study of the worker population at risk.

Discussion

The use of epidemiology is essential for the identification of hazards within the environment when dealing with humans. Human epidemiological study is necessarily independent of chemical structure studies, laboratory toxicological research, or animal toxicological studies--short or long term. Although most human toxins have been shown to be toxic or carcinogenic in a bacterial or animal system, thus providing a method with high sensitivity for detecting such agents, their specificity--the ability to exclude an agent as potentially toxic--is considerably less. Most laboratory and animal test systems are designed to determine the toxic potential of agents and are not designed to determine actual human risks. Vinyl chloride is a unique illustration of this. It is an essential component in the manufacture of plastics, a material of universal necessity. It is a simple molecule compared to other synthetic compounds. Structural evidence suggests a potential for toxicity because of its double bond and chlorine molecule. However, anesthetic agents with very similar structural formulas have been used within certain limits to great human benefit. In fact, vinyl chloride was once used briefly as an anesthetic agent in the postwar period. Because of its cardiac toxicity and explosive characteristics, it was not considered suitable for general medical use. In animal studies, its toxic potential was considered to be minimal and its carcinogenic potential was unsuspected. Long-term animal studies did, however, identify both its chronic liver injury potential and its carcinogenicity. It should be noted, that although liver cancer was identified, the

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type of liver cancer produced was so rare a variety that it attracted immediate attention. If vinyl chloride exposure had produced hepatocellular carcinomas rather than angiosarcomas, it may not have received the same degree of attention. In addition, vinyl chloride may be the source of other malignancies in the lymphatic system, brain, lung and kidney in man. Retrospective studies of human populations exposed to vinyl chloride, however, have only begun to analyze vinyl chloride's causal relationship to malignancies other than liver angiosarcoma. Even now, eight years after the discovery in humans of liver angiosarcoma, there remains a question as to what role vinyl chloride plays in the development of lymphatic, lung and brain tumors. Although there has been a marked reduction in the occurrence of liver angiosarcoma in vinyl chloride workers throughout the world, this reduction began shortly after the initial discovery. Considering that vinyl chlorideinduced liver angiosarcoma has a 10-or-more year latency period, it is impossible to attribute the rapid decrease in the occurrences of liver angiosarcomas solely to the reduction in the exposure level that occurred in the post 1974 era. Epidemiological data increasingly supports the idea that the decrease in angiosarcoma cases occurred too soon to have been influenced by the corrective measures instituted in 1974 alone [22].

This observation highlights the need for a more effective system of detecting such occupationally-induced diseases. It is, therefore, essential that epidemiological methodology be applied prospectively if prevention is to be effective and meaningful.

Summary

The Occupational Health Surveillance System described herein has provided the experience and data to clearly demonstrate that prospective, epidemiological application to the problem of health surveillance in the occupational environment is feasible and economical. It has demonstrated that the approach is implementable in industries of any size or type, can be operated without interference with industrial productivity, is extremely cost-effective at the epidemiological surveillance program level, provides the best means to identify and characterize agents which may produce occupationally-related disease in the human population, provides an ongoing means of assessing the effectiveness of intervention or preventive measures and be provided through the expertise of health sciences centers with economic benefit to the universities and industry and a significant social benefit to the community.

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REFERENCES

1. Tribukh, S.L., N.P. Tikhomirova, S.V. Levina & L.A. Kozlov. (1949): Gigiena Sanit. 10:38.
2. Wilson, R.H., W.E. McCormick, C.F. Tatur & J.L. Creech. (1967): J. Am. Med. Assoc. 201:577-581.
3. Creech, J.L., Jr. & M.N. Johnson. (1974): J. Occupational Med. 16:150-151.
4. Creech, J.L., Jr. & L. Makk. (1975): ANYAS. 246:88-94.
5. Greenberg, R.A., C.H. Tamburro, & C.E. Kupchella. (1978): Prevention and Detection of Cancer, N.Y.: Part II, Vol. 2 pp. 1921-1928 (Neiburgs, H. ed.), Marcel Dekker, Inc.
6. Ames, B.N. (1979): Science, 204:587-593.
7. Pienta, R.J., J. A. Poiley & W.B. Lebherz, III. (1977): Int. J. Cancer, 19:642-655.
8. Weisburger, J.H. (1976): Chemical Carcinogens, Searle, C.E. (ed.) ACS Monography 173. American Chemical Society, Washington, D.C.
9. Tamburro, C.H., C.S. Davidson, M.M. Fisher, et al. (1979): Guidelines for Detection of Hepatotoxicity Due to Drugs and Chemicals. Davidson, C.S., Leevy, C.M. & Chamberlain, E.C. (eds.) U.S. Department of HEW, NIH Pub. No. 79-313, pp. 60-80.
10. Greenberg, R.A. & C.H. Tamburro. (1981): J. Occupational Med., 23:353-358.
11. Tamburro, C.H., R.A. Greenberg, L.F. Newby & D.M. Turns. (1978): Report on Implementation and Assessment of a Demonstration Cancer Control Detection and Prevention Program in a Cohort of Industrial Workers. National Cancer Institute Program Contract NO-1-CN-55212.
12. Whelan, J.G., Jr., R. Greenberg & C.H. Tamburro. (1980): Gastroenterology, 79:1129.
13. Tamburro, C.H. (1979): Medical Clinics North America. 63:545-566.
14. Tamburro, C.H., U.N. Streips & J.L. Wong. (1982): Clinical Medicine for the Occupational Physician, pp. 255-295. M.H. Alderman & M.J. Henley (eds.). Marcel Dekker, Inc., New York, New York.
15. Tamburro, C.H., J.L. Creech, A. Davis & R.A. Greenberg. (1978): Gastroenterology 75:989.
16. Tamburro, C.H., L. Makk & H. Popper. (1979): Gastroenterology 77:A43.
17. Tamburro, C.H. & R.A. Greenberg. (1982): Hepatology 2:149.
18. Tamburro, C.H. & R.A. Greenburg. (1981): Environmental Perspectives, 41:117-122.
19. Liss, G. & C.H. Tamburro. (1982): The Pharmacologist. 24:247.
20. Liss, G. & C.H. Tamburro. (1982): Hepatology. 2:692.
21. Tamburro, C.H. (1978): Texas Reports on Biology & Medicine. 37:126-144.
22. Tamburro, C.H. & R.A. Greenberg. (1982): Clinical Research. 30:307A.