

Risks to the Offspring from Parental Occupational Exposures

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Risks to the offspring of workers with occupational chemical exposures may derive from mutagenic, teratogenic or carcinogenic effects of industrial agents to which the parents are exposed. Evidence for impaired pregnancies and hazards to the offspring of working populations with chemical exposures is, however, very limited. Perhaps the best documented example is increased spontaneous abortion rates in female operating room personnel who have first trimester exposure to waste anesthetic gases. Evidence is reviewed for hazards to the offspring resulting from parental occupational exposure to vinyl chloride, benzene, chloroprene, radiation and petroleum-derived hydrocarbons. It is essential in investigating the role of occupational factors that other environmental and behavioral factors with major effects on pregnancy outcome be accounted for. These include smoking, alcohol, and drug exposures. An approach to surveillance for chromosomal abnormalities in offspring of occupationally exposed parents is outlined.

Derived from the Greek word "τερας," meaning a marvel, prodigy or monster, the word "teratogenic" was used by 1857 to mean the "production of monstrous formations or births."¹ The term has been refined to refer to the biological science dealing with "the causes, mechanisms, and manifestations of developmental deviations of either structural or functional nature."² An agent may act as a teratogen when administered in a number of ways, whether to the male or female before mating, to the female during pregnancy, or to the fetus directly.¹ Agents in the environment may produce alterations in the genome, mutations, and by that mechanism lead to abnormalities of development in the offspring. Viral, drug or chemical agents acting through common pathways may produce indistinguishable results. The outcome of such mutations may theoretically be fetal defects or predis-

position to neoplasia. Agents which alter the rate of growth of the fetus or are lethal to the fetus without producing specific anatomic or functional anomalies are better termed developmental toxins than teratogens.

Cancer in the offspring of individuals exposed to a carcinogen may theoretically be the result of any of three types of exposure: prezygotic, by alteration of parental germ cells; transplacental, by passage of carcinogenic substances across the placental barrier, or postnatal, by contamination of the environment with carcinogenic substances, primarily through ingestion (including substances excreted in human breast milk) and through inhalation.

Evidence for risks to the offspring of humans occupationally exposed to potentially hazardous substances is reviewed in the present work. The term trans-generational carcinogenesis is used to describe the occurrence of cancers in the offspring which can be attributed to parental exposures. This term is proposed to encompass not only the established process of transplacental carcinogenesis, by which a substance administered to the mother during pregnancy results in cancer in the offspring, but also the controversial issue of preconception alterations in genetic matter resulting in increased teratogenic or cancer risk in the offspring. The latter effect could theoretically result from each of three distinct mechanisms: chromosome breakage, point mutation, or abnormalities in gametogenesis or fertilization.

Mutagenic and Teratogenic Characteristics of an Agent and Trans-Generational Carcinogenesis

Mutagenesis, teratogenesis and carcinogenesis are related phenomena, but the nature of their relationship is complex and occasionally controversial. It has been argued that the "same chemical that causes abortion in the early stages may produce malformations during organ development and neoplasia when exposed later in pregnancy. Therefore, screening for transplacental hazards should include, whenever possible, the entire range of fetal response, including cancers that may develop sometime after birth."³ Teratogenic, mutagenic and carcinogenic activities are all demonstrable for a number of com-

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pounds, but transplacental carcinogenic potential has rarely been demonstrated for known teratogens and mutagens. Teratogenic effects may reflect a variety of actions involving the mother, the placenta or the fetoplacental unit. These effects can be indirect and may not involve immediate action of the agent on the target fetal tissue.¹ Transplacental carcinogens may act directly on the fetal tissues which are inherently more vulnerable because of the high rate of cell division, high proportion of undifferentiated cells and immaturity of immunosurveillance mechanisms.

To appreciate potential danger from an environmental exposure to offspring of the exposed organism, the outcome of all exposed pregnancies should be considered. Early fetal wastage commonly results from abnormal fetal development. At the other extreme, transplacentally-induced tumors hardly ever appear in rodent species until the animal reaches maturity. In the only documented example of chemical transplacental carcinogenesis in humans, vaginal adenocarcinoma following diethylstilbestrol (DES) exposure, the tumor occurs decades following exposure. Thus, since transplacentally-induced tumors, unlike malformations, are rarely present at birth, one must also observe the offspring into adulthood to see the full spectrum of resulting tumors.

Environmental Threats to Pregnancy Outcome

Recognized threats to pregnancy outcome are not uncommonly encountered in the environment and must be excluded when new problems are suspected. Threats are posed by biologic, chemical and physical agents, and may derive from medical therapeutic interventions, drug and substance abuse, and environmental or occupational exposures to chemical agents.

Alcohol.—The most widespread documented threats to the fetus come not from the maternal physical environment but from the use of tobacco and alcohol during pregnancy. Only recently has the risk of alcohol ingestion in pregnancy been evaluated and the concept of the fetal alcohol syndrome refined.² Of infants born to recognized chronic alcoholic mothers, 83.3% had birth weights under the tenth percentile, compared with 2.3% in a comparable non-alcoholic population.³ In addition to intrauterine growth retardation, the infants had retarded post-natal growth and intellectual development. A characteristic facies, with short palpebral fissures, hypoplastic philtrum, thin vermilion line of the upper lip and retrognathia, has also been described.

In addition to these features of the fetal alcohol syndrome, congenital malformations of various types occur with excess frequency. Recognition of an associated increase in the occurrence of congenital malformations ironically re-emphasizes ancient observations and admonitions against alcohol use during pregnancy.⁴ The adverse effects on the fetus of maternal alcohol abuse during pregnancy were further quantified by Ouellette et al,⁵ who classified women at the first prenatal visit into four categories according to alcohol consumption and independently evaluated pregnancy outcome. Compared to those born to abstinent or moderate drinkers, infants born to heavy drinkers had twice the risk of having an abnormality at birth. The frequency of congenital abnormalities in the offspring of heavy drinkers was extremely

high—32% when minor abnormalities were included, 17% if only major anomalies were considered. Multiple abnormalities were present in 20% of the offspring of heavy alcohol users. Major, minor and multiple abnormalities occurred significantly less often among abstinent or moderate drinkers. Animal models, including chicks, rats and guinea pigs, have been developed for evaluating the effects of ethanol alone on offspring, and support the view that ethanol itself is a harmful agent, and that its teratogenic potential is common to several species.¹¹

Smoking.—Another factor influencing pregnancy outcome, maternal smoking habits, should be addressed in efforts to tie environmental exposures of the parents to the survival and integrity of the fetus. Kline et al¹² suggest that the odds of spontaneous abortion among women who smoke are 1.8 times those of nonsmokers. This association remains statistically significant after maternal age, and number and outcome of previous pregnancies are taken into account.

The manner in which smoking affects fetal survival is controversial. Smoking results in lowered birth weight, which may or may not be related to the increased frequency of spontaneous abortion.^{11,14} Lowered birth weight may result from impaired maternal nutrition or fetal anoxia, neither of which produces an excess of chromosomal abnormalities in the conceptus. Alternate explanations for an association between smoking and spontaneous abortion have been proposed. Since spontaneous abortion serves as a means of selectively terminating abnormal conceptions and since 95% of abnormal pregnancies are believed to terminate this way, an association between an environmental factor and increased spontaneous abortion should always evoke suspicion of a teratogenic phenomenon.¹⁵ Smoking increases the risk of spontaneous abortions by a factor of 1.8, yet the percentage of abortuses which are chromosomally abnormal is close to that expected. The absolute risk of a chromosomally abnormal fetus appears, therefore, to be higher in smoking mothers.

The relationship of karyotypic abnormalities in spontaneously aborted products of conception to maternal smoking habits is complicated by variation in the proportion of chromosomally abnormal fetuses with increasing maternal age and by the fact that a large proportion of smokers are younger women.¹⁴ An increase in the rate of chromosomally abnormal conceptions might be masked in a proportionate ratio analysis if there was also an increased loss of conceptions without demonstrable cytogenetic abnormalities.

Evidence for an increase in congenital malformations in children of smoking mothers is limited and conflicting. In a cohort of births occurring in the first week of March, 1958, in England, Scotland and Wales, Fredrick and colleagues¹⁷ identified a 60% increased risk of congenital heart disease among children of women who had smoked at least one cigarette per day after the fourth month of pregnancy (7.3 vs. 4.7 cases per 1000 live births). This effect remained statistically significant after adjustment for maternal age, parity and social class. An investigation of congenital defects of all systems registered in South Wales from 1964 to 1966 which took into account maternal age, parity, social class, area of residence and date of delivery did not associate maternal smoking habits with

congenital malformations in any system.¹⁸ It is possible that moderate increases in relative risk might have gone undetected.

Analysis of data from a mailed survey of a large number of professional women in medicine identified a relative risk of up to 1.7 for spontaneous abortion and a risk of congenital abnormalities of up to 2.3 in heavy smokers after the effects of age, parity and exposure to anesthetic gases were considered.¹⁹

Drug Exposure.—In utero exposure to diethylstilbestrol (DES), with the subsequent development of vaginal adenocarcinoma, is the prototype for transplacental oncogenesis in humans. Appreciation of the causal role played by in utero exposure to DES followed hard upon the report of seven cases of the hitherto exceedingly rare tumor, adenocarcinoma of the vagina, presenting in young individuals, 14 to 22 years of age.^{20,21} The syndrome appears to involve not only cases of vaginal adenocarcinoma, but a spectrum of abnormalities of the vagina and cervix. Only when exposure to DES occurred during the first four months of gestation were neoplasms or abnormalities observed.

The DES vaginal adenosis-adenocarcinoma relationship is the only documented example in humans of cancer in the offspring attributable to parental environmental chemical exposure. The therapeutic agent was given in a high dose, commonly more than 10 grams in the first half of pregnancy. DES, a synthetic nonsteroidal estrogen analogue, was likely to have a direct effect on the development of the target tissue at a crucial point in embryogenesis. Since the risk to the offspring appears limited to exposures which occur during the first four months of gestation, direct exposure of the fetus is likely to be essential to the pathogenic mechanism. The long latent period, with exposure in utero and emergence of clinical sequelae in adolescence, probably reflects the importance of pubertal endogenous estrogens as promoting factors, and is a reminder of the need for an extended period of observation following suspect trans-generational carcinogenic exposures. The association between DES and vaginal adenocarcinomas, as important as it is, does not serve as a model for preconception parental occupational exposures and trans-generational carcinogenesis. Teratogenic effects of a multiplicity of drugs are now documented or suspected and these will not be discussed here further except to reiterate the need to remove the potentially confounding effects of such agents in investigations of other possible causes of impaired fetal development.²⁴

Given the current status of our understanding, it is essential that in the search for exogenous causes of teratogenesis and abnormal pregnancy outcomes, the potential confounding impacts of maternal smoking, drinking, and medication intake be taken into account.

Radiation.—If preconception radiation exposure increases cancer risk in the offspring, it would heighten concern over other agents which produce chromosomal damage. Chromosomal aberrations attributed to vinyl chloride and benzene exposure, for example, are reminiscent of those produced by radiation.

While the genetic consequences of irradiation from the atomic bombings might be expected to produce some lethal mutations in the offspring of survivors, this effect

has been difficult to demonstrate. Cohort studies of offspring of survivors classified by radiation exposure level did not show excess mortality in the children of the high exposure group. Neither were excess congenital malformations, increased infant mortality, nor impaired survival during the first ten years of life detected, regardless of exposure level to either parent. Thus, although animal experience strongly suggests that such effects should be manifest in offspring of individuals exposed to ionizing irradiation, studies of Japanese atomic bomb survivors have not demonstrated measurable effects.²⁵

No substantial increase in leukemia risk has been detected among offspring of survivors. Analyses having a 90% chance of detecting a four-fold increase in risk of leukemia among children of heavily exposed survivors were negative. Neither did age-at-onset of observed leukemia cases nor type of leukemia in offspring differ by level of parental radiation exposure. Despite the documented persistence of chromosomal aberrations in the somatic cells of adults exposed to the atomic bomb, no measurable impact on mortality, congenital malformations or leukemogenesis has been detected in their offspring.²⁶

In addition to radiation exposures related to the atomic bombings, diagnostic and therapeutic medical radiation of the parents has been investigated to assess risks to the offspring. The magnitude of leukemia risk associated with previous radiation was estimated, after adjustment for maternal age and pregnancy history, to be 1.73 times that of mothers who had not been x-rayed. Despite the suggestion of greater risk in women with higher x-ray exposure, no clear-cut dose-response gradient was demonstrated. The relative risk of leukemia in the child associated with preconception diagnostic radiation of the father (1.31) was not statistically different from unity. When both mother and father had histories of preconception diagnostic x-rays, the order of magnitude of the relative risk, 1.49, was about the same as that for children whose mothers alone had received radiation.²⁷

Exposure to medical radiation has been widespread. By the early 1960's, approximately 35% of a group of mothers of healthy children reported having received diagnostic radiation prior to conceiving. Similarly, about 22% of fathers of the same children reported having had some sort of diagnostic radiation at some time prior to the child's conception. Self-reporting considerably underestimates the extent of x-ray exposures.²⁸ The tendency to substantially underreport x-ray exposure points up the difficulty of excluding differences in prior radiation exposure as a basis for observed differences in chromosomal aberrations. Neither is it reasonable to automatically presume that medical radiation exposures have been equally present in the study and comparison groups, especially if these groups have not been matched by age or calendar period of observations.

Occupational Exposures and Pregnancy Outcome

Vinyl Chloride.—Chromosomal abnormalities may occur more often than expected in persons exposed to vinyl chloride, especially following intense exposures of long duration. The import of such abnormalities for reproductive outcome remains ill-defined.

Chromosomal aberrations were reported in 1975 in

Swedish vinyl chloride workers. Abnormalities appeared in cells drawn from seven males with occupational exposure histories of nine to 29 years (mean 16.6 years) at vinyl chloride concentrations which had declined to 20-30 ppm by 1974.¹¹ The group exposed to vinyl chloride had aberrations in a total of 9.52% of all cells, compared to 1.94% for cells of three unexposed controls. Differences in the frequency of chromatid and isochromatid breaks accounted for most of the disparity. Considerable variation was exhibited, with cells considered abnormal ranging from 1.5% to 18% in the exposed workers. There was no apparent relationship between duration of exposure to vinyl chloride and the proportion of cells which were abnormal. Age, radiation exposure or other environmental factors were not evaluated, nor was it clear on what basis individuals had been selected for study.

In New York State, chromosomal aberrations were reported in somatic cells of 11 men who had worked in a polyvinyl chloride polymerization plant and who were believed to have experienced intense intermittent exposures to vinyl chloride in concentrations of over 500 ppm, as well as chronic, but unquantitated exposure for four to 28 years (mean, 15 years). Control samples were drawn from four males in the same factory who were not known to have had vinyl chloride exposure, and from six males from outside the factory. Complex chromosomal aberrations (rings, dicentric, fragments) occurred significantly more frequently in the exposed than in the control group, a result which was properly interpreted with caution. The authors point out the absence of age-matched controls and the substantial age difference between study group and controls. The frequency of chromosome breaks and gaps was unexpectedly high in both control and study groups.¹² No relationship could be defined between dose or duration of exposure and frequency of chromosomal aberrations.

Investigators reporting from the United Kingdom studied 56 men who had had chronic exposure to vinyl chloride monomer in the course of manufacturing polyvinyl chloride and compared them with 24 unexposed individuals.¹¹ Vinyl chloride exposure of men employed in its manufacture could not be easily quantitated. Individuals with exposures to radiation or with recent viral infections or prolonged drug treatment were excluded. Samples were coded and read blindly. A higher proportion of cells with chromosomal aberrations, the majority of which were breakages, was found in vinyl chloride-exposed workers than in controls. Unstable and stable chromosomal aberrations and breaks were all significantly more common in cells from exposed workers.

Not all investigators have identified such changes. No differences were found in frequency of chromosomal aberrations between a group of 209 employees of a vinyl chloride plant (occupational exposures averaging 48.3 months) and a group of 295 individuals undergoing pre-employment physicals.¹³ No relationship was established between duration of vinyl chloride exposure and degree of chromosomal damage. The absence of blind evaluation in this study, as well as inclusion of individuals with minimal exposures in the exposed group, makes interpretation difficult. This difficulty is compounded by the substantial difference in mean age of study and control group members.

Pregnancy outcome in the wives of men exposed to vinyl chloride monomer (VCM) has been said to be less favorable than that experienced by wives of a group of polymerization and polyvinyl chloride (PVC) fabrication workers.^{11, 14} One comparison group, the polymerization workers, was believed not to have been exposed to VCM, whereas PVC workers had low VCM exposure. Data on pregnancies and pregnancy outcomes in the wives were derived from interviews and questionnaires administered to male workers. Participation rates for the groups queried ranged from 62% to 77%. Fetal death was defined as any known conception which did not result in a live birth and rates were adjusted by paternal age. Maternal age was not known, but was presumed to correlate closely with paternal age. Analysis of questionnaire responses suggested that the number of fetal deaths per 100 conceptions was higher in the VCM-exposed group than in the comparison group. This difference was reported only for the period following vinyl chloride exposure. Adjustments removing women who were chronic aborters eliminated statistically significant differences. While the authors felt that these observations were likely to reflect a real difference in pregnancy outcome not attributable to either interviewer or patient recall bias, the conclusions were based on indirect sources of information and could not take into account the multiplicity of maternal factors known to affect pregnancy outcome. The study design precluded documenting in even the crudest manner the validity of pregnancy histories. Without such adjustments and validation, the inferences made by Infante and colleagues^{11, 14} cannot be sustained and little light is shed on the possible association of abnormal pregnancy outcome with paternal occupational exposure to VCM.

Studies of pregnancy outcome (i.e., spontaneous abortion, late fetal death [stillbirth], low birth weight, neonatal death) in other settings have shown the profound and subtle effects of confounding variables such as race, socioeconomic status, maternal age, birth order, parity, smoking and alcohol exposure during pregnancy, maternal infections, and previous pregnancy outcomes. These effects may readily reverse the direction of the relationship between a suspect antecedent factor and the outcome of pregnancy.¹⁵ Future efforts to document a relationship between impaired pregnancy outcome and occupational exposures of fathers must validate information on pregnancies and take into account known confounding factors.

Chloroprene.—Structural similarities between vinyl chloride and chloroprene have raised questions about long-term hazards resulting from chloroprene exposure. Chloroprene is mutagenic in certain systems and possibly carcinogenic. The possibility that it has induced excessive miscarriages in the wives of male workers and led to chromosomal aberrations has been asserted but not well documented.¹⁶

Benzene.—Benzene also may cause chromosomal aberrations following heavy occupational exposures. Twenty males working in a factory in which benzene had been used as a solvent were studied for chromosomal aberrations. Members of this group had one to 20 years of benzene exposure; 14 were known to have previously been neutropenic. Chromosomal abnormalities were reported in 2.5% of all cells from exposed workers, com-

pared to 1.0 to 1.4% for controls. Most of the excess was due to chromosomal aberrations of the unstable types. In addition to the excess of abnormal cells in the exposed group, the number of unstable alterations per abnormal cell was higher in the exposed group than in the controls.¹⁷

In a separate investigation, ten workers in an Italian rotogravure plant who had had sequential exposures, first to benzene and later to toluene and xylene, were studied. These workers had been subjected to concentrations of benzene ranging from 125 ppm to 532 ppm or higher. The maximal allowable concentration at the time of these exposures had been 25 ppm. Another group of 24 workers had primarily toluene exposures except for trace contamination with xylene. These 34 workers were matched with healthy controls of similar age and sex, who had been drawn from the general population and who had no history of benzene or radiation exposure. A significantly higher proportion of abnormal cells was found in the benzene-exposed individuals than in their matched controls. In the group with toluene exposure, no such excess was present. When the benzene and toluene groups were compared to each other, an excess of chromosome changes was present in the benzene group. Most of the excess was attributable to unstable chromosomal alterations.¹⁸

These studies and others¹⁹ support the impression that exposure to benzene, particularly exposures intense enough to result in acute toxicity, can be followed by a measurable excess of chromosomal aberrations which may persist for years. If similar effects occur in germ cells of exposed individuals, the consequences in fetal wastage, congenital anomalies and even neoplasms might be manifest in their progeny. To date no excess of such abnormalities has been reported in offspring of benzene-exposed individuals.

Anesthetic Gases. — Occupational exposures of female operating room personnel to waste anesthetic gases have been held responsible for decreased fertility, increased rate of spontaneous abortion, low birth weight and possibly impaired development in the offspring. An excess of spontaneous abortions in wives of men professionally exposed to anesthetic gases has been suggested but not confirmed.

Among operating room nurses, 29.7% of pregnancies terminated with spontaneous abortion, compared to 8.8% among control nurses. A similar excess of spontaneous abortion was observed for female physician anesthesiologists compared to female physicians in other specialties.²⁰ Spontaneous abortions occurred two weeks earlier on the average among the operating room exposure groups than among controls, at an average of eight rather than ten weeks of gestation. Another survey suggested that for female nurse-anesthetists who had worked during pregnancy, the frequency of birth defects in the offspring was 16.4% compared to 5.7% for pregnancies in which the mother had not worked.²¹

Studies from Finland and the United Kingdom also suggested a deleterious effect on pregnancy outcome from maternal exposure to operating room environments. An increase in frequency of early spontaneous abortions, as well as low birth weight, has been reported for Finnish female operating room staff.²² Among female physicians in

England and Wales, greater incidence of congenital defects, lower birth weights and higher stillbirth rates, but not higher spontaneous abortion rates, were reported from pregnancies of women holding anesthesiology appointments than from those of other women physicians.²³

The effects of paternal exposure to anesthetic gases are uncertain. Congenital anomalies were reported to be increased by 25% in the offspring of male anesthesiologists compared to offspring of male members of the American Academy of Pediatrics, but no difference was reported for spontaneous abortion rates among wives of male operating room personnel compared to controls.²⁴ Questionnaires completed by 5119 married male physicians in the United Kingdom suggested an increase in minor but not in major congenital anomalies, and no difference in frequency of infertility, spontaneous abortion or cancer in the offspring of male anesthesiologists compared to control physicians.²⁵

Hydrocarbons. — Two studies offer conflicting evidence with respect to the risk of cancer in children of men whose work might lead them to be exposed to petroleum-derived hydrocarbons. Fabia and Thuy²⁶ reviewed death certificates in Quebec during 1965 to 1970 to identify children who had died from malignant disease while under five years of age. For 386 of 402 such children, birth certificates were also found in the Quebec population register. A control group of 772 children (two for each cancer death) was selected using the birth registration record preceding and following that of each case in the official files. This effectively matched for season, calendar period, and province of birth. Occupation of the father at the time of birth was taken from the birth certificate. An industrial hygienist independently grouped the fathers into three levels of probable exposure to petroleum-derived hydrocarbons. Occupation of the father was unknown for 30 cases and 56 controls. The distribution of occupation of the father at birth differed for cases and controls. Most of this difference was the result of an excess among cases of paternal occupations considered to be hydrocarbon-related. The relative odds of cancer in the children of men holding hydrocarbon-related jobs at the time of the child's birth were 3.1, an increase which was unlikely to have occurred by chance. Most of the excess in exposed occupations was accounted for by motor vehicle mechanics, machinists, miners and painters. When similar analyses were conducted by the type of cancer in the child, the excess of hydrocarbon-related occupations prevailed for the following groupings: leukemia-lymphoma, nervous system malignancy, other tumors. Fathers of four of five cases of Letterer-Siwe disease were in the hydrocarbon-related work groups. No such excess was present for children with Wilms' tumor. The differences observed could not be attributed to differences in parental age or in geographic residence at the time of birth. The investigation was based on deaths in children under five, and it is possible that social class bias may have been introduced in that fashion. If, of those with a childhood neoplasm, children of more affluent parents are more likely than children of poorer parents to survive beyond age five, they would not be included in the study group. This would lead to a higher proportion of children with parents of lower socio-economic status in

the cancer death group and would have the distribution of father's occupation. Moreover, it was not possible to confirm that fathers in the so-called "exposed" group did, in fact, have contact with hydrocarbon-derived chemicals. While not ideal, the death certificate probably is a valid source of diagnostic information for cancer deaths in young children. The cancer groupings employed in the analysis — "leukemias and lymphomas," "nervous system" and "others" — were quite broad and included many histopathologic entities. Occupational association was not restricted to specific entities within the broader categories. Because the epidemiologic features of the various histopathologic types of leukemias, lymphomas, and nervous system tumors are distinctive, a specific chemical exposure or class of exposures, if assumed to be of causal significance, would more likely be linked with specific histopathologic as well as organ-system effects.

A study with a similar design but different findings was conducted in Finland.⁴⁷ Children under 15 years of age who developed cancer were identified from the Finnish Cancer Registry, 1959-1968. Of 1409 cancer cases so identified, the final series consisted of 852 pairs for whom birth records which included father's occupation were available. Each case was matched with a child whose birth date immediately preceded that of the case and who was born in the same maternity welfare district. This procedure matched effectively by calendar period, season and domicile at the time of birth. Father's occupation was drawn not from birth registration records but from records of the free, nationwide antenatal care system in operation in Finland. Father's occupation was classified by likelihood of hydrocarbon exposure in a manner which was shown to be comparable with that employed in the study done in Quebec. No excess risk for hydrocarbon-exposed fathers was detected for any class of neoplasms either for children whose cancers occurred under five or under 15 years of age.

The two studies differed primarily in the source of information on father's occupation. For the Finnish study, that information was drawn from antenatal records compiled for the most part in the first trimester of gestation. This may be a better index of exposure at the time of conception than information recorded at the time of birth in the birth certificate itself. Although a large number of pairs were discarded in Finland because father's occupation was not recorded, these came from a circumscribed calendar period. Since a matched pairs design was maintained throughout the analysis, removal of these cases should not influence the result. The Finnish study used incident cancer cases and looked at age groups up to 15 years at the time of cancer diagnosis. The Quebec group identified only cancer deaths up to five years of age. Variation in terminology of occupational classification might also contribute to the differences, although efforts were made to establish their comparability. At present, the contradictory findings of the two studies are not readily reconciled.

Surveillance of Spontaneous Abortions as a Strategy of Environmental Monitoring

The relationship between mutagenic, teratogenic and carcinogenic effects in the offspring of persons exposed to noxious environmental agents is a complex one.

Surveillance of spontaneous abortions may have a number of advantages as a prospective means of monitoring for such effects since defective conceptions are aborted selectively. As a result, studies of teratogenesis focusing on spontaneous abortions may be considerably more efficient than those conducted in newborns. Because the frequency of abnormalities is higher in spontaneous abortions, the sample size needed to demonstrate a change in risk is much smaller than that required for a parallel query addressed to defects recognized at birth. The magnitude of this difference can be dramatic. If chromosomal defects diagnosable on the appearance of the newborn are considered alone, the sample size required may be hundreds of times that required in an investigation examining prevalence of chromosomal anomalies in early abortion.⁴⁸ In addition to sample size considerations, study of spontaneously aborted conceptions offers a lead time of at least six months over studies of live births. The abortion specimen can be studied with care and thoroughness, permitting detection of anomalies lethal to the fetus which might escape detection in studies of live births.

The problem of power and sample size is only one of the issues which beleaguer investigators of associations between exposures to parents and outcomes of pregnancy. Related factors are the timing of the exposure, maternal or paternal, in relation to conception and/or gestation, and the specific measures of pregnancy outcome.⁴⁹ Paternal exposures may act in two ways — by contamination of the maternal environment resulting in secondary maternal exposures, or directly by affecting paternal germinal tissue. Since spermatogenesis is a continuous process, paternal exposures occurring shortly before conception are those requiring the most investigative attention. Cumulative or delayed effects are more likely to be of importance in maternal exposures. By focusing on early pregnancy wastage, particularly if the frequency of chromosomal abnormalities in the aborted product of conceptions can be determined, the objectives of study are better focused and achieved with reduced sample size, and the confounding effects of the maternal in utero environmental factors are minimized.

In conclusion, while the potential clearly exists for teratogenesis and trans-generational carcinogenesis in the offspring of workers exposed to mutagenic and carcinogenic agents, such effects have been difficult to demonstrate conclusively in humans. Future investigations must take into account a variety of environmental and behavioral factors which can affect fetal development if causal associations between occupational exposures and pregnancy outcome are to be identified.

References

- 1 O.E.D.: The Compact Edition of the Oxford English Dictionary. Oxford: Oxford University Press, 1971, cites *Dunglison Medical Lexicon*, 1857.
- 2 Wilson JG. *Environment and Birth Defects*. New York: Academic Press, 1973.
- 3 Staples RE. Definition of teratogenesis and teratogen, in *Methods for Detection of Environmental Agents that Produce Congenital Defects*, T. H. Shepard et al (Eds.). *Proceedings of the Guadalupe Conference*. Amsterdam: North Holland Publishing Company, 1975.
- 4 Faumeni JF, Jr: The susceptibility of the fetus and child to chemical pollutants. *Chemicals in human teratogenesis and transplacental carcinogenesis* *Pediatrics* 53:807-812, 1974.

5. DiPaolo JA and Kohn P. Fetal alcohol syndrome: A study of possible relationships. *Arch Pathol* 81:121, 1974.
6. Rice JM. An overview of transplacental chemical carcinogenesis. *Teratology* 8:113-125, 1973.
7. Claxton SK and Smith DW. The fetal alcohol syndrome. *N Engl J Med* 298:1063-1067, 1978.
8. Lillienfeld CN. The offspring of alcoholic mothers. *Ann NY Acad Sci* 197:167-169, 1972.
9. Jones KL and Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2:993-1001, 1973.
10. Ouellette EM, Rosett HL, Rosman PN, and Weiner L. Adverse effects on offspring of maternal alcohol abuse during pregnancy. *N Engl J Med* 297:528-530, 1977.
11. Klonick JB. Teratogenic effects of ethyl alcohol administered to pregnant mice. *Am J Obstet Gynecol* 124:676-680, 1976.
12. Kline J, Stein Z, and Warburton D. Smoking: A risk factor for spontaneous abortion. *N Engl J Med* 297:793-796, 1977.
13. Rush D and Kass E. Maternal smoking: A reassessment of the association with perinatal mortality. *Am J Epidemiol* 96:183-196, 1972.
14. Meyer MB, Jones BS, and Tomascak JN. Perinatal events associated with maternal smoking during pregnancy. *Am J Epidemiol* 103:464-476, 1976.
15. Stein Z, Susser M, and Warburton D. Spontaneous abortion as a screening device: The effect of fetal survival on the incidence of birth defects. *Am J Epidemiol* 102:275-290, 1975.
16. Alberman E, Cressy M, Elliott M, et al. Maternal factors associated with fetal chromosomal anomalies in spontaneous abortions. *Br J Obstet Gynaecol* 83:621-627, 1976.
17. Frederick J, Alberman ED, and Goldstein H. Possible teratogenic effect of cigarette smoking. *Nature* 235:529-530, 1971.
18. Richards IDG. Congenital malformations and environmental influence in pregnancy. *Br J Prev Soc Med* 23:218-225, 1969.
19. Himmelfarb DJ, Brown BW, Jr, and Cohen EN. Cigarette smoking during pregnancy and the recurrence of spontaneous abortion and congenital abnormality. *Am J Epidemiol* 108:470-479, 1978.
20. Herbst AL and Scully RE. Adenocarcinoma of the vagina in adolescence: A report of 7 cases including 6 clear-cell carcinomas (so called mesonephricomas). *Cancer* 25:745-757, 1970.
21. Herbst AL, Ulfelder H, and Poskanzer DC. Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 284:878-881, 1971.
22. Herbst AL, Kurzman RJ, Scully RE, and Poskanzer DC. Clear cell adenocarcinoma of the genital tract in young females. *N Engl J Med* 287:1259-1264, 1972.
23. Herbst AL, Poskanzer DC, Robboy SJ, et al. Prenatal exposure to stilbestrol: A prospective comparison of exposed female offspring with unexposed controls. *N Engl J Med* 292:333-339, 1975.
24. Hehonen OP. Birth Defects and Drugs in Pregnancy. Littleton, Mass.: PSC Publ. Co., 1977.
25. Kato H, Schull WJ, and Neel JV. A cohort-type study of survival in the children of parents exposed to atomic bombings. *Am J Hum Genet* 29:339-373, 1956.
26. Hoshino T, Kato H, Finch SC, and Hrubec Z. Leukemia in offspring of atomic bomb survivors. *Blood* 30:719-729, 1967.
27. Graham S, Levin ML, Lilienfeld AM, et al. Preconception, intrauterine, and postnatal radiation as related to leukemia. *Natl Cancer Inst Monogr* 19:347-371, 1966.
28. Graham S, Levin ML, Lilienfeld AM, et al. Methodological problems and design of the white leukemia survey. *Ann NY Acad Sci* 286:339-373, 1966.
29. Funck-Craviato F, Lambert B, Lindsten J, et al. Chromosome aberrations in workers exposed to vinyl chloride (letter). *Lancet* 1:459, 1975.
30. Ducatman A, Hartman K, and Spikoff H. Vinyl chloride exposure and human chromosome aberrations. *Mutat Res* 31:163-168, 1975.
31. Pritchard JFH, Richardson CR, and Anderson D. Chromosomal and dominant lethal effects of vinyl chloride. *Lancet* 2:1104-111, 1975.
32. Picciano DJ, Flake RE, Gay PC, and Kilian DJ. Vinyl chloride cytophenics. *J Occup Med* 19:527-530, 1977.
33. Infante PF, Waggoner JK, and Michael AJ, et al. Genetic risks of vinyl chloride. *Lancet* 1:734-735, 1976.
34. Infante PF, Waggoner JK, Michael AJ, et al. Genetic risks of vinyl chloride. *Lancet* 1:734-735, 1976.
35. Daling JR and Emanuel L. Induced abortion and subsequent outcome of pregnancy in a series of American women. *N Engl J Med* 297:1241-1245, 1977.
36. Infante PF, Waggoner JK, and Young RJ. Chlorophene: Observations of carcinogenesis and mutagenesis. In: *Origins of Human Cancer*. Book A. Incidence of Cancer in Humans. H. H. Hiatt, J. D. Watson, and T. A. Wiseman (eds). Cold Spring Harbor Laboratory, 1977, pp 205-217.
37. Tough IM and Court Brown WK. Chromosome aberrations and exposure to ambient benzene. *Lancet* 1:864, 1975.
38. Forni A, Pacifico E, and Linvorta A. Chromosome studies in workers exposed to benzene or toluene or both. *Arch Environ Health* 22:373-378, 1971.
39. Forni AM, Cappellini A, Pacifico E, and Vigliani EC. Chromosome changes and their evolution in subjects with past exposure to benzene. *Arch Environ Health* 23:385-391, 1971.
40. Cohen EN, Bellville IV, and Brown BW. Anesthesia, pregnancy and miscarriage: A study of operating room nurses and anesthetists. *Anesthesiology* 35:343-347, 1971.
41. Corbett TH, Cornell RC, Endres JL, and Leding K. Birth defects among children of nurse-anesthetists. *Anesthesiology* 41:341-344, 1974.
42. Rosenborg P and Kives A. Miscarriages among operating room theatre staff. *Acta Anaesthesiol Scand (Suppl)* 33:37-42, 1973.
43. Pharoah POD, Alberman E, and Doyle P. Outcome of pregnancy among women in anesthetic practice. *Lancet* 1:34-36, 1977.
44. Cohen EN, Brown BW, Jr, Bruce DL, et al. Occupational disease among operating room personnel: A national study. *Anesthesiology* 41:321-340, 1974.
45. Knill-Jones RP, Newman BJ, and Spence AA. Anesthetic practice and pregnancy: Controlled survey of male anesthetists in the United Kingdom. *Lancet* 2:807-809, 1975.
46. Fabia J and Thuy TD. Occupation of father at time of birth of children dying of malignant diseases. *Br J Prev Soc Med* 28:98-100, 1974.
47. Hakulinen T, Salonen T, and Teppo L. Cancer in the offspring of fathers in hydrocarbon-related occupations. *Br J Prev Soc Med* 30:138-140, 1976.
48. Kline J, Stein Z, Strobino B, et al. Surveillance of spontaneous abortions: Power in environmental monitoring. *Am J Epidemiol* 106:345-350, 1977.
49. Strobino BR, Kline J, and Stein Z. Chemical and physical exposures of parents: Effects on human reproduction and offspring. *Environ Health Perspect* 33:371-399, 1978.

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A CROSS-SECTIONAL EPIDEMIOLOGIC SURVEY OF VINYL CHLORIDE WORKERS

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ABSTRACT

A considerable number of studies have associated occupational vinyl chloride monomer (VCM) exposure with a variety of adverse health effects. The extent to which VCM induces these abnormalities in the workforce is not well defined. This cross-sectional medical survey of 433 predominantly white male employees, divided into four VCM exposure groups (never, light, heavy, former), determined the prevalence of illnesses and abnormalities based on data gathered by interview, medical examination, blood and pulmonary function tests, liver scans, and hand and chest x-rays. Age-adjusted analyses indicated that hepatomegaly, central nervous system symptoms, diastolic hypertension and spouses' fetal wastage (the latter two statistically significant at $p < 0.05$) were more prevalent among past or present VCM exposed workers than among controls. Although VCM-related respiratory system problems, acroosteolysis, Raynaud's phenomenon, and chromosome aberrations have been identified by other investigators, no excessive prevalence of these toxic effects was found in this population compared with industrial worker controls.

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INTRODUCTION

The causal relationship between occupational exposure to vinyl chloride monomer (VCM) vapor and the development of liver angiosarcoma is now well established. Following the first cluster of VCM-induced human cases of liver angiosarcoma discovered by Creech and Johnson (1), there have been a number of corroborative findings including animal bioassay tests (2,3), additional case reports of VCM-induced liver angiosarcoma (4), and formal epidemiologic studies (5-7).

Available evidence also indicates that VCM can induce non-malignant liver alterations (9-15), portal fibrosis in particular, long before the development of clinically manifest liver malignancy. Furthermore, pathophysiological effects do not appear to be limited to the liver. For example, experimental animal research (2,18), as well as clinical (17) and epidemiologic (5,7,8,16,19) studies of workers exposed to VCM and polyvinyl chloride (PVC) plastic dust, indicate a toxic effect on the respiratory system. Some of these same studies have also found increased risk of hematopoietic and central nervous system tumors. Microbial test system studies (20-22) and cytogenetic studies of VCM-exposed workers (23-26) indicate possible genetic effects. The anesthetic properties of vinyl chloride monomer (14) have been implicated as causing numerous central nervous system symptoms such as headaches, dizziness, and fainting in exposed workers (27).

The extent to which VCM induces clinically detectable abnormalities among workers occupationally exposed has not yet been well defined. Consequently, in order to determine the range of health effects associated with VCM, the National Institute for Occupational Safety and Health (NIOSH) and the Bureau of Epidemiology of the Center for Disease Control (CDC), in collaboration with the Occupational Health Studies Group (OHSO) of the University of North Carolina, conducted a cross-sectional medical survey at a chemical plant in Pottstown, Pennsylvania, which has a PVC polymerization operation, a PVC fabrication operation, and a rubber tire production operation. The specific objectives of the survey were: 1) To compare the prevalence of liver abnormalities and liver disease in VCM-exposed workers and appropriately selected control workers at the plant; 2) To identify those tests best suited for detection of other illnesses and abnormalities in these groups of workers.

METHODS

The plant selected is one of the older PVC polymerization plants in the United States, having operation continuously since 1948. The plant thus provided a favorable research opportunity, since sufficient time had elapsed for the appearance of VCM-induced chronic effects. In addition, the plant provided the unique situation where a PVC polymerization ("chemical") plant, a PVC fabrication ("plastics") plant, and a non-VCM plant (a rubber tire operation) were located next to each other within one large corporate facility, although the individual plants were physically distinct from one another. Further, selection of non-VCM-exposed controls was facilitated because the University of North Carolina had conducted prior industrial hygiene surveys within these plants as part of an ongoing joint company-union research project.

Shown in Table 1 are the four groups of hourly (production) employees who were requested to participate in the study. The first three groups are ordered by current VCM exposure. The first group consisted of a 9% sample of the 2400 rubber workers in the plant who were not exposed to VCM. These workers were age-frequency matched to the VCM-exposed chemical workers, and were chosen from departments in the plant identified as having the least exposure to other potentially confounding toxins such as solvents, dusts, and fumes.

The second group, the plastics workers, included everyone currently working in the PVC fabrication operation who had never worked in the chemical polymerization operation. Since these men were working with solid PVC plastic, their 8 hour time weighted average exposure to VCM was probably below 10 ppm prior to this survey. However, for the third group listed, the chemical workers, the VCM exposure before 1974 was considered to be very much higher than in the plastics area. Every employee working in the chemical plant at the time of this survey was included in this group. All former chemical workers working elsewhere in the plant made up the fourth group surveyed. Participation rates of those requested to participate varied from a low of 62% in the rubber workers to a high of 77% in the chemical workers.

Using these four groups, two etiologic models were designed for classifying subjects in the analysis of the relationship of health status to VCM exposure. The first, the Acute Exposure Model, reflects the abovementioned sampling design, and is based on the subject's job at the time of participation in this health survey. The former chemical workers were treated as a separate group for this analysis, regardless of their current jobs, since under an assumption of acute exposure etiology, their past VCM exposures,

however brief, might be associated with some residual health effects. A second etiologic model, a Cumulative Exposure Model, based on each worker's entire work history at the plant, afforded no meaningful comparisons because of the extremely high correlation between age and dose, which precluded any legitimate age adjustment. Data presented here are therefore confined to the cross-sectional ("Acute Exposure") comparisons.

The health testing program, as outlined in Appendix A, consisted of a comprehensive 210 item questionnaire, including the Rose cardiovascular and British Medical Research Council respiratory symptom (BMRC) questions, administered to participants by trained medical interviewers, a thorough physical examination performed by NIOSH and CDC physicians, pulmonary function tests, chest x-rays, and a series of laboratory tests including a complete blood count, platelet count, urinalysis, liver function, serum protein electrophoresis, hepatitis antigen, and sputum cytology. In addition, all study subjects who had been chemical workers for at least ten years underwent liver-spleen scans with lead markers and hand x-rays performed at a nearby hospital. Cytogenetic studies were carried out on a very small sample of workers (Appendix B) (39).

Participants from all three shifts were tested during the shift they worked during the month of October, 1974. All physicians, interviewers, and technicians were blind to the occupational status of each worker; occupational status was determined independently, by use of the company's personnel records.

Individual consent was obtained from each participating worker. Results of testing were released only to the participant himself and to the physician(s) designated by each worker. Detailed medical reports on all of the questionnaire and physical examination findings, as well as most of the laboratory findings, were sent to the designated physicians within two months of the examination. Summary letters of these findings were sent to all the workers at the same time. Meetings were held with study participants before, during, and after the medical examination to discuss procedures as well as findings.

The United Rubber, Cork, Linoleum and Plastics Workers of America and the local union (URW Local #336) Health and Safety Committee at the Pottstown plant provided considerable support in obtaining participation of workers in the study. Almost all examination were performed during working hours, and the plant personnel department and local union safety representatives assisted in the examination scheduling.

Similarity of the groups was measured in terms of age, race, sex, alcohol consumption, and cigarette smoking. All of the study subjects were male except for two plastics workers. Eleven (3%) of the study subjects were black and were distributed fairly evenly over the four occupational groups. All sex-race groups were included in the analysis. The age distributions of the current chemical workers and rubber worker controls

were similar since they had been group-matched on age initially. However, when all four occupational groups were considered, the age distributions were significantly different (Table 2). Therefore, age adjustment of all test results was carried out using the direct method with the age distribution of the entire 411 persons as the standard.

Analysis of daily alcohol consumption based on current drinking habits showed that the four groups were nearly identical; thus no adjustment for alcohol consumption was deemed necessary (Table 3). Although there were no statistically significant differences in smoking habits, the distributions did vary sufficiently for pulmonary function testing and respiratory symptom results to be smoking adjusted.

Liver

Only one person, a chemical worker, gave a history of cirrhosis. Approximately 3% of those interviewed in each occupational group gave a positive history of gall bladder disease, whereas hepatitis (Table 4) was slightly more prevalent among persons who had been exposed to vinyl chloride.

The four liver function tests used - serum glutamic oxaloacetic transaminase (SGOT), total bilirubin, lactic dehydrogenase (LDH), and alkaline phosphatase - were analyzed by comparison of mean value, and by prevalence and severity of abnormalities (Table 4).

In the total study population reported herein, 21% had an abnormal SGOT, 5% an abnormal total bilirubin, 4% an abnormal LDH, and 13% an abnormal alkaline phosphatase. For the most part, similar abnormality prevalences were found in each of the occupational groups, the major exception being abnormal LDH levels in 11.8% of the former chemical workers. Neither the overall mean values nor distribution of the abnormalities by severity differed notably among the occupational groups.

Two methods were employed to detect hepatomegaly: physical examination (measured by both palpation and percussion) and liver scan. The liver scan procedure, described in Appendix A, consisted of six pictures with lead markers to aid in liver size determination. However, when the liver size measurements from the scans were tested for inter-reader variation, it was found that reader number one averaged 3 centimeters in height and 2.4 centimeters in width greater than reader number two. These differences were statistically significant ($p < .001$) in a matched pairs t-test. Standardization of measuring techniques among the readers was therefore deemed insufficient for their use in the analysis of hepatomegaly.

Hepatomegaly as measured by palpation or percussion is somewhat subjective. To determine whether one physician might have been overzealous in diagnosing hepatomegaly, thus possibly biasing the results, prevalence of palpated hepatomegaly by individual physician was calculated. No statistically significant difference was observed. Of the two measurements on physical examination, palpation (as defined by palpable liver) appeared to be the more sensitive, diagnosing 11% of the total population as having

hepatomegaly compared with 6% by percussion (> 11 centimeters) (Table 5). The good consistency between the two techniques for determining hepatomegaly was demonstrated by agreement in over 90% of the cases diagnosed by percussion.

One of the more interesting findings in this study was the Relationship Between Hepatomegaly and VCM Exposure. Current chemical workers had almost twice the age-adjusted prevalence (13.22%) of palpated hepatomegaly as did rubber workers (7.1%) and plastics workers (7.3%). A gradient in the same direction from chemical workers to plastics workers and rubber workers also existed when hepatomegaly was diagnosed by percussion alone (5.2%, 5.0%, 3.4%), and by both percussion and palpation (4.6%, 3.5%, 0.8%). However, no differences were found between current chemical workers in high, medium, and low exposure jobs (not shown).

Two of the eleven people with hepatomegaly by percussion and palpation were heavy drinkers and one of these two also had a history of hepatitis. To investigate the occurrence of liver problems evidenced by combinations of abnormalities, cases were analyzed that had two or more of the four liver function tests abnormal and hepatomegaly by both percussion and palpation. All four cases that met these criteria had been exposed to VCM. One was a former chemical worker and the other three were current chemical workers. All of them had an elevated SGOT.

Of the 123 liver scans performed on long term VCM-exposed workers (a few salaried and hourly employees not in the four major occupational groups were included in this number), 94 were read as normal by all three nuclear medicine specialists independently. Of the 29 scans read as abnormal, only four were read as abnormal by two reviewers and none were read as abnormal by all three reviewers. One reviewer read a total of two scans as abnormal, and the other two read 13 and 18 scans, respectively, as abnormal (Table 6).

The four cases read as abnormal by two readers included 1) a 33 year old salaried process control engineer (not a member of the four occupational groups) whose LDH was elevated, 2) two chemical workers who worked as polymer reactor cleaners (the job associated with the highest VCM exposure in the chemical plant) aged 44 and 47, both of whom were light drinkers and had no abnormal liver function tests, and 3) a 52 year old former polymer reactor cleaner now working elsewhere in the chemical plant who was a greater-than-moderate drinker and had no abnormal liver function tests.

Other Abnormalities

There were no significant differences between groups for symptoms suggestive of Raynaud's phenomenon (Table 7). In addition, there was no difference between groups for the presence of an abnormal Allen Test (which has been suggested as an indicator for acroosteolysis).

Twenty-two of the 207 hand x-rays taken were read as abnormal for some state of acroosteolysis by at least one of the two independent radiologists. Most of the abnormal findings reported were from Reader #2. All but two of the abnormalities related to damage to the tufts of the cortex, a less

severe state of acroosteolysis, and many were possibly related to other causes such as trauma. Although the other two x-rays showed possibly more severe changes of the shaft, they were only read as positive by one reader. One of the two cases had worked since 1952 in the chemical plant, while the other, a maintenance man since 1964, had worked intermittently in the chemical plant.

Central nervous system symptoms elicited during the interview (Table 8) showed that severe persistent headaches were slightly more prevalent among chemical and plastics workers, compared to rubber and former chemical workers. A history of having ever lost consciousness on the job was less common in the rubber workers. On neurologic examination, the four occupational groups were found to be similar, with the exception of slightly diminished reflexes in the chemical group.

Since some of the known effects of VCM on humans (angiosarcoma, acroosteolysis, and Raynaud's phenomenon) involved the circulatory system, there was a specific interest in the results relating to the cardiovascular system. No noticeable differences among the occupational groups were found for prevalence of angina pectoris, as measured by the Rose Questionnaire, but a much higher prevalence of systolic hypertension (≥ 140 mm) in the former chemical workers, and a higher prevalence of diastolic hypertension (≥ 90 mm) in all three VCM-exposed groups compared to rubber workers, were seen (Table 9). Current and former chemical workers also had an increased history of having been told of hypertension in the past by a physician, and an increased history of having taken either "water pills" or blood pressure medication in the past, compared to rubber workers. Furthermore, the age-adjusted (by analysis of covariance) mean diastolic blood pressures were significantly different among the four groups ($p < .05$).

Tables 10 and 11 present prevalences of Pulmonary Function (PF) impairment among job groups. In Table 10, smoking, age, and height differences between study subjects were automatically controlled by comparing actual PF value with expected PF value derived from the appropriate smoking category of the total plant population. In Table 11, the actual PF values of study subjects in each job group and smoking category were compared to expected values derived from the literature, and the prevalence reported in other VCM workers. FEF₅₀/FVC and FEF₇₅/FVC impairment cut-off points have been shown to be effective in distinguishing normal subjects from those with obstructive lung disease (33).

There was no difference between job or smoking groups in the prevalence of volume impairment (FVC). Flow impairment was not consistently associated with any job group. For example, the former chemical workers had the highest prevalence of impaired FEF₂₅₋₇₅, FEV/FVC (non-smokers), FEF₅₀/FVC and FEF₇₅/FVC (smokers) and FEV₁ (smokers). Present chemical workers had the lowest prevalence of impairment of airflow (FEF₂₅₋₇₅, FEV₁/FVC, FEF₅₀/FVC), but highest prevalence for FEV₁ (overall) and FEV₁ (non-smokers). Rates of

airflow impairment $> 10\%$ of lowest values were observed in non-smoking former chemical workers (42%) compared to hourly chemical workers (22%) for FVC1/FVC, and smoking former chemical workers (65%) compared to rubber (50%), plastics (56%), and hourly chemical (51%) for FEF₇₅/FVC. With regard to FEF₇₅/FVC, rates of impairment were consistently high for all groups. Nearly half of the study subjects had small airways obstruction to which this test pertains. Former chemical workers also had the highest prevalence of CVVC impairment, and rubber workers the lowest prevalence. The greatest and most consistent effects were those of smoking. Except for FVC, smokers had consistently higher prevalence of impairment by all PF tests.

Because of the possibility of more recent, or more subtle, exposure effects among workers in this study population, before-and-after shift PF tests were carried out on a sample of 56 of the participating workers (Figure 1). Since there was a higher proportion of smokers within the subset of chemicals workers, compared to the rubber and plastics subsets, results are presented separately for smokers and non-smokers.

Smokers overall had statistically significant reductions for all seven PF tests. Non-smokers, however, showed little reduction, with the most obvious being for flow rates at low lung volumes, FEF₅₀ and FEF₇₅ (measuring small airways performance). Chemical workers who were smokers had significant reductions for five of the seven tests, predominantly reflecting small airways obstructive change. However, both the plastics and rubber workers who smoked showed reductions of similar magnitude, although the smaller number of plastics smokers precluded their attaining statistical significance. The other two respiratory system health tests, sputum cytology and chest x-rays showed minor inter-occupational group differences. No sputum cytology findings revealed more than moderate atypia. Mild and moderate atypia age-adjusted prevalence rates were 26%, 29.4%, 33.3% and 17.9% for the four groups, respectively. When the chest x-rays were read by three radiologists by the UICC/ILO criteria for pneumoconiosis, only one definite case was detected; and he was a former silica worker.

The health questionnaire incorporated the British Medical Research Council's chronic respiratory system questionnaire (see Appendix A). A comparison of age-smoking-adjusted respiratory symptom prevalence rates in the four occupational categories is presented in Table 12. For three of the four symptoms analyzed, the current hourly chemical workers had symptom rates slightly higher than those of the rubber worker control group. The plastics workers, and former chemical workers however, had rates substantially higher than the rubber workers.

Information on the pregnancy outcomes of the workers' wives, gathered as part of the questionnaire, were analyzed by age of father at time of conception, both before and after exposure at the plant. Since the number of pregnancies was so small, all workers in the chemical and former chemical

groups were included in the primary VCM exposure group; and since the two other groups did not differ by fetal wastage either before or after employment, they were combined in this analysis as a control group. Paternal age-specific fetal death rates are given in Table 13.

Pre-exposure fetal death rates did not differ between the two groups when adjusted for age (6.9% versus 6.1%). However, subsequent to the husband's exposure, the primary VCM exposed group had a statistically significant higher fetal death rate ($p < .05$) than the control group after age adjustment (15.8% versus 8.8%). Although not discussed here, this difference persists even when pregnancies of women considered to be chronic aborters are excluded from the analysis (26).

Cytogenetic studies of peripheral blood lymphocytes carried out on a small subsample of the workers indicated VCM exposed workers had a slightly higher proportion of chromosome breakage than rubber workers (Table 14). The plastics workers with presumed lower VCM exposure than the chemical workers had a slightly higher breakage proportion than all other groups. None of these intra-plant differences were statistically significant. Each of the three groups studied at the plant had a higher breakage rate than a non-industrial set of controls drawn from CDC personnel of approximately the same ages (see also Appendix B).

DISCUSSION

None of the liver function tests showed striking inter-occupational group differences, with one exception. LDI abnormalities were found in only 2-4% of three of the work groups but in 12% of the former chemical workers including three persons with values greater than 250. Other studies done on populations of active and retired VC workers (29,30) with lower mean ages found approximately 2% with LDI abnormalities, which is consistent with most groups in this study. Since the results are age-adjusted, age can be ruled out as being responsible for this excess in the former chemical workers. (However, since the current chemical workers include only 3.6% with abnormal LDI, and since there is no dose-response gradient in the chronic model, self-selection out of the chemical area related to symptoms of associated abnormalities may be taking place.) Prevalence of alkaline phosphatase, and total bilirubin abnormalities are also similar to, but slightly lower, than in the two other studies. With respect to SGOT, Wyatt's study (29) found approximately 8% abnormal in VCI exposed workers and 14% in unexposed workers both of which are substantially lower than our figure. Ljiljs, et al. (30) using a more restrictive abnormality criterion for SGOT (> 50 is defined as abnormal rather than > 40) found 6% abnormal. Using this criteria 4.9%, 3.1%, 6.1% and 7.2% abnormalities were found in the four groups, respectively. It is particularly noteworthy that all three studies have shown over 10% of VCI exposed workers with elevated alkaline phosphatase, since the laboratories set the demarcation point for abnormality as the upper 5% tail in the general population. The fact that all four work groups display this high prevalence of alkaline phosphatase abnormality in this study could possibly be explained by either demographic (e.g., age) differences between the study populations and the laboratory reference population or by the existence of some unidentified plant-wide hepatotoxin(s).

The most numerically impressive test difference between VCH-exposed and non-VCH-exposed workers is hepatomegaly. Despite the acknowledged inconsistency of determining hepatomegaly by physical examination, the consistency of the results seen here is striking. Hepatomegaly prevalence followed a weak dose-response gradient to VCI exposure from the chemical workers to the plastics workers to the rubber workers when measured by palpation, percussion, or both; degree of hepatomegaly followed the same exposure gradient. A gradient of hepatomegaly prevalence by duration of VCH exposure, unadjusted for age, has been reported elsewhere (30).

The liver scan appears to be of doubtful value as a screening test to detect possible early liver damage, not only because of the radiation exposure, inaccessibility of equipment, and high cost, but also because of the difficulty of standardizing reported findings when dealing with minimal

or early changes. It is possible, however, that with continued collaboration in an ongoing testing program, these problems could be overcome. The divergent liver scan results reported by our three readers could be secondary to a number of factors: a) Center where the scans were performed and the respective institutions of the three reviewers, despite a major effort on our part to standardize techniques before the study started, b) different standards for the interpretation of normal and abnormal by the three reviewers, and c) the possibility that a number of these scans represent truly equivocal findings, i.e., changes that are minimal or borderline and for which agreement or diagnosis would be difficult to attain. The latter interpretation is supported by the fact that many of the reported findings were in the possible or probable categories, rather than the definite category.

There were only four workers who were judged as having hepatomegaly and who also had two or more abnormal liver function tests (one of which was always the SGOT). In addition, liver scans of four other workers were read as abnormal by two readers. The fact that all eight were exposed to VCM suggests the possibility that such screening tests, separately or jointly are detecting early VCM-induced liver disease. Only by following this, and other, populations prospectively would it be possible to fully assess the predictive value of any of these tests for detecting VCM-induced disease.

Splenomegaly and decreased platelet counts, two findings which have been noted in earlier studies of VCM-exposed workers (30,13), were not seen in this study. The extent to which these VCM-associated changes are related to primary disease in the spleen or secondary to portal hypertension is not entirely clear, but this study does suggest that these screening tests may be related to a slightly more advanced stage of the disease than might have existed in this survey.

Other previously recognized health effects due to vinyl chloride exposure were not very frequent in this population. Prevalence of symptoms of Raynaud's phenomenon were not increased, and Allen test abnormalities were no more common among VCM-exposed than non-exposed workers. Although indications of acroosteolysis were seen in over 10% of the hand x-rays, poor inter-observer reliability among the x-ray readers, the fact that most of the x-ray changes noted were for the earlier stages of acroosteolysis, and the absence of increased symptoms or physical findings suggestive of acroosteolysis indicate that this disease is not a major problem at the plant now. (A review of serial x-ray taken in prior years would provide a clearer picture for the development of this disease over time.) A history of central nervous system symptoms, expected from the anesthetic effect of vinyl chloride, was found more often in vinyl chloride exposed workers. This is consistent with an earlier study by Spirtas, et al. (27) of the same plant. Because of changing working conditions over time, it is quite possible that many of the central nervous system symptoms reported in the medical history occurred well in the past, and although no neurologic abnormalities were noted during this cross-sectional examination, one should

Standardized

not rule out the possibility that such abnormalities might have been present at a time when central nervous system symptoms were more prevalent. Overall, there is little proof that current VCM exposures are high enough to induce these VCM-related central nervous system health effects.

The substantially lower prevalence in the rubber workers of diastolic hypertension, measured as greater than 90mm Hg, is difficult to explain. The excess hypertensives in the other three groups are all in the 90-105mm Hg range. While the anxiety levels may have been higher in workers currently or formerly exposed to VCM (since most of them were aware of its carcinogenic potential), if such emotions were responsible for the differential prevalence of diastolic hypertension one would expect a concomitant differential prevalence of systolic hypertension - which did not exist except in the former chemical workers. Additionally, pulse rates were similar in the four groups which argues against an anxiety etiology. More chemical and former chemical workers reported previously diagnosed hypertension than rubber workers, and there was also an increased history for having taken water pills or anti-hypertensive medication in the past; however, it was impossible to tell from interview data whether their exposures or hypertension came first. The increased prevalence in former chemical workers of systolic hypertension, if due to VCM, would also be expected in the current chemical workers, unless the systolic hypertension temporarily follows a diastolic hypertension-induced selection out of the chemical area. Such a hypothesis, although very tenuous, would be consistent with Table 9.

While these cardiovascular findings may be unrelated to VCM exposure, VCM has definite known vascular effects such as angiosarcoma, acroosteolysis, and Raynaud's phenomenon. Therefore, it is plausible, at least by analogy that VCM in some way is responsible for the hypertension. Although there was a random allocation of subjects to the various examining physicians, it is well known that a single blood pressure reading is a somewhat unreliable finding in epidemiologic studies, and the relationship noted here between systemic hypertension and VCM exposure warrants more detailed investigation.

Experimental studies and case histories suggest that VCM acts as a lung irritant at high exposure levels (10,13,14). The reported epidemiologic study of VCM-PVC workers tends to support this literature (19). This study suggests no difference in PF on respiratory symptoms related to VCM exposure. Former chemical workers tended to have higher rates of impairment, but this could be due to exposure in their non-VCM jobs, or could reflect some self-selective migration away from that work area by individuals most prone to develop symptoms in response to exposure to the chemical plant environment. However, in the absence of information on jobs held subsequent to chemical plant jobs, no conclusions can be made.

The environmental factor having the greatest effect on baseline lung function was smoking. Smokers in all job groups had higher rates of flow impairment when compared to non-smokers. This was a consistent finding, and the impairment was of greater magnitude than any differences observed between job groups.

The interval age, height, and smoking adjusted comparisons between job groups in Tables 10 and 13 suggest no apparent effect of VCM exposure on other PF or respiratory symptoms. An external comparison relative impairment prevalence of this population to the findings of Miller, et al. in another population of current and former VCM workers (Table 11). Using their criteria for impairment, their values for volume impairment (FVC) are slightly lower than this study. This may be due however to their excluding any individual with flow impairment (FEV1 < 75% of FVC).

Former chemical workers who also smoked had flow impairment (FEV1/FVC) prevalence of 65%, a rate 10-15% higher than the other job groups, and the same prevalence as Miller, et al. (19) found in their study. This was the highest prevalence of impairment in any of the job groups, and for any PF parameter. Non-smokers in each job group had roughly comparable prevalence of FEV1/FVC impairment.

Impairment rates for FEV1/FVC may be elevated in the Miller, et al. (19) study because 41% of the group from which flow-volume curves were obtained were selected because of abnormal spirometric findings. Prevalence of FEV1/FVC impairment in this study was elevated, perhaps because there was no corresponding reduction in FVC. At least two reports in the literature (13,17) describe restrictive changes in the lung in PVC workers. In this study the baggers (chemical workers) and banbury operators (plastics) have the greatest exposure to PVC dust, and so volume impairment in these workers alone is unlikely to affect the results of the entire job category.

FEV1 impairment, an indicator of larger airways obstruction, was not elevated when compared to cotton textile (34) or hemp workers, and was comparable to non-exposed populations (35-38). FEV1, a sensitive test for small airways obstruction, revealed a high prevalence (>50%) of impairment. Prevalence of impaired FEV1, also a sensitive indicator of small airways obstruction, was similar to FEV1. Unfortunately the significance of the cutoffs for FEV1 and FEV1/FVC (expressed as a percentage of FVC) has not been fully evaluated. Prevalence of impaired CV/VCM, also an indicator of small airways function, was intermediate between the flow rate (FEV1/FVC) and FEV1/FVC impairments.

Flow impairment prevalence in this study does not appear elevated when compared to other working populations. For about one of every five workers compared to have some impairment is too high, however. This high prevalence of PF impairment, and the absence of differences in either respiratory function or symptoms among the job groups, suggests that all of the workers may be experiencing significant exposures. Indeed for several of the PF tests, the chemical workers had better results than the other job groups.

To assess the possibility of the current exposure hazard, before-and-after shift tests were carried out on some workers. Any reduction in PF over the shift suggests the likelihood of some harmful exposure. Smokers overall had significant reductions in PF, most obviously for flows at low lung volume. Non-smokers showed little reduction. Smokers in all job groups experienced reductions of similar magnitude, supporting the idea that all job groups face some respiratory insult.

While the increased frequency of chromosomal aberrations among the different occupational groups, compared with controls from outside the plant, may be due to exposure to VCM and/or other plant-wide chemicals, the results reported in Table 14 might also be due, at least partially, to age or socioeconomic status differences. Additionally, it should be noted that although the magnitude of the differences between the occupational groups studied at the plant do not support other investigations associating VCM exposure with chromosomal aberrations (23-26), there are differences among these various studies in the composition of the populations under study which might make direct comparison somewhat difficult, and the sample size in this study was small.

The significant excess of fetal loss experienced by the wives of workers subsequent to their husband's VCM exposure must be assessed against the weaknesses inherent in a questionnaire survey. These weaknesses have been discussed elsewhere (28) lending credence to the belief that these findings are not spurious. This excess is biologically consistent with the previously demonstrated mutagenic response to VCM in microbial test systems (20-22), and the increased frequencies of chromosomal aberrations in VCM-exposed workers found by other investigators (23-26). This evidence mandates further research into this new adverse health consequence of VCM and additional agents found to be mutagenic in laboratory test systems and which are in broad use in the plastics and rubber industries.

Finally, while no cases of hepatic angiosarcoma, far advanced liver disease, or cancer of other sites were detected by the study among those currently employed, this should not be misconstrued with regard to the recent extensive documentation of VCM liver carcinogenicity and toxicity; nor does it preclude the existence of such VCM-related conditions within this study population. In fact, liver angiosarcoma has been found previously at this VCM polymerization period, and with a short period of time elapsing between earliest clinical manifestation and death. Hence, only a small proportion with such silent and difficult-to-diagnose diseases could be expected to be found in a cross-sectional medical survey.

It should be pointed out that there are differences between plants with respect to work practices, production techniques, working conditions, and composition of workforce, in the presence or absence of various associated toxins, and other factors. This potential diversity of exposure within the PVC industry cautions against drawing general conclusions from this single study, about the hazards of VCM exposure, and the usefulness of screening tests in general VCM-exposed working populations. It is, therefore, necessary to put these into perspective alongside those reported from other plants, both in this country and elsewhere. Nevertheless, there are some tentative conclusions based on our findings which merit further evaluation.

Finally, with regard to the currently recommended liver screening procedures, the apparent low specificity of the liver function tests as a screening procedure taken together with their unknown sensitivity and predictive value, emphasize the generally perceived need for a more specific test for detecting early liver damage in VCM exposed workers. Simultaneously, the true early screening value of these standard liver function tests used in this study needs to be determined by a longitudinal medical surveillance program of the workers.

REFERENCES

1. Creech, J. and Johnson, H.: Angiosarcoma of Liver in Manufacture of Polyvinyl Chloride, *J. Occ. Med.*, 16, 150-151 (1974).
2. Maltoni, C. and Lefemine, G.: Carcinogenicity Bioassays of Vinyl Chloride: Current Results, *Ann. N.Y. Acad. Sci.*, 246, 195-218 (1975).
3. Keplinger, H., Goode, J., Gordon, D., and Calandra, J.: Interim Results of Exposure of Rats, Hamsters, and Mice to Vinyl Chloride, *Ann. N.Y. Acad. Sci.*, 246, 219-220 (1975).
4. Lloyd, W. Angiosarcoma of the Liver in Vinyl Chloride/Polyvinyl Chloride Workers, *J. Occ. Med.*, 17, 333-334 (1975).
5. Tabershaw Cooper Associates Inc.: Supplementary Epidemiological Study of Vinyl Chloride Workers I, Report May 30, 1975.
6. Nicholson, W., Hammond, E., Seidman, H. and Selikoff, I.: Mortality Experience of a Cohort of Vinyl Chloride-Polyvinyl Chloride Workers, *Ann. N.Y. Acad. Sci.*, 246, 225-230 (1975).
7. Waxweiler, R., Stringer, W., Wagoner, J., Jones J., Falk, H. and Carter, C.: Neoplastic Risk Among Workers Exposed to Vinyl Chloride, *Ann. N.Y. Acad. Sci.*, 271, 40-48 (1976).
8. Ott, G., Langer, R. and Holder, B.: Vinyl Chloride Exposure in a Controlled Industrial Environment, *Arch. Env. Health*, 30, 333-339 (1975).
9. Harsteller, H. and Leibach, W.: Unusual Splenomegalic Liver Disease as Evidenced by Peritoneoscopy and Guided Liver Biopsy Among Polyvinyl Chloride Production Workers, *Ann. N.Y. Acad. Sci.*, 246, 95-134 (1975).
10. Lester, D., Greenberg, L. and Adams, W. Effects of Single and Repeated Exposures of Humans and Rats to Vinyl Chloride, *Amer. Ind. Hyg. Assoc. J.*, 24, 265-275 (1963).
11. Suciu, I., Prodan, L., Ilea, E., Paduraru, A., and Pascu, L.: Clinical Manifestations in Vinyl Chloride Poisoning, *Ann. N.Y. Acad. Sci.*, 246, 53-69 (1975).
12. Gedigk, P., Muller, R., and Bechtelsheimer, H.: Morphology of Liver Damage Among Polyvinyl Chloride Production Workers. A Report of 51 Cases, *Ann. N.Y. Acad. Sci.*, 246, 278-285 (1975).

13. Lange, C., Juhn, S., Stein, G. and Vellman, G.: Further Results in Polyvinyl Chloride Production Workers, Ann. N.Y. Acad. Sci., 246, 18-20 (1975).
14. Pally, F., Yant, W. and Maile, E.: Acute Response of Guinea Pigs to Vapors of Some New Commercial Organic Compounds, Public Health Reports 45, 1963 (1930).
15. Viola, P.: Pathology of Vinyl Chloride, Med. Lavoro, 61, 174-179 (1970).
16. Wegman, D.: Discussion, Ann. N.Y. Acad. Sci., 246, 20-32 (1975).
17. Szende, B., Kapis, K., Nemes, A. and Pinter, A.: Pneumoconiosis Caused by Inhalation of PVC Dust, Med. Lavoro, 61, 433-436 (1970).
18. Frongia, N., Spinazzola, A., and Bacarelli, A.: Lesioni Pulmonari Sperimentali da inalazione prolungata di polveri di PVC, Med. Lavoro, 65, 321-342 (1974).
19. Miller, A., Tierstein, A., Chuang, M. and Selikoff, I.: Changes in Pulmonary Function in Workers Exposed to Vinyl Chloride and Polyvinyl Chloride, Ann. N.Y. Acad. Sci., 246, 42-52 (1975).
20. Bartsch, H., Malavielle, C. and Montesano, R.: Human, Rat and Mouse Liver-Mediated Mutagenicity of Vinyl Chloride in *S. Typhimurium* Strains, Int. J. Cancer, 15, 429 (1975).
21. Loprieno, N., Barale, R., Baroncelli, S., et al.: Evaluation of the Genetic Effects by Vinyl Chloride Monomer (VCM) Under Mammalian Metabolic Activation: Studies in Vitro and in Vivo, Mutation Res., 40, 85 (1976).
22. Rannung, U., Johansson, A., Ramel, C. and Wachtmeister, C.A.: The Mutagenicity of Vinyl Chloride After Metabolic Activation, Ambio 3, 194 (1974).
23. Ducatman, A., Hirschhorn, K. and Selikoff, I.J.: Vinyl Chloride Exposure and Human Chromosome Aberrations, Mutation Res., 31, 163 (1975).
24. Funes-Cravioto, F., Lambert, B., Linsten, J. et al.: Chromosome Aberrations in Workers Exposed to Vinyl Chloride, Lancet, i, 459 (1975).
25. Purchase, I.F.H., Richardson, C.R. and Anderson, D.: Chromosomal and Cominant Lethal Effects of Vinyl Chloride, Lancet, ii, 410 (1975).
26. Hansteen, I.L., Hillestad, L. and Thiss-Evensen, E.: Chromosome Studies on Workers Exposed to Vinyl Chloride, Mutation Res., 38, 112 (1976).

27. Spirtas, R., McMichael, A.J., Gotsch, J.F., and Van Ert, M.D.: The Association of Vinyl Chloride Exposures with Morbidity Symptoms, *Am. Ind. Hyg. J.*, 779-789 (1975).
28. Infante, P., Wagoner, J., McMichael, A., Waxweiler, R., and Falk, H.: Genetic Risks of Vinyl Chloride, *Lancet*, 1, 734-735 (1976).
29. Wyatt, R., et al.: An Epidemiologic Study of Blood Screening Tests and Illness Histories Among Chemical Workers Involved in the Manufacture of Polyvinyl Chloride, *Ann. N.Y. Acad. Sci.*, 246, 80-87 (1975).
30. Lillis, R., Anderson, H., Nicholson, M.J., et al.: Prevalence of Disease Among Vinyl Chloride and Polyvinyl Chloride Workers, *Ann. N.Y. Acad. Sci.*, 246, 22 (1975).
31. Morris, J.F., Kosk, A., and Johnson, L.L.: Spirometric Standards for Healthy Non-smoking Adults, *Am. Rev. Resp. Dis.*, 103, 57 (1971).
32. Buist, S.A. and Ross, B.B.: Predicted Values for Closing Volumes Using a Modified Single Breath, Nitrogen Test, *Am. Rev. Resp. Dis.*, 107, 44, (1973).
33. Lapp, N.L. and Hyatt, R.E.: Some Factors Affecting the Relationship of Maximum Expiratory Flow to Lung Volume in Health and Disease, *Dis Chest*, 51, 475 (1967).
34. Zuskin, E., Wolfson, R.L., and Harpel, G.: Byssinosis in carding and spinning workers: prevalence in the cotton textile industry, *Arch. Env. Hlth.*, 19, 666-673 (1969).
35. Bouhuys, A., et al.: Chronic Respiratory Disease in Hemp Workers, *Am. J. Med.*, 46, 526-37 (1969).
36. Bouhuys, A.: The Forced Expiratory Volume (FEV₇₅) in Healthy Males and in Textile Workers, *A.R.R.D.*, 87, 63-8 (1963).
37. Olson, H.C., and Gilson, J.D.: Respiratory Symptoms, Bronchitis and Ventilatory Capacity in Men: An Anglo-Danish Comparison, with Special Reference to Differences in Smoking Habits, *Brit. Med. J.*, 1, 450-6 (1960).
38. Reid, D.D., et al.: Cardiorespiratory Disease and Diabetes Among Middle-aged Male Civil Servants, *Lancet* 1, 469-73 (1974).
39. Heath, C.W., Jr., Dumont, C., Gamble, J., et al: Chromosomal Damage in Men Occupationally Exposed to Vinyl Chloride Monomer and Other Chemicals, *Envir. Res.*, In press (1977)

TABLE 1

Subgroups of Workers Included in Survey

VCM Exposure	Occupational Group (N)	Sample Sought	# Participants (Participation Rate)
None	Rubber (2400)	9%	134 (62%)
Lightly Exposed	Plastics (105)	All	80 (76%)
Exposed	Chemical (164)	All	126 (77%)
Past Exposure	Former Chemical (101)	All	71 (70%)

TABLE 2

Age Distribution of the Four Occupational Groups

<u>Age</u>	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>	<u>Total</u>
15-29	36 (27%)	19 (24%)	26 (21%)	12 (17%)	93 (23%)
30-39	23 (17%)	7 (9%)	13 (11%)	13 (18%)	56 (14%)
40-49	34 (25%)	12 (15%)	47 (36%)	29 (41%)	122 (30%)
≥ 50	41 (30%)	42 (51%)	40 (32%)	17 (24%)	140 (35%)
Total	134 (100%)	80 (100%)	126 (100%)	71 (100%)	411 (100%)
Mean Age	40.3	44.4	42.3	42.4	42.1

chi square = 29.83 p = .01

TABLE 3

Alcohol Consumption by Occupational Group

<u>Alcohol Score*</u>	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>	<u>Total</u>
0	31 (23%)	13 (16%)	26 (21%)	14 (20%)	84 (20%)
.01 to .74	35 (26%)	24 (30%)	36 (29%)	18 (25%)	113 (28%)
.75 to 3.75	58 (43%)	37 (46%)	58 (46%)	35 (49%)	188 (46%)
>3.75	10 (8%)	6 (8%)	6 (5%)	4 (6%)	26 (6%)
Total	134 (100%)	80 (100%)	126 (100%)	71 (100%)	411 (100%)

* Equivalent ounces of pure alcohol per day
 $\chi^2 = 2.54$ ($p > .05$)

TABLE 4

Severity of Liver Function Abnormalities

	Rubber	Plastics	Chemical	Former Chemical
SGOT (>39 Abnormal)				
Mean	31.6	32.1	32.6	34.5
Total Abnormal	22	19	25	19
40-49	16	16	17	14
>49	6	3	8	5
Prevalence*	17.1%	22.8%	19.8%	26.9%
Total Bilirubin (>1 Abnormal)				
Mean	.69	.63	.64	.63
Total Abnormal	8	5	4	4
1.01-1.40	6	4	4	3
>1.40	2	1	0	1
Prevalence*	5.4%	5.4%	3.5%	4.8%
LDH (>225 Abnormal)				
Mean	171	174	170	185
Total Abnormal	2	4	4	8
226-250	1	3	2	5
>250	1	1	2	3
Prevalence*	1.8%	4.2%	3.6%	11.8%
Alkaline Phosphatase (>85 Abnormal)				
Mean	67	66	66	69
Total Abnormal	18	10	16	11
86-115	15	8	15	8
>115	3	2	1	3
Prevalence*	13.1%	11.9%	12.5%	15.6%
History of Hepatitis				
Number	3	1	5	4
Prevalence *	1.9%	.8%	3.7%	5.6%

*Directly Age adjusted

TABLE 5
Prevalence of Hepatomegaly

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Palpation				
Number	9	8	17	10
Prevalence*	7.1%	7.3%	13.2%	13.0%
Percussion				
Number	4	5	7	1
12-13 cm	3	4	4	1
>13 cm	1	1	3	0
Prevalence*	3.4%	5.0%	5.2%	.8%
Both Palpation and Percussion				
Number	1	3	6	1
Prevalence*	.8%	3.5%	4.6%	.8%

* Directly Age Adjusted

TABLE 6

Liver Scan Results

Total number of liver scans performed in study: 123
 Normal to all 3 readers: 94
 Abnormal to 1 reader only: 25
 Abnormal to 2 readers: 4
 Abnormal to all 3 readers: 0

<u>Reader</u>	<u>Definitely Abnormal</u>	<u>Probably Abnormal</u>	<u>Focal Defect</u>	<u>Diffuse Disease</u>	<u>Other</u>
#1	-	13	2	7	4
#2	2	16	9	13	-
#3	-	2	2	-	-
	<u>2</u>	<u>31</u>	<u>13</u>	<u>20</u>	<u>4</u>

TABLE 7

Prevalence* of Raynaud's Symptoms

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Had attacks of numbness, cold blue coloration in fingers				
a. Unilateral	4.5%	2.0%	4.1%	5.8%
b. Bilateral	2.4%	3.8%	3.1%	1.8%
c. Such attacks precipitated by cold	4.1%	1.5%	3.8%	6.9%
d. Such attacks precipitated by emotional upset	.6%	0%	.6%	2.5%

*Age Adjusted

25

Prevalence* of Central Nervous System Symptoms

History of:

Former Chemical	Chemical	Plastics	Rubber	Severe Persistent Headaches	Losing Consciousness or Fainting on the Job	*Directly Age Adjusted
6.4%	13.7%	12.7%	8.6%	2.1%	5.2%	5.8%

TABLE 8

TABLE 9

Severity of Hypertension

	<u>Rubber</u>	<u>Plastics</u>	<u>Chemical</u>	<u>Former Chemical</u>
Systolic				
Number Hypertensive (≥ 140 mm Hg)	40	31	48	31
140-160 mm Hg	32	22	41	22
161-180 mm Hg	8	6	3	7
>180 mm Hg	0	3	4	2
Prevalence*	36.6%	32.5%	37.5%	45.6%
Mean*	132.4	135.7	134.9	137.2
Diastolic				
Number Hypertensive (> 90 mm Hg)**	31	33	51	26
90-94 mm Hg	17	14	25	17
95-105 mm Hg	10	12	21	5
>105 mm Hg	4	7	5	4
Prevalence*	24.3%	39.9%	39.4%	41.0%
Mean*	82.0	86.1	85.7	84.4
History of taking water pills or blood pressure medication	4.7%	11.5%	9.7%	16.0%
Previously told of high blood pressure by a physician*	19.6%	20.5%	25.7%	24.7%

• Age Adjusted

** Rubber vs χ^2 (Mantel-Haenszel) significant ($p < .05$)

TABLE 10

Prevalence of Pulmonary Function (PF) Impairments*
Among Job Groups Adjusted for Age, Height and Smoking

PF	<u>% Impairment</u>			
	Rubber	Plastics	Hourly Chemical	Former Chemical
FEV1 < 0.80 predicted	9.8	3.8	10.4	8.5
FVC < 0.80 predicted	4.5	8.8	6.4	5.6
FEF ₂₅₋₇₅ < 0.80 predicted	16.5	21.3	17.6	25.4
CV/VC > 1.20 predicted	17.6	26.6	24.8	30.0

* Expected values based on total worker population categorized by smoking

TABLE 11

Prévalence of Pulmonary Function (PF) Impairment
Among Occupational Groups by Smoking Category

PF	% Impairment				
	Rubber	Plastics	Chemical	Former Chemical	Miller et al.
FEV1/FVC < 0.75					
Non-Smokers	31.4	37.8	22.2	41.9	32
Smokers	44.4	53.5	41.3	47.5	48
All	39.9	46.3	34.4	45.1	45
FEV1 < 0.80 Predicted*					
Non-Smokers	8.2	8.1	11.1	9.7	--
Smokers	13.9	14.0	18.8	20.0	--
All	11.3	11.3	16.0	15.5	--
FVC < 0.80 Predicted					
Non-Smokers	8.2	5.4	6.7	12.9	3.9
Smokers	6.9	11.6	8.8	7.5	4.7
All	7.5	8.8	8.0	9.9	4.6
FEF50/FVC < 0.56					
Non-Smokers	4.9	10.8	2.2	3.2	--
Smokers	18.1	18.6	10.0	20.0	--
All	12.0	15.0	7.2	12.7	--
FEF75/FVC < 0.30					
Non-Smokers	39.3	46.0	42.2	48.4	44
Smokers	50.0	55.8	51.3	65.0	63
All	45.1	51.3	48.0	57.8	60
CV/VC > 1.20 Predicted**					
Non-Smokers	6.8	10.8	15.6	16.1	--
Smokers	25.0	35.7	35.0	38.5	--
All	16.8	24.1	28.0	28.6	--

* Based on regressions from Ref. 31

** Based on regressions from Ref. 32

Figure 18. Mean Percent Change in Pulmonary Function (APF) of Subjects in Chemical, Plastics and Rubber Workers (With Standard Error).

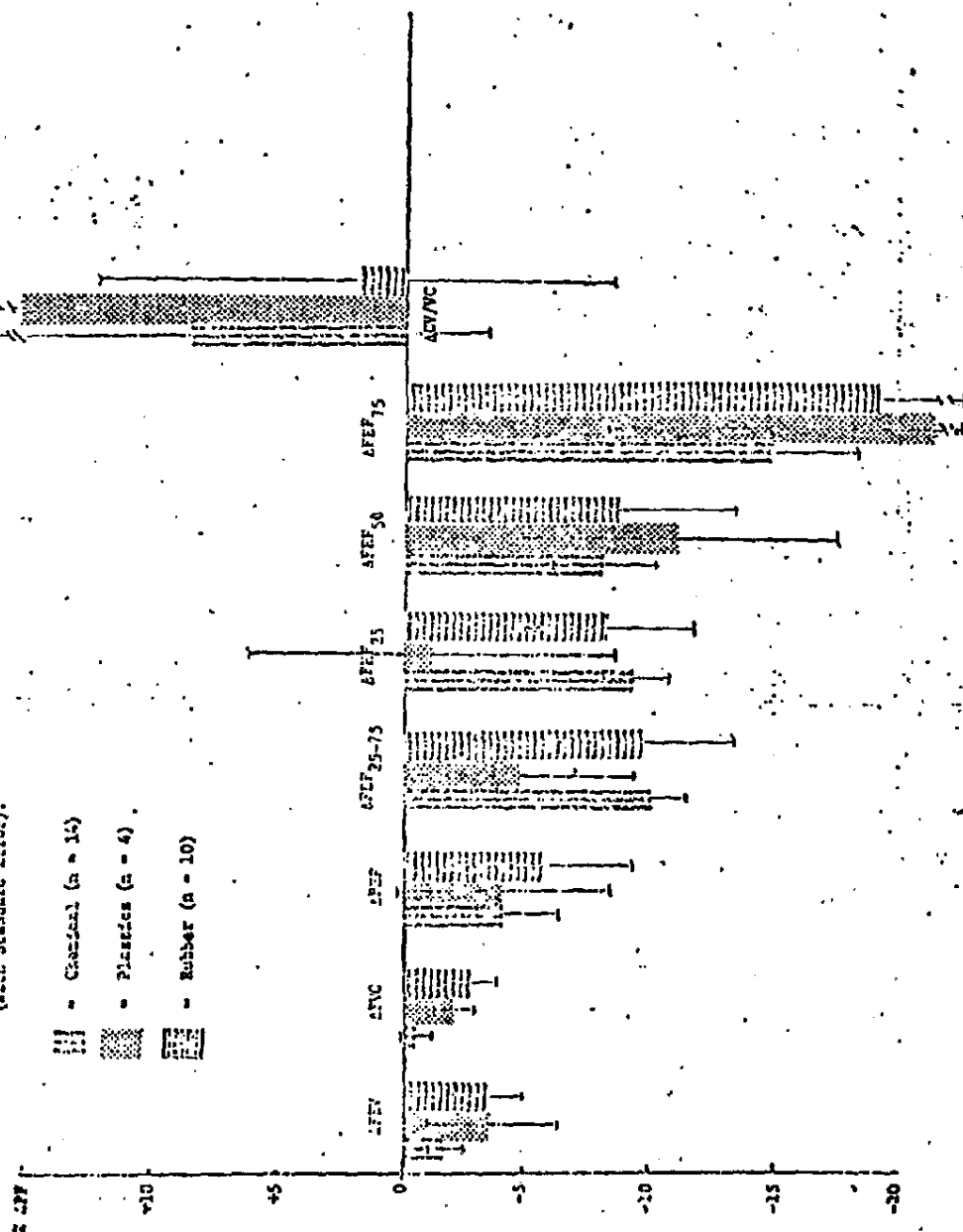


TABLE 12
Age and Smoking Adjusted Prevalence Rates
of Respiratory Symptoms

Symptom †	Rubber	Plastics	Chemical	Former Chemical
Cough 1 and 2	10.0*	21.0	15.7	13.7
Phlegm 1 and 2	16.8*	26.5	14.8	28.0
Persistent Cough and Phlegm	6.8*	13.5	7.9	9.8
Breathlessness (Grade 2,3,4)	19.8**	20.4	22.3	25.7*
N	133	80	126	71
Age (years)	40.31 (12.8)*	44.4 (13.7)	42.1 (13.2)	42.2 (11.0)
Height (inches)	69.8 (3.4)*	69.2 (2.4)	69.5 (2.2)	69.6 (2.8)

* = 1 missing
 ** = 3 missing
 † Scored according to BMRC criteria

TABLE 13

Paternal Age Distribution for Fetal Deaths
According to Husband's VC Exposure

Paternal Age Group (Years)	<u>"Controls"</u>			<u>Primary VC Exposure</u>		
	<u>Pregnancies</u> (N)	<u>Fetal</u> (N)	<u>Deaths</u> (%)	<u>Pregnancies</u> (N)	<u>Fetal</u> N	<u>Deaths</u> (%)
Prior to Husband's Exposure						
<20	31	2	6.5	7	0	0.0
20-24	80	4	5.0	44	2	4.5
25-29	38	4	10.5	56	7	12.5
30-34	6	1	16.7	27	5	18.5
≥35	4	0	0.0	14	1	7.1
ALL AGES	159	11	6.9	148	15	10.1
AGE-ADJUSTED			6.9			6.1
Subsequent to Husband's Exposure						
<20	1	0	0.0	0	0	0.0
20-24	43	4	9.3	22	3	13.6
25-29	87	3	3.4	48	11	22.9
30-34	87	7	8.0	36	3	8.3
≥35	55	10	18.2	33	6	18.2
ALL AGES	273	24	8.8	139	23	16.5
AGE ADJUSTED			8.8			15.8*

* Mantel-Haenszel χ^2 significant At $p < 0.05$ for the comparison of the two post exposure groups

TABLE 14
CYTOGENETIC STUDIES

<u>Exposure</u>	<u>Number of Subjects</u>	<u>Average Age</u>	<u>Average Months Worked</u>	<u>Number of Metaphases Scored</u>	<u>Number With Breakage</u>	<u>Percent With Breakage</u>
Chemical	14	49.4 (44-65)	291.1 (215-346)	1105	74	6.7
Plastics	4	52.5 (46-58)	315.8 (261-341)	180	14	7.8
Rubber	17	48.5 (31-58)	305.8 (114-357)	1306	77	5.9
Controls*	4	44.3 (37-51)	-	586	21	3.6

* CDC male employees not exposed to laboratory chemicals

APPENDIX A

TEST PROCEDURES

I. Medical Questionnaire

Administered by trained medical interviewers (U.S.P.H.S. Venereal Disease Representatives), the questionnaire contained sections on demographic information, a past history with complete review of systems and emphasis on prior drug use, a family history with special emphasis on liver diseases, a respiratory symptom questionnaire based on the British Medical Research Council Questionnaire, and a cardiovascular symptom questionnaire (the Rose questionnaire). Specific questions relating to potential VCM induced effects such as Raynaud's phenomenon were included. In addition, a section related to the occurrence of stillbirths, miscarriages, and birth defects in offspring of workers was included.

II. Physical Examination

A general thorough physical examination by CDC physicians including tests chosen a priority for their relevance to possible vinyl chloride induced disease, such as the Allen Test, liver examination by both palpation and percussion, a careful neurologic examination, and a gum guaiac stool examination.

III. Hematologic Test

10 ml of blood was drawn. A smear was made immediately for a qualitative platelet estimation and the remainder was refrigerated and sent to Upjohn Laboratories in King of Prussia, Pennsylvania, where hemoglobin hematocrit, white blood cell count, and platelet count were performed within four hours of the time the blood was drawn.

IV. Serologic Procedures

30 ml of blood was drawn, centrifuged, and the serum pipetted off and refrigerated immediately at the test site. (Sera for the sorbitol dehydrogenase procedure was immediately frozen in dry ice.) At the end of each eight hour testing session the serum was transported by direct auto courier to National Health Laboratories in Alexandria, Virginia, for a standard SMA-12 run including total bilirubin, alkaline phosphatase, lactic dehydrogenase, serum cholesterol, serum glutamic oxaloacetic transaminase, total protein, albumin, blood urea nitrogen, glucose, inorganic phosphate, calcium, and uric acid. Additionally, serum protein electrophoresis, hepatitis antigen, sorbitol dehydrogenase, and ornithine carbamyl transferase were run.

V. Urinalysis

Each subject had a routine urinalysis with microscopic examination performed by Upjohn Laboratories in King of Prussia, Pennsylvania. Specimens were transported together with the hematologic specimens.

VI. Sputum Cytology

Each subject was given a 10% propylene glycol mist and asked to cough into a jar of carbowax solution. At the end of each week the samples were sent to Dr. Geno Saccomano's laboratory in Grand Junction, Colorado for analysis.

VII. Chest X-Ray

For persons who had received a chest x-ray within the last six months, that x-ray was obtained and used for our review. All other people in the study were given 14 x 17 posterior - anterior x-rays on a mobile unit at 70-80 KV by a licensed x-ray technician. Films were developed on site and quickly read by a physician for quality and problems requiring immediate medical attention. Later, all films were sent to three UICC/ILO certified radiologists, Dr. Benjamin Felson at the University of Cincinnati, Dr. Martin Donner at Johns Hopkins Hospital, Dr. H. Dennis at the University of Maryland, who read them according to the 1970 UICC/ILO criteria for pneumoconiosis and other chest diseases.

VIII. Hand X-Rays

For a number of study participants, hand x-rays that had been previously taken by the company within the last six months were used. The rest of the subjects were given routine hand x-rays (45 KV, 90 MAS, with cardboard holders) at Pottstown Memorial Medical Center by their staff. The hand-x-rays were then sent along with the attached forms to Dr. Martin Donners and Dr. Walter Whitehouse at the University of Michigan Hospital for reading.

IX. Liver Scan

Five people had previous recent liver scans done at the request of the plant administration at the Pottstown Memorial Medical Center and these scans were used. The other 118 people were also scanned at the Pottstown Memorial Medical Center using a diverging collimator (gamma camera). One milliliter of Technetium 99 Sulfur Colloid was injected into patients 10 to 15 minutes before scanning. A lead marker was placed on the right costal margin to aid in liver size determination. Six pictures including anterior-posterior and lateral views of the spleen and liver were taken. A standard reading form was developed

by Dr. Mallow in conjunction with the three nuclear medicine specialists who later read the films, Dr. Edward Silberstein at the University of Cincinnati, Dr. Mansfield at the Jefferson Medical Center, and Dr. T.P. Haynie at the University of Indiana.

X. Pulmonary Function Testing

All workers performed the pulmonary function tests seated and with a noseclip. At least 5 forced exhalations were obtained. The equipment used was Model 220 waterless spirometer and Model 750 Recorder, made by Cardio Pulmonary Instruments, Houston, Texas. For spirometry and flow volume parameters, the following procedure was followed: 1) several relaxed breaths, 2) inhale to about 2/3 full capacity, 3) forcibly exhale to RV, 4) inhale to full capacity, 5) forcibly exhale to RV. Three curves for calculations were selected on the following basis: 1) FVC and FEV_{1.0} within 10% of each other and 2) appearance of curve - if it were possible to have a choice between curves, they were selected on the basis of a) partial exhalation between 60 and 75% of FVC, b) initial forced expiration done with full force and without hesitation and c) similarity in the shape of the curves. Calculations of flow are expressed as percent of FVC exhaled.

At least three single-breath Nitrogen (SBN₂) maneuvers were performed, with inhaled and exhaled N₂ differences less than 5%. Exhaled flow from full vital capacity was maintained below 0.4 liters/sec. The criteria for selection of two curves were that VC be within 10% of each other, and exhaled flow rate was not greater than 0.7 liters/sec. for longer than 1/2 second. Individuals having less than two acceptable curves were not recorded. Closing volume (CV) was determined by drawing a straight line by eye along the latter part of the alveolar plateau. The volume between the first convincing point of departure from this line and the full VC was recorded as CV.

APPENDIX B

CHROMOSOMAL DAMAGE IN MEN OCCUPATIONALLY EXPOSED
TO VINYL CHLORIDE MONOMER AND OTHER CHEMICALS

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Running head: Chromosomes and Vinyl Chloride

Introduction

Data from various sources suggest that the biologic effects of vinyl chloride monomer (VCM) include mutagenicity as well as oncogenicity. Pertinent studies include observations concerning the mutagenic effects of VCM in bacterial test systems (Kannug, et al, 1974; Bartsch, Malaveille, and Montesano, 1975), mutagenicity of VCM metabolites in mammalian cells (Huberman, Bartsch, and Sachs, 1975), and cytogenetic studies of polyvinyl chloride (PVC) polymerization workers (Ducatman, Hirschhorn, and Selikoff, 1975; Funes-Gravioto, et al, 1975; Kilian, Picciano, and Jacobson, 1975; Purchase, Richardson, and Anderson, 1975). Also relevant may be observations suggesting increased fetal loss in families of PVC workers (Infante, et al, 1976). Among the several cytogenetic studies reported, 3 have suggested increased chromosomal breakage among polymerization workers (Ducatman, Hirschhorn, and Selikoff, 1975; Funes-Gravioto, et al, 1975; Purchase, Richardson, and Anderson, 1975), and one has not (Kilian, Picciano, and Jacobson, 1975). This report concerns cytogenetic analyses conducted on workers employed at a rubber and plastics plant, some exposed to VCM and others not.

Materials and Methods

The work described here was part of a cross-sectional study designed to provide multiphasic medical screening data on the health status of men employed at a large rubber and plastics plant. The

overall study was conducted jointly by the Center for Disease Control (CDC) (National Institute for Occupational Safety and Health and Bureau of Epidemiology) and the Occupational Health Studies Group of the University of North Carolina in cooperation with the Firestone Corporation and the United Rubber Workers. Results of the entire study, together with a detailed description of the study's design and methodology, will be published separately.

Cytogenetic analyses, primarily designed to measure frequencies of chromosomal breakage, were performed on peripheral blood lymphocytes from 35 men; specimens were obtained from 18 men in October 1974 and 19 in January 1975 (2 on both occasions). Subjects were restricted to men primarily or exclusively employed for 10 years or longer, in 3 different employment categories: 14 in PVC polymerization (presumed high exposure to VCM, intermittent or sustained), 4 in PVC processing (presumed low exposure to VCM), and 17 in rubber tire manufacture (industry controls; presumed negligible exposure to VCM). Work history details were obtained by interview and confirmed by review of company records.

Initially, the study was designed to compare breakage frequencies in workers exposed to VCM with frequencies in other workers. However, when initial analyses showed no significant differences among worker groups, a control group was selected (April 1975) consisting of 4 male employees at CDC not exposed directly to any laboratory

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chemicals. Material for cytogenetic analysis was prepared in the same manner with the same reagents as the earlier material from workers at the plant. To assess comparability in microscopic reading of slides between April 1975 and the earlier dates, previously-read slides from the high VCM and industry control groups were blindly interspersed among the CDC worker slides. Breakage frequency recorded on the second reading of high VCM/industry control slides (6.0% of 150 scored metaphases) did not differ significantly from the first reading. Cytogenetic material was processed using standard procedures (Moorhead, et al, 1960). Cells were cultured for 72 hours in the presence of phytohemagglutinin. Giemsa staining was used without banding.

Results

Frequencies of chromosomal breakage in each group are shown in Table 1. Levels of breakage in all 3 industry groups, whether exposed to VCM or not, were significantly increased over the CDC control level, the high VCM group at the $p < 0.01$ level, the low VCM and industry control groups at the $p < 0.05$ level. At the same time, no significant differences were noted between the 3 industry groups themselves. Groups were comparable in terms of age and number of months worked. Breakage frequencies for individual subjects within groups did not vary significantly one from another.

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An effort was made to relate levels of breakage to duration of employment and hence extent of potential toxic exposure (Table 2). While a significant gradient was seen for industry controls, interpretation is uncertain because of small numbers and because the mean age of subjects increased with employment duration. No gradient was seen for the high VCM group, whether in terms of total employment or of employment in contact with VCM. The low VCM exposure group was too small to permit analysis by exposure duration.

Chromatid gaps comprised the majority (86%) of aberrations seen (Table 3). Similar types of aberrations were seen with similar frequencies among all 4 groups.

Discussion

When reviewed in terms of comparisons between worker and non-worker groups, the present observations are not inconsistent with prior studies suggesting that industrial exposure to VCM is associated with an approximately twofold increase in levels of chromosome breakage as measured in culture of peripheral blood lymphocytes. In contrast with at least one prior report (Huberman, Bartsch, and Sachs, 1975), however, breakage consisted mostly of simple chromatid gaps rather than more complex forms.

The fact that overall breakage levels were similar in workers exposed heavily, lightly, or negligibly to VCM may imply, in this

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particular work setting at least, the presence of agents other than VCM capable of inducing chromosome breaks. Because of the wide range of chemicals to which rubber workers at this plant were exposed (primarily solvents of various kinds), it was impossible to relate any particular agents to the abnormal effects observed. No clear-cut pattern was seen to relate degree of breakage to duration of exposure.

Summary

Measurements of chromosomal breakage were made in peripheral blood lymphocytes from workers exposed heavily, lightly, or negligibly to VCM at a large rubber/plastics plant. Breakage levels in all 3 groups were significantly increased over levels in nonindustrial controls. Breakage consisted mostly of simple chromatid gaps. The results suggest that other agents, in addition to VCM, may cause cytogenetic damage in workers employed in the rubber/plastics industry.

Page 1

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Acknowledgments

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References

- Bartsch, H., Malaveille, C., and Montesano, R. (1975). Human, rat, and mouse liver-mediated mutagenicity of vinyl chloride in S. Typhimurium strains. *Int J Cancer* 15:429-437.
- Bucatman, A., Mirschhorn, K., and Selikoff, I.J. (1975). Vinyl chloride exposure and human chromosome aberrations. *Mut Res* 31: 163-168.
- Funes-Graviato, F., Lambert, B., Lindsten, J., et al (1975). Letter to editor. *Lancet* 1:459.
- Huberman, E., Bartsch, H., and Sachs, L. (1975). Mutation induction in Chinese hamster V79 cells by two vinyl chloride metabolites, chloroethylene oxide and 2-chloroacetaldehyde. *Int J Cancer* 16: 639-644.
- Infante, P.F., Wagoner, J.K., McMichael, A.J., et al (1976). Genetic risks of vinyl chloride. *Lancet* 1:734-735.
- Kilian, D.J., Picciano, D.J., and Jacobson, C.B. (1975). Industrial monitoring: a cytogenetic approach. *Ann NY Acad Sci* 269:4-11.
- Moorhead, P.S., Nowell, P.C., Mellman, W.J., et al (1960). Chromosome preparation of leukocytes cultured from human peripheral blood. *Exp Cell Biol* 20:613-616.

Chromosomes and Vinyl Chloride - Heath

Purchase, I.F.H., Richardson, G.R., and Anderson, D. (1975). Letter to editor. Lancet 2:410-411.

Rannug U., Johansson A., Ramel, C., and Wachtmeister, C.A. (1974). The mutagenicity of vinyl chloride after metabolic activation. Ambio 3:194-197.

Table 1

LEVELS OF CHROMOSOMAL BREAKAGE BY EXPOSURE GROUP

<u>Exposure</u>	<u>Number of Subjects</u>	<u>Average Age (Range)</u>	<u>Average Number of Months Worked (Range)</u>	<u>Metaphases</u>		
				<u>Number Scored</u>	<u>Number with Breakage</u>	<u>Percent with Breakage*</u>
High VCM	14	49.4 (44-65)	291.1 (215-326)	1105	74	6.7
Low VCM	4	52.5 (46-58)	315.8 (261-341)	180	14	7.8
Industry Controls	17	48.5 (31-58)	305.8 (114-357)	1306	77	5.9
CDC Controls	4	44.3 (37-51)	-	586	21	3.6

* Levels of statistical significance:

High VCM vs. CDC Control	$\chi^2 = 7.09$	$p = < 0.01$
Low VCM vs. CDC Control	$\chi^2 = 4.64$	$p = < 0.05$
Industry Control vs. CDC Control	$\chi^2 = 3.95$	$p = < 0.05$
High VCM vs. Low VCM	$\chi^2 = 0.18$	$p = > 0.05$
High VCM vs. Industry Control	$\chi^2 = 0.31$	$p = > 0.05$

Table 2

Exposure	Months Worked	Number of Subjects	Average Age	Average Number of Months Worked	Number Scored	Metabolites	
						Number with Breasts	Percentage with Breasts
High VCM (Total Employment)	100-199	0	-	-	-	-	-
	200-299	8	47.4	254.6	700	49	7.0
	300-399	6	52.2	325.5	405	25	6.2
			$\chi^2(1 \text{ D.F.}) = 0.16$	$p > 0.05$			
High VCM (VCM Employment)	100-199	2	60.0	159.0	100	7	7.0
	200-299	9	47.7	252.3	755	53	7.0
	300-399	3	47.7	318.3	250	14	5.6
			$\chi^2(2 \text{ D.F.}) = 0.58$	$p > 0.05$			
Industry Controls	100-199	2	31.0	132.5	100	0	0
	200-299	2	44.5	265.5	76	1	1.3
	300-399	13	51.8	335.6	1130	75	5.7
			$\chi^2(2 \text{ D.F.}) = 9.92$	$p < 0.01$			

Table 3

TYPES OF CHROMOSOMAL ABERRATIONS OBSERVED

Chromosomal Aberration	High VCM		Low VCM		Industry Controls		CDC Controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Chromatid Gaps	59	5.3	12	6.7	74	5.7	18	3.1
Isochromatid Gaps	7	0.6	0	0	6	0.5	1	0.2
Chromatid Breaks	2	0.2	0	0	2	0.2	2	0.5
Isochromatid Breaks	5	0.5	2	1.1	9	0.7	1	0.2
Isochromatid Fragments	3	0.3	0	0	0	0	0	0
Exchange Figures	1	0.1	0	0	0	0	0	0
Ring Chromosomes	1	0.1	0	0	0	0	0	0
Total Breakage	78	7.1	14	7.8	91	7.0	22	3.8
Total Cells with Breakage	74	6.7	14	7.8	77	5.9	21	3.6
Hypodiploid Cells	121	11.0	33	18.3	155	11.9	61	10.4
Hyperdiploid Cells	2	0.2	0	0	3	0.3	1	0.2
Total Cells Scored	1105	-	180	-	1306	-	386	-

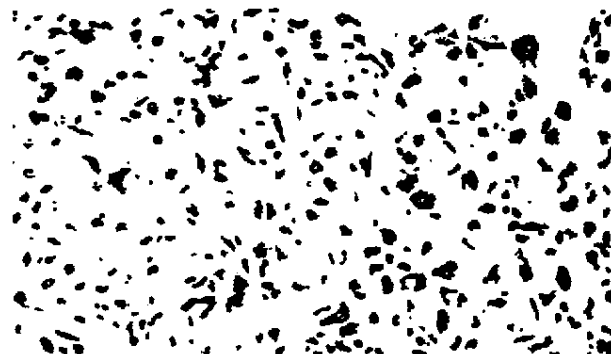
Angiosarcoma of liver associated with phenelzine

Angiosarcoma of the liver is extremely rare.¹ It has been associated with thorium dioxide, organic arsenic, and vinyl chloride monomer.² Phenelzine (phenethylhydrazine; Nardil), a monoamine oxidase inhibitor, causes angiosarcoma of the liver in mice.³ We describe a woman who developed angiosarcoma while taking phenelzine.

Case report

A 64-year-old woman admitted for investigation of anaemia gave a four-month history of malaise, bruising tendency, and cough productive of small blood clots. She had been taking phenelzine for at least six years. The initial dose was 45 mg daily, which was reduced to 15 mg daily after three years. Diazepam 5 or 10 mg occasionally was the only other regular medication. There was no history of exposure to thorium dioxide, arsenic, or vinyl chloride. Examination showed pallor, generalised wasting, and several large bruises. The liver was enlarged and palpable. Full blood count showed haemoglobin concentration 7.8 g/dl, white cell count $7 \times 10^9/l$ (7000/mm³), platelet count $155 \times 10^9/l$ (155 000/mm³), and reticulocytes 6.5%. Blood film showed fragmentation of red cells. Prothrombin time, thrombin clotting time, and activated partial thromboplastin time were all prolonged. Concentration of fibrin degradation products (FDP) was 160 mg/l. Moderate haematuria was present. Urea and electrolyte concentrations, initial liver function tests, serum α -fetoprotein value, and bone marrow appearances were normal.

The haematological findings suggested mild chronic disseminated intravascular coagulation (DIC). The haematuria and haemoptysis were ascribed to this process after exclusion of other causes. Subsequent platelet counts ranged between 20 and $100 \times 10^9/l$, and the raised titre of FDP persisted. Isotope liver scan showed multiple areas of decreased uptake, and computerised axial tomography of the liver confirmed areas of abnormal texture. In the lateral epicondyle of the right humerus there was an osteolytic area suggestive of metastatic disease. Results of barium meal and excretion urography were normal. Laparoscopy of the liver surface showed multiple umbilicated nodules up to 2 cm diameter, unlike cirrhosis or metastatic carcinoma. Laparoscopic needle biopsies disclosed normal liver tissue with focal areas of bile-duct proliferation with large pleomorphic cells suggestive of malignancy. At laparotomy numerous haemorrhagic nodules were seen on the liver and parietal peritoneum overlying the right lobe. These were sampled for biopsy. Histologically the liver showed distorted sinusoids lined by malignant cells adjacent to the focal areas of bile-duct proliferation (see figure). There was no evidence of cirrhosis. The peritoneal nodules comprised blood-filled spaces lined by malignant endothelial cells with pleomorphic nuclei. These changes were considered to be diagnostic of angiosarcoma.



Liver biopsy specimen showing distorted sinusoids lined by malignant cells. H and E $\times 840$ (original magnification).

The patient recovered from laparotomy and the haematuria and haemoptysis lessened. Gross bloodstained ascites developed, however, which required drainage. She died at home five months after presentation.

Comment

In animals substituted hydrazine derivatives induce a variety of tumours, including tumours of blood vessels.¹ Phenelzine given to female Swiss mice significantly increased the incidence of angiosarcoma at various sites, including the liver.³ Hence the angiosarcoma

in our patient may have been related to phenelzine. Although such an association in a patient has not been recorded before, this may represent failure in documenting drug history.

The presenting features of this case were probably manifestations of chronic DIC, which is associated with liver angiosarcoma.⁴ This process may have contributed to the bloodstained ascites. Naked-eye appearances of the liver were not diagnostic at laparoscopy or laparotomy. Primary liver tumour was diagnosed by multiple biopsy at laparotomy. We cannot be certain whether the peritoneal angiosarcomatous lesions and the lesion in the right humerus were metastases from a primary liver tumour or represented multifocal tumour growth, which is true in experimental animals.⁴

We suggest that inquiry about hydrazine compounds—for example, phenelzine, isoniazid, and procabazine—should be made in future cases of angiosarcoma of the liver.

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¹ Baxter, P J, *et al*, *British Medical Journal*, 1978, 2, 919.

² Ishak, K G, in *Hepatocellular Carcinoma*, ed K Okuda and R L Peters, p 247. New York, Wiley, 1976.

³ Toth, B, *Cancer Research*, 1976, 36, 917.

⁴ Toth, B, *Cancer Research*, 1975, 35, 3693.

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Multiple lipomas in pregnancy

Lipomas are benign tumours of adult fat cells. We report a case in which multiple lipomas first appeared during pregnancy.

Case report

The patient, aged 31, was in her second pregnancy. Her first pregnancy, in 1975, had ended in spontaneous abortion at 12 weeks. She had stopped taking a combined oral contraceptive in 1974 after two years' use. Her periods had remained irregular ever since.

She was seen first at the antenatal clinic when 20 weeks pregnant. She was of normal build, with weight 33.2 kg and height 156 cm. Physical examination showed no abnormality and the pregnancy was continuing normally, the uterine size being as expected from the duration of amenorrhoea. At her next visit at 28 weeks (care being shared with her general practitioner) she mentioned isolated, soft, painful subcutaneous swellings on both forearms. These were about 2 cm diameter and had been present for three weeks. Later, a further six swellings on the anterior aspects of her thighs became palpable. The swellings continued to enlarge slowly throughout the rest of her pregnancy, the largest, on her left forearm, reaching 3 cm diameter. Biopsy of a swelling on her right forearm showed the histological features of a simple lipoma. There was no vascular proliferation to suggest angiolipoma.

The pregnancy was otherwise normal: she gained 10 kg. She was delivered at 42 weeks by forceps of a healthy boy weighing 3400 g. In the immediate puerperium the lipomas became less and at the postnatal check six weeks later all but a swelling 0.5 cm diameter on her left forearm had disappeared. No lumps on her thighs could be seen or felt. She was breast-feeding and had begun an oral contraceptive containing only progesterone. So far as she knew none of her relatives had multiple lipomas.

Comment

Lipomas are slow-growing, benign tumours of adipose tissue. Multiple tender lesions, especially if there is a family history, are characteristic of angiolipomas.¹⁻³ Though her lipomas were tender, she had no family history, and histopathological findings were not consistent with angiolipomas.

Lipomas are common, but this is apparently the first report of multiple lipomas appearing in pregnancy and regressing in the puerperium. Possible explanations include: (a) that the hormonal