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# 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 "repa," meaning a marvel, prodigy or monster, the word "teratogenic" was used by 1857 to mean the "production of monstrous formations or births." 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."<sup>1</sup> 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.<sup>1</sup> 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."<sup>2</sup> Teratogenic, mutagenic and carcinogenic activities are all demonstrable for a number of com-

From Cornell University Medical College and Memorial-Sloan-Kettering Cancer Center, Box 60, 1275 York Ave., New York, NY 10021.  
Supported in part by a contract with the American Petroleum Institute.

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.<sup>5</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> The adverse effects on the fetus of maternal alcohol abuse during pregnancy were further quantified by Ouellette et al.,<sup>10</sup> 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.<sup>11</sup>

**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 al.<sup>12</sup> 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.<sup>13,14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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 colleagues<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup>

**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.<sup>20,21</sup> 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.<sup>22</sup>

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.<sup>23</sup>

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.<sup>24</sup>

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.<sup>25</sup>

—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.<sup>26</sup> 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 or 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.<sup>19</sup> 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13,14</sup> 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<sup>13,14</sup> 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.<sup>15</sup> 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.<sup>16</sup>

**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.<sup>17</sup>

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.<sup>18</sup>

These studies and others<sup>19</sup> 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 Cases.** — 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.<sup>40</sup> 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.<sup>41</sup>

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.<sup>42</sup> 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.<sup>43</sup>

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.<sup>44</sup> 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.<sup>45</sup>

**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 Thuy<sup>46</sup> 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 bias 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.<sup>47</sup> 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 or 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.<sup>48</sup> 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.<sup>49</sup> 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.

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