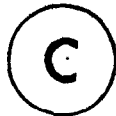


A STUDY OF THE HEALTH RISKS OF WORK IN MEDICAL  
LABORATORIES

A PROTOCOL FOR A RETROSPECTIVE COHORT ANALYTIC  
STUDY TO DETERMINE THE RELATIVE RISK OF ABNORMAL  
REPRODUCTIVE OUTCOMES FOR MEDICAL LABORATORY  
TECHNOLOGISTS COMPARED TO PHYSIOTHERAPISTS.

BY



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A Thesis

Submitted to the School of Graduate Studies  
in Partial Fulfillment of the Requirements

for the Degree

Master of Science

McMaster University

March 1981

MASTER OF SCIENCE (1981)  
(Medical Sciences)

McMASTER UNIVERSITY  
Hamilton, Ontario

TITLE           A Protocol For A Retrospective Cohort Analytic Study  
                  To Determine The Relative Risk Of Abnormal Reproduc-  
                  tive Outcomes For Medical Laboratory Technologists  
                  Compared To Physiotherapists

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NUMBER OF PAGES 141

## ABSTRACT

A retrospective cohort analytic study will be conducted to compare the incidence of abnormal reproductive outcomes of members of the Canadian Society of Laboratory Technologists with that of members of the Canadian Physiotherapy Association in order to identify exposures which may pose a threat to the reproductive process.

Members of each of the organizations will be mailed a questionnaire requesting demographic and health information. A second questionnaire requesting detailed information about reproductive outcomes will be sent to those subjects who have experienced pregnancies in the previous five years. Additional mailings by conventional mail and special delivery will be used to increase the response rate. Subjects who have given birth to stillborn children or children with congenital abnormalities and a random sample of those who have had miscarriages will be asked to provide written consent for their physician to be contacted to provide confirmatory information from their medical record.

The analyses will compare rates of abnormal reproductive outcomes in total and by specific type between laboratory technologists and physiotherapists controlling for age, parity, smoking status, infection, X-ray, drug and alcohol exposure during pregnancy.

## ACKNOWLEDGMENTS

The author wishes to acknowledge his appreciation for the guidance and restraint provided by his thesis supervisor, Larry W. Chambers, during this elucubration.

I also wish to express my gratitude to all the faculty, staff and students of the Department of Clinical Epidemiology and Biostatistics for the education I have received in their midst during the last eighteen months.

The cooperation of the Canadian Society of Laboratory Technologists is gratefully acknowledged. I would in particular like to express my thanks for the encouragement and advice provided by Mr. Archie Shearer and Ms. Val Booth, the previous and current executive directors of the Canadian Society of Laboratory Technologists.

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## CHAPTER I

### INTRODUCTION

This study will attempt to determine whether medical laboratory technologists in Canada compared to physiotherapists are at increased risk of having abnormal reproductive outcomes including children with congenital abnormalities. Two analytic surveys of laboratory workers in Sweden (Meirik et.al. 1978, Jansa et.al. 1978) have suggested that they have an increased risk of having children with congenital abnormalities. In addition, case reports (Holmberg 1978, Kucera 1968), animal studies (Kucera 1968, Watanabe and Yoshida 1970) and one case control study (Holmberg 1979) have implicated organic solvents commonly used in laboratories as teratogens.

Exposure to different potentially hazardous agents varies both by the type of laboratory and also the nature of work performed.

It has to be ascertained whether abnormal reproductive outcomes are associated more with one specific type of laboratory or task or whether the risk posed is common to all medical laboratory work.

Different organ systems undergo development at different times during embryogenesis. While some teratogens may cause a variety of abnormalities depending on when they are presented to the embryo, others may only have a single effect for a very limited period.

In determining specific research questions the following possibilities have been considered:

- (1) That work in a medical laboratory may be associated with abnormal reproductive outcomes;
- (2) That work in laboratories which contain a higher potential for exposure to suspected teratogens may be more hazardous to the reproductive process;
- (3) That abnormal reproductive outcomes may be related to the total length of time that either the parent or the fetus has been exposed to a laboratory environment;
- (4) That a combination of length of exposure and different types of exposure may interact to produce a particular abnormal reproductive outcome.

## CHAPTER II

### LITERATURE REVIEW

This review is divided into five sections. Sections A, B, C and D review respectively the literature associating various abnormal reproductive outcomes with laboratory work, organic solvent exposure, microbiologic agents and lifestyle and health care related factors. Criticism of the methodology of the studies reviewed is offered for each of the four topics. At the conclusion of each section a table summarizes the evidence reviewed, the methodologic criticisms and an application of the nine diagnostic lists for causation (Hill 1967). These nine tests are defined and described in section E which also contains conclusions concerning the strength of the evidence supporting causal relationships for each factor discussed in the earlier sections.

#### A. Laboratory Work and Abnormal Reproductive Outcomes

##### 1) Epidemiologic Studies

Meirik et.al. (1979) conducted an analytic survey of 310 children born to female laboratory workers at the University of Uppsala. These investigators found that 14 children were born with serious congenital abnormalities when 5 were expected based on Swedish national statistics (Relative Risk 2.8  $p < .01$ ). Four children were born with either anal or oesophageal atresia when the overall incidence of these two defects in Sweden is believed to be less than 1 per 1000 births.

In the same study similar analyses of the occurrence of minor abnormalities were not conducted, however, 7 of the 310 children had

talipes calcaneovalgus.

Meirik and his colleagues (1979) attempted to retrospectively classify their subjects into groups according to work status during pregnancy, but found that only 65 members of the cohort had not worked during pregnancy. No analysis of the differences in pregnancy outcome between those who had and had not worked during pregnancy was conducted and Swedish national statistics were used as the reference or control population. Although adjustment was made in the analysis for differences in both age and parity between the study cohort and the national averages no account was taken of possible confounding variables such as social and economic status differences despite the fact that the study cohort was employed in a skilled occupation. In the analysis, the apparently high incidence of talipes calcaneovalgus among the children of the subjects who had worked in laboratories was not taken into account and no explanation was offered for this deficiency.

Case reports of birth abnormalities (4 perinatal deaths and 2 liveborn children with intestinal atresia in 35 deliveries) (Jansa et. al. 1978) among women employed at a quality control laboratory in a pharmaceutical plant prompted a cohort study of 3 large pharmaceutical companies throughout Sweden (Hansson et.al. 1980). In this study the incidences of abnormal reproductive outcomes in women who worked in chemical laboratories was compared to that of women working in non-chemical laboratories.

The miscarriage rate in the chemical laboratory employed group was found to be 1.8 times the rate of the non-chemical laboratory group

(18% vs 10%). The relative risk observed for the chemical exposed group of bearing a malformed child was 8.65 (chi square = 7.89 p = .005, my calculation). Six point eight per cent (6.8%) (7 of 103) of infants born to the group exposed to chemicals died in the neonatal period and 5.8% (6 of 103) had one or more major malformations.

The above study (Hansson et.al. 1980) compares workers in laboratories exposed to chemicals to laboratory workers not so exposed. How this classification is made is unclear and given the nature of laboratory work it would be surprising if the non-chemical exposed group was not in fact subject to some chemical exposure. Inexplicably the authors compare numbers of abnormal births (stillbirths and congenital abnormalities) in total and not each outcome separately. Miscarriage data was derived from self administered questionnaires or personal interviews, but was not validated with medical records. Diagnoses of congenital abnormalities and causes of neonatal death also obtained by questionnaire were validated by comparing questionnaire responses with data from the Swedish Medical Birth Register.

The manner in which questionnaires were applied varied considerably in that some data was obtained during interviews by company medical officers and some by mailed questionnaires. No comparison is made between the two methods of their effect on the response to questions. Although there are some serious methodologic concerns with this study, the very strong association between chemical laboratory work and abnormal reproductive outcomes cannot be ignored.

Table I summarizes the literature relating abnormal reproduc-



tive outcomes to laboratory work, methodologic criticisms of the studies and applies Hill's nine diagnostic tests for causation to the evidence presented.

Table I: Summary and Interpretation of Literature Associating Laboratory Work With Abnormal Reproductive Outcomes

AUTHORS	MEIRIK et.al (1979)	HANSSON et.al. (1980)	JANSA et.al.(1978)
STUDY DESIGN	Retrospective cohort analytic	Retrospective cohort analytic	Case reports
CASES	310 children of female clinical chemistry workers	Female chemical lab. workers	Female chemical lab. workers
CONTROLS	National statistics	Female non-chemical lab. workers	None
FINDINGS	R/R 2.8*for serious congenital abnormalities	R/R 8.65 for serious congenital abnormalities, 17 for stillbirth, 1.8 for miscarriage	2 congenital abnormalities and 4 stillbirths in 35 deliveries
BIASES PRESENT	Non-contemporaneous controls	Sampling, data collection	Reporting

B. Application of "Nine Diagnostic Tests"

EXPERIMENTS	None
STRENGTH*	R/R 2.8, 8.65 for congenital abnormality
CONSISTENCY	Both controlled studies agree
SPECIFICITY	No other health effects of lab work other than abnormal reproductive outcomes have been studied
TEMPORALITY	Events occurred after exposure but relationship to exposure during pregnancy unclear
GRADIENT	No evidence
BIOLOGIC SENSE	No evidence
EPIDEMIOLOGIC SENSE	No evidence
ANALOGY	Related occupations such as nursing also at elevated risk (Klingberg and Papier 1979)

\*Ratio of events among those exposed to those not exposed

## B. Organic Solvents and Abnormal Reproductive Outcomes

### (i) Case-Control Epidemiologic Study

Holmberg (1978) used a matched pairs case-control study to test the hypothesis that exposure to organic solvents during the first trimester of pregnancy is associated with the birth of children with severe central nervous system defects. The 118 cases in this study include every child reported to have been born with a severe central nervous system defect in Finland in the two years from June 1st, 1976 to May 31st, 1978. Information on exposure to solvents was obtained during personal interviews. The first children born in the same health district prior to the birth of the defective child, of women in the same age groups were selected as controls. Table I summarizes the results of Holmberg's study. The relative risk of having children with severe central nervous system defects was 6.5 for mothers exposed to organic solvents and this result was statistically significant (chi square with 1 d.f. = 6.67,  $p = .01$ ).

The manner in which solvent exposure was determined and classified in Holmberg's study may have led to some bias. Exposure was determined during a personal interview with subjects and controls. The interviewer was personally aware of the purpose of the study and whether subjects were cases or controls prior to conducting the interview. The possibility exists therefore that the personal feelings of the interviewer no matter how unconsciously may have caused him or her to be more assiduous in the application of the questions to cases or controls. The time during the first trimester of pregnancy at which exposure occurred was not determined and exposure itself was classified as exposure to

Table II: Comparison of solvent exposure among the mothers of children with severe central nervous system defects and matched control mothers of normal children

		CONTROLS	
		SOLVENT EXPOSED	NOT SOLVENT EXPOSED
CASES	SOLVENT EXPOSED	1	13
	NOT SOLVENT EXPOSED	2	102

$$R/R = 13/2 = 6.5$$

(Data from Holmberg, 1978)

any organic solvent in any amount rather than using more specific criteria.

(ii) Case Reports

Xylene used in large amounts in histopathology laboratories has been linked with other organic solvents to the appearance of caudal agenesis in humans. Among nine cases of this rare abnormality occurring in Czechoslovakia between 1959 and 1966, six of the mothers had worked during pregnancy in high concentrations of common organic solvents, principally xylene and acetone (Kucera 1968). In a study of women employed in the reinforced plastics industry and exposed principally to styrene and acetone (Holmberg 1977), it has been observed that 2 of 12 children born to exposed mothers were anencephalic compared to an expected 0.0067 cases based on Finnish national statistics.

While case reports may be an important first step in the identification of phenomena requiring further study, their use as scientific evidence in the establishment of causal relationships is inappropriate. The principal methodologic deficiencies in case reports or case series are 1) their lack of control populations and 2) the subjective manner in which exposure is related to the outcome observed. In cases however in which events are extremely rare a case series or report may be the necessary stimulus for further more rigorous study.

(iii) Animal Studies

Organic solvent exposure during pregnancy and subsequent birth defects have been reported in the following studies in which animals were randomly assigned to "treatment" groups.

Xylene has been found to be potently teratogenic in chicks (Kucera 1968) causing rumplessness in 50% of those surviving exposure via the chorioallantoic membrane.

Toluene of high purity has also been linked experimentally to skeletal and other abnormalities in chick embryos (Elovaara et.al. 1979).

Rats exposed in utero to chloroform have been demonstrated to have a significantly higher incidence of anal atresia than rats not so exposed (Schwetz et.al. 1974).

Animal studies of alleged causal relationships while useful in confirming their biologic plausibility, cannot be used as evidence that the same effect will be expressed in humans. This is particularly true in the investigation of congenital abnormalities since teratogenic effects observed in one animal species may not be demonstrated in another. Thalidomide is an example of this phenomenon as the drug was originally tested in rabbits (Klingberg and Papier 1979). In this species no teratogenic effect was observed, but in humans the reverse was true. Conversely acetyl salicylic acid is teratogenic in rabbits, but has not been demonstrated to be so in humans.

Table III summarizes the literature relating abnormal reproductive outcomes to organic solvent exposure, summarizes methodologic criticisms of the studies and applies Hills nine diagnostic tests for causation to the evidence presented.

Table III: Summary and Interpretation of Literature Associating Organic Solvent Exposure with Abnormal Reproductive Outcomes

Authors	Holmberg (1978)	Kucera (1968)	Holmberg (1977)
Study Design	Matched pairs case-control	Case reports	Case reports
Cases	All children with severe central nervous system defects born in Finland 1976-78	9 children with caudal agenesis	12 children born to women at plastics factory
Controls	Next child born in same district	None	None
Findings	R/R 6.5 for solvent exposure	6/9 mothers exposed to xylene or acetone	2 anencephalic
Biases Present	Case/control status known prior to determination of exposure	Data collection	Case ascertainment

B. Application of "Nine Diagnostic Tests"

EXPERIMENTS	None
STRENGTH	R/R 6.5
CONSISTENCY	Only one study
SPECIFICITY	Related to many other health effects, subjects studied exposed to mixtures not specific solvents
TEMPORALITY	No evidence
GRADIENT	No evidence
BIOLOGIC SENSE	Supported by animal studies
EPIDEMIOLOGIC SENSE	No evidence
ANALOGY	Other chemicals and drugs also related to abnormal reproductive outcomes e.g. thalidomide

### C. Microbiologic Agents

Medical laboratory workers are unique in their occupational exposure to human pathogens. While laboratory acquired infections are a hazard which can to some extent be controlled, the potential for fetal infection or an embryopathic effect of biologic agents is one which would appear to exist.

#### 1) Epidemiologic Studies

Several epidemiologic investigations (reviewed by Dudgeon 1976) have concluded that maternal rubella virus infection during the first trimester of pregnancy is associated with the birth of children with cardiac abnormalities, deafness, cataracts and other optic abnormalities. The principle methodologic challenge in the investigation of this effect of rubella virus has been the determination of exposure. Since infection frequently passes unnoticed in the mother, reliance has had to be placed on studies which have associated epidemics of rubella infection with subsequent increases in the incidence of congenital abnormalities.

In an analytic survey of 6,147 children born after an influenza epidemic in Helsinki (Hakosalo 1973) it was concluded that while there were slightly more central nervous system defects among children exposed in utero to infection than among those not exposed that the difference was not statistically significant. Hakosalo suggested that the observed increase may have been due to factors other than the influenza virus such as the increased use of patent medicines to relieve symptoms. Other studies of the relationship of influenza virus to congenital abnormalities reviewed by Hakosalo are equivocal in their conclusions.



ii) Case Reports and Animal Studies

Several commonly encountered viruses have been associated with human congenital abnormalities in case reports. It has been suggested that Cytomegalovirus (Watanabe and Yoshida 1970) is related to the genesis of microcephaly and microphthalmia. While up to 1% of babies may show evidence of infection with this virus at birth (Hanshaw et.al. 1973), only 10% of these have been estimated to have congenital abnormalities.

Two case reports (South et.al. 1969) have associated the recovery of herpes simplex virus (type 2) from skin lesions of a newborn infant to the simultaneous presence of microcephaly and microphthalmia.

Herpes simplex virus (type 2) has also been suggested to be related to congenital abnormalities observed in animals (Heath et.al. 1956).

Other viruses, in particular varicella/Zoster have also been associated anecdotally with the occurrence of congenital abnormalities in humans (Manson et.al. 1960).

The reservations expressed about case reports and animal studies as scientific evidence in the diagnosis of causation in the section on organic solvents apply equally to the above section.

Table IV summarizes the literature relating abnormal reproductive outcomes to infection with microbiologic agents, summarizes methodologic criticisms of the studies and applies Hills nine diagnostic tests for causation to the evidence presented.

**Table IV: Summary and Interpretation of Literature Associating Exposure to Microbiologic Agents To Abnormal Reproductive Outcomes**

Authors	Dudgeon (1976)	Hakosalo (1973)	South et.al. (1969)	Watanabe (1970)
Study Design	Descriptive	Cohort analytic	Case report	Case report
Cases	Subjects with infection (rubella)	Subjects with infection (influenza)	1 subject with infection (H.S.V. 2)	1 subject with infection (cytomegalovirus)
Controls	(implicitly) uninfected subjects	Uninfected subjects	None	None
Findings	Exposure to rubella during 1st trimester associated with optic, cardiac defects	Low increased risk for influenza in infected subjects	Microcephaly Microphthalmia	Microcephaly Microphthalmia
Biases Present	Sampling	Cointervention		
EXPERIMENTS	B. Application of "Nine Diagnostic Tests"			
STRENGTH	None			
CONSISTENCY	Unknown for rubella, H.S.V., C.M.V., weak for influenza			
SPECIFICITY	Present for rubella only			
TEMPORALITY	Rubella syndrome associated with rubella infection in pregnancy			
GRADIENT	Abnormalities described have all followed infection			
	No evidence			

Table IV: Summary and Interpretation of Literature Associating Exposure to Microbiologic Agents To Abnormal Reproductive Outcomes (continued)

BIOLOGIC SENSE	Animal studies show same effects
EPIDEMIOLOGIC SENSE	Principle argument to support causal relationship of rubella to congenital abnormalities
ANALOGY	No evidence

#### D. Lifestyle and Health Care Related Factors

A number of lifestyle and health care related factors have been related to the genesis of abnormal reproductive outcomes. While these are not peculiar to either laboratory workers or physiotherapists, their effect must be taken into account in case of a synergistic or antagonistic effect on the above mentioned putative causal factors.

Table V lists the lifestyle and health care related factors which will be considered in this study. The evidence that any of these is directly related to the genesis of abnormal reproductive outcomes at the levels likely to be encountered by subjects in the study is weak and the methodologic deficiencies in the studies themselves so profound that a full summary will not be presented.

##### i) Cigarette Smoking

Studies which have attempted to relate cigarette smoking to abnormal reproductive outcomes are equivocal in their findings. Kelsey et.al. (1978) found a relative risk of 1.1 for congenital abnormalities among the children of smokers compared to those of non-smokers using a case-control design. The participation rates were however 71% for cases and 90% for controls which suggests differences between cases and controls in addition to smoking status. In the same study the relative risk found for congenital abnormality as a pregnancy outcome among "heavy" (greater than 20/day) smokers was 1.6. Himmelberger et.al. (1978) found relative risks of up to 2.3 for congenital abnormalities and 1.7 for miscarriages as pregnancy outcomes among smokers compared to non-smokers. This study was however conducted "post facto" on data gathered for another study (oc-

cupational disease among operating room personnel, Cohen et.al. 1974) in which the response rate to mailed questionnaires was only 53.2%.

In contrast to the two previously mentioned studies of cigarette smoking and pregnancy outcome, a study of all deliveries occurring in Cardiff, Wales in a ten year period (Evans et.al. 1979) found no increased risk for congenital abnormalities among the children of smokers relative to those of non-smokers. In this study, of 69,062 deliveries occurring, smoking history information was obtained from mothers in 67,609 (97.9%).

ii) Alcohol

The use of alcohol during pregnancy has been suggested to be related to a variety of congenital abnormalities. Fetal alcohol syndrome (Mulvihill and Yeager 1976) is a recognized pattern of low birth weight, microcephaly, heart murmurs and facial and joint abnormalities. It is considered unlikely however that many of the subjects participating in this study will be the chronic alcoholics to whom children with the syndrome are born. Drinkers classified as heavy compared to medium or light have been found to have a relative risk of 2.0 for congenital abnormality as a pregnancy outcome compared to non-drinkers (Oullette et.al. 1977). No elevated risk was found for moderate and light drinkers. The study was conducted among referred cases to a tertiary gynecology clinic who were predominantly black which raises serious concerns regarding its generalizability.

iii) Drugs

A number of prescription drugs have been associated with the

genesis of congenital abnormalities (Berry 1976). In particular, androgenic hormones, Folate antagonists and anti-convulsants are considered to place the fetus at risk (Klingberg 1979) and the possibility that they might have been prescribed for subjects in the proposed study must be considered.

iv) X-rays and Other Ionising Radiation

Exposure of the fetus to ionising radiation has been associated with the genesis of congenital abnormalities as have radiation induced mutagenic events which take place prior to pregnancy.

While the evidence collected in human studies which associates ionising radiation to abnormal reproductive outcomes is not strong, both laboratory technologists and physiotherapists may potentially be exposed to X-rays during their work and laboratory technologists may be exposed to radioisotopes used in laboratory tests.

iv a) Epidemiologic Studies

An analytic survey of radiologists was conducted using mailed questionnaires to obtain exposure and outcome information (Mach and Lawrence 1955). The response rate was low (45%) and the reference population consisted of other medical specialists. No statistically significant increase was detected in congenital abnormalities among the children of the radiologists. Originally female radiologists were included in the study but were excluded from the analysis because their numbers were low. An epidemiologic study of female medical radiation workers has never been conducted.

iv b) Case Reports

No case reports have been published suggesting an association

of occupational exposure to radiation to the occurrence of birth or reproductive abnormalities. Case reports have suggested that microcephaly and ocular defects may result from exposure of the fetus to high therapeutic and accidental doses of ionising radiation (Goldstein and Murphy 1929, Dekabon 1968, Report of the Advisory Committee on the Biological Effects of Ionizing Radiation 1972).

iv c) Animal Studies

It has been observed that doses of X-rays as low as 25 rads induce skeletal abnormalities in mice (Hicks and D'Amato 1966) and that chronic exposure of mouse embryos to low doses (1 rad or less) of X-rays may lead to impairment of gonadal and skeletal development (Russel 1957).

The evidence relating the preceding lifestyle and health care related factors to abnormal reproductive outcomes is summarised in table V.

Other factors which have been associated with an elevated risk of abnormal reproductive outcomes such as socio-economic status, season of conception and quality of pre-natal care (McKeown 1976) have only been studied descriptively and will not be considered in the proposal investigation.

Table V: Lifestyle and Health Care Related Factors to be Considered in This Study

Factor	Effect	Evidence of Association to Abnormal Reproductive Outcomes
1) Cigarette-smoking	Congenital abnormalities, miscarriage	Contradictory Low relative risks
2) Alcohol	Congenital abnormalities	Studies not generalizable No increased risk except for chronic heavy use
3) Drugs	Congenital abnormalities	Case reports only, most drugs not studied
4) Radiation	Congenital Abnormalities	No studies or case reports of low dose effects in humans. Association found with acute high doses, but studies methodologically flawed



#### E. Conclusion

Sir Austin Bradford Hill (1967) suggested the uses of nine "diagnostic tests" to apply to the evidence relating putative causal factors to human disease. The strength of the evidence supporting the causal relationship could thus be estimated. The nine tests are as follows:

- 1) The results of randomized clinical trials or experiments in humans;
- 2) The strength of the relationship, that is the degree of risk associated with exposure;
- 3) The consistency of the association: that the same observation has been demonstrated by different investigators in different circumstances;
- 4) The specificity of the association: that the association observed is peculiar to the type of putative causal factor and outcome being studied;
- 5) Temporality: that the effect follows exposure to the suspected causal factor;
- 6) Gradient: that the frequency or severity of the outcome increases with either the length or amount of exposure;
- 7) Biologic sense: that the same effect is observed in animal studies and is consistent with the present understanding of human biology;
- 8) Epidemiologic sense: that the frequency of a particular outcome has increased or decreased with the general prevalence of the putative causal factor;
- 9) Analogy: that a similar effect is associated with a similar cause.

An application of the "nine diagnostic tests" proposed by Hill to the evidence for a causal relationship between laboratory work and abnormal reproductive outcomes is presented in part B of table I. No randomized trials have been or could ethically be conducted. The strength of the association found of laboratory work to abnormal reproductive outcomes is high for stillbirth (R/R 17) moderate for congenital abnormality (2.8, 8.65) and low for miscarriage (1.8). Major methodologic concerns however as described previously such as the specificity of exposure and outcome measurements and sampling procedures preclude a high level of confidence in these figures.

With the exception of analogy and temporality, none of the other diagnoses for causation are indicated by the evidence on laboratory work.

Consistency:

Only two epidemiologic studies have been conducted and published, while their results are consistent, more confirming studies are required.

Specificity:

Abnormal reproductive outcomes are not the only health effect related to laboratory work. A variety of others have been described (Yager 1973). No specific congenital abnormality has been associated with laboratory work, but increases in the incidence of a variety of such events have been reported.

Temporality:

The case-control and retrospective cohort analytic designs of existing studies provide evidence that exposure to a laboratory environmental preceded an abnormal reproductive outcome. It is however not pos-

sible to discern from previous studies whether exposure during or prior to pregnancy carries a similar excess risk.

Gradient:

No gradient of effect has been demonstrated for either length of time of exposure to a laboratory environment or the quality of that environment.

Biologic Scene:

No animals have been exposed to a laboratory environment to determine its effect on their reproductive outcomes. Components of a laboratory environment such as organic solvents and microbiologic agents have been associated with abnormal reproductive outcomes in controlled animal studies.

Epidemiologic Sense:

No studies have been conducted which have examined the incidence of abnormal reproductive outcomes in areas with a high concentration of laboratory workers.

Analogy:

Other health professions such as nursing have been found to be at increased risk of abnormal reproductive outcomes (Cohen et.al. 1974).

In the case of solvents, only one epidemiologic investigation (Holmberg 1979) has been conducted which found a strong (R/R 6.5) relationship between organic solvent exposure and congenital abnormalities.

This observation is supported by animal studies, but methodologic flaws in data collection as reviewed previously undermine confidence in the results of the study.

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With the exception of high "strength", biologic sense and some analogous chemical associated abnormal reproductive outcomes, the evidence relating organic solvent exposure to these outcomes passes no other "tests".

The evidence relating microbiologic agents to abnormal reproductive outcomes is weak.

No epidemiologic studies have determined the strength of the association between any of the microbiologic agents and abnormal reproductive outcomes with the exception of influenza virus for which no increased risk was found. Studies that have been conducted have consistently associated rubella infection with the genesis of congenital abnormalities. These have been "before/after" studies.


Infection with rubella in pregnancy is specifically related to defects of the eye, ear and heart (the rubella syndrome).

In all the infectious agents considered, the abnormalities described have all followed infection.

In the case of rubella, animal studies have found the same effects as for humans confirming the biologic plausibility of the relationship.

Epidemiologic sense has only been demonstrated in the case of rubella in that the rate of infection with rubella is mirrored by a subsequent increase in the incidence rate of congenital abnormalities.

The evidence for the association of all of the lifestyle and health care related factors to be considered in this study to the genesis of abnormal reproductive outcomes fails to meet any of the criteria for the demonstration of a causal relationship.



The proposed study to be described in the following sections attempts to overcome the major methodologic challenges posed by an investigation of this type. It will estimate the degree of risk posed by laboratory work to the reproductive process and generate specific hypotheses which may be tested in subsequent investigations.

## CHAPTER III

### DESIGN OF STUDY

#### Introduction

Three study designs were considered to address the research questions posed, a prospective cohort analytic study, a case-control study and a retrospective cohort analytic study. The sequence of exposures, events and data collection for each of these designs is shown in table VI.

Two other designs, the randomized controlled trial and the descriptive study were not considered, the first because deliberate exposure of human subjects to potential hazards is unethical and the second because a descriptive study does not provide an estimate of relative risk in the absence of control populations with which to make comparisons.

The advantages and disadvantages of the different study designs and in particular the possibilities of bias in each one are summarized in table VII.

#### A) Prospective Cohort Analytic Study

As may be seen in table VI, the prospective cohort analytic study's major advantage is that exposure information is collected before health events occur. For example, all chemical and biologic agent exposures for each subject could be monitored and documented throughout the study period by data collection systems within laboratories as well as by subjects' reporting.

Table VI: Sequence of Events and Data Collection in Study Designs Considered for this Investigation

<u>Study Design</u>	<u>Time When Data Collected</u>		
	<u>Past</u>	<u>Present</u>	<u>Future</u>
Prospective Cohort Analytic		Select Cohorts Classify Exposure Category Manoeuvre or Exposure initiated	Determine Pregnancy Outcomes Quantify Exposures Draw Conclusions
Retrospective Cohort Analytic	Both Exposures and Events Occur	Identify Exposure Category and Determine Pregnancy Outcomes	Draw Conclusions
Case-Control	Both Exposures and Events Occur	Determine Exposure Category of Subjects With and Without Abnormal Reproductive Outcomes	Draw Conclusions

Birth and pregnancy outcomes could also be determined by establishing reporting procedures in which data on congenital abnormalities and stillbirths would be collected in a central location. Since the composition of the cohorts could be determined and selected prior to the study period their comparability for important risk factors could also be continuously monitored.

A major potential source of bias resulting from the use of a prospective cohort analytic design would be the over reporting of abnormal reproductive outcomes as subjects become aware of the purpose of the study. Over reporting of suspected hazardous exposures could also occur unless these were objectively monitored. Over reporting of stillbirth is unlikely, but in cases of minor congenital abnormalities and particularly miscarriage it is possible that subjects would report an event when it would not ordinarily be considered to be one. This might occur for example in the reporting of a minor limb distortion as a congenital abnormality when this ordinarily would not have been detected and if detected, not reported. Likewise subjects may imagine themselves to be exposed to a particular chemical when they sense exposure to another with similar properties.

Disadvantages which ruled out the use of the prospective cohort analytic design were a) at least five years would be required to obtain data throughout Canada on the 350 stillbirths and congenital abnormalities necessary for a clinically meaningful result expected to occur in this period among the 25,000 medical technologists and physiotherapists; b) the cost of such a study would be prohibitive given the necessity of maintaining exposure histories on an extremely large number of subjects most of whom would not have been pregnant let alone had abnormal reproductive outcomes;



B) Case Control Study

A case control study of the work histories of parents of stillborn children or children with congenital abnormalities compared to those with normal children could, if these events were rare and the occupations common, be the design of choice.

Parents of such children and suitable controls identified from vital statistics could be interviewed to determine their occupational history and the proportion of laboratory technologists in each group compared. While the amount of time taken to conduct such a study should be small this may well be increased by difficulty in finding the parents of some of the children. Because of the relatively small numbers of interviews normally necessary in a case-control study the cost would be low.

As summarized in table VII, sources of bias to which a case-control study of this nature would be subject are profound. Reporting of cases to central registries is incomplete and may be biased in that the reporting of the abnormal reproductive outcomes of health care workers may be more complete than others. Variation in the degree of hospital and physician compliance in reporting congenital abnormalities and stillbirths to registries (Querec 1980) also raises concerns about the representativeness of data in the federal registry which could be used as the source of cases. Perhaps the most important reason for not using a ~~case-control~~ design is the relative rarity of laboratory technology as an occupation in Canada. Approximately 1 in 500 women in Canada work as laboratory technologists. Thus, if a registry drawing data on congenital abnormalities and stillbirth from the general population was used it would be necessary even with an expected doubling of the risk

of stillbirth or congenital abnormality in laboratory technologists to locate and interview 250 sets of parents to find one laboratory technologist mother. Similarly, 500 control parents of normal children would have to be interviewed (to find one laboratory technologist mother). Under these circumstances the case-control design is less efficient than a cohort design to investigate the association of work as a laboratory technologist with either the occurrence of stillbirth or congenital abnormality.

C) Retrospective Cohort Analytic Study

Because of the inherent problems described for the prospective cohort analytic and case-control designs when examining possible hazards which may attend the reproductive process in laboratory technologists it is proposed to use a retrospective cohort analytic design.

The first section following this introduction considers the strengths and weaknesses of the retrospective cohort analytic design in general while the second describes briefly the design of this study in particular.

i a) The Retrospective Cohort Analytic Study Design

In this type of study cohorts are selected on the basis of exposure in the past and events of interest determined for a period of time up to the present.

i b) Strengths

The length of time needed to complete a retrospective cohort analytic study can be short since all the information needed to com-

plete the study is based on events which have already occurred. In situations where both exposure information and records of events are available and complete the retrospective cohort analytic design is an attractive compromise.

For studies where mortality from all causes and certain diseases such as carcinoma are the outcomes of interest national vital statistics or disease registries can be used as reference groups to estimate relative risks for the cohort being studied.

i c) Limitations

It is obligatory in any epidemiologic study that once having selected a group of subjects to study they all be followed up to determine whether or not they have experienced outcomes of interest. In many retrospective cohort analytic studies the formation of the cohort occurs many years in the past. Losses frequently occur as subjects change occupations and addresses. The greater the time expired since identification of the cohort the greater the probability of losses.

The determination of exposures is frequently difficult in retrospective cohort studies. If exposure information has been recorded by employers, unions or regulatory bodies at the time of exposure the study can be greatly facilitated. If exposures have not been recorded and residues present in subjects cannot be measured, exposure levels have to be estimated and as such are subject to bias.

National statistics on registries are frequently used in retrospective cohort analytic studies as a reference population for the estimate of relative risks. This is necessary because appropriate control populations similar in nature to the exposed cohort cannot be identified.

Ideally the control cohort should be very similar in demographic characteristics to the exposed cohort and with the exception of the putative causal factor under investigation should have similar distributions of other confounding variables. In the event that exposure to confounding variables is different in the two cohorts some post hoc adjustment must be performed at the time of analysis.

ii a) The Retrospective Cohort Analytic Design and ~~Its~~ Study

The design of the proposed study will be discussed in the four stages of its execution: The selection of the cohorts, the determination of exposures, the ascertainment of events and the analysis of results. Each of these stages is discussed in detail in other sections of this proposal, but a brief discussion of each component will be provided here.

ii b) Selection of Cohorts

In selecting a cohort exposed to a laboratory environment the following were taken into consideration: The cohort must broadly represent the varying exposures in different types of laboratory. It should be distributed geographically in the same manner as the national population to facilitate comparisons with registries. Basic information such as names and addresses must be available to permit initial contact to be made and to enable data held in official registries to be accessible.

The membership of the Canadian Society of Laboratory Technologists fulfills all three of these specifications and in addition the society itself supports the proposed study.

If this study was to adopt the conventional approach to a retrospective cohort study in occupational health, the rates of stillbirth and

Table VII: Advantages and Disadvantages of Different Study Designs

	Randomized Controlled Trial	Prospective Cohort Analytic	Retrospective Cohort Analytic	Case-Control	Descriptive
Comparability of groups	Ensured by randomization	May be continuously monitored	Moderate problem contemporary controls must be selected	Large problem as bias in selection of cases/controls	Large problem Selection of cases may be biased
Determination of exposure	May be continuously monitored	As R.C.T.	Complete for occupational category but problems of awareness/recall for specific exposures	Recall/awareness problems	Recall/awareness problems
Determination of abnormal reproductive outcomes	No bias, complete for both groups but may detect more than in contemporary practice	As R.C.T.	Can be validated by attending physician and central registry possible under detection for both groups and over reporting of events	Under detection/over reporting leading to bias	Detection bias
Cost	High in resources efficient use of subjects	As R.C.T.	High in subjects moderate in resources	Low in subjects and resources	Low
Analysis	Direct R/R calculation	As R.C.T.	As R.C.T.	Indirect risk (odds ratio) calculation	None except descriptive statistics

Table VII: Advantages and Disadvantages of Different Study Designs (continued)

Ethics	Unethical	Unethical if subjects aware of study	Ethical	Ethical	Ethical
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birth of congenitally abnormal children among the laboratory technologists would be compared to existing national vital statistics concerning those events matching the characteristics of registry subjects to the characteristics of the study cohort. While vital statistics are available in Canada on stillbirths and congenital abnormalities the data is seriously deficient in both quality and the number of provinces reporting events. The possibility of comparing members of the C.S.L.T. exposed to a laboratory environment during pregnancy with those who did not work during pregnancy was considered for the primary estimate of a relative risk, but rejected. Such a control group would be unsuitable for two reasons: 1) This group may be at increased risk of abnormal reproductive outcomes because of their exposure to a laboratory environment prior to pregnancy; 2) This group and the group exposed during pregnancy may not be able to recall exact dates of either the beginning of a pregnancy or leaving a laboratory environment. Because the use of registry data and unexposed subjects within the study cohort would be unsuitable in this investigation a separate reference cohort consisting of members of the Canadian Physiotherapy Association has been selected.

The membership of the Canadian Physiotherapy Association is comparable in many ways to that of the Canadian Society of Laboratory Technologists. Differences between the two cohorts in factors which may be related to abnormal reproductive outcomes will be adjusted for in the statistical analyses.

Addresses are available for all persons currently registered as medical laboratory technologists or physiotherapists. In addition, addresses are retained for subjects whose memberships have lapsed enabling us to include all who are now or have been members of either the Can-

adian Society of Laboratory Technologists or Canadian Physiotherapy Association with the exception of those who have moved and left no forwarding address.

Members of the two organizations have similar demographic characteristics, but distinctly different occupational environments. The qualifications necessary for membership in each of the organizations is unique and the type and frequency of exposure to potential hazards differs considerably between the two professions. Basic demographic information maintained on computer by each organization is available for use in this study. Movement out of the two occupations is small (executive directors Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association) thus reducing problems of completeness of this data file in determining who were employed in these occupations in the past five years. Addresses are still available for those subjects whose membership has lapsed between 1975 and 1980 up until the year in which the membership lapse occurred. In both organizations 70% of those who were members in 1975 are currently registered members. A substantial proportion of the "missing" 30% may be due only to name changes occurring after marriage. Previous health surveys of one organization (Canadian Society of Laboratory Technologists) have obtained responses of up to 80% after one mailing.

Other characteristics of the two cohorts including consideration of the size of the samples necessary to conduct this investigation are discussed in Section VI, Study Population on page 54.

### iii) Determination of Exposure

The conduct of a retrospective cohort analytic study is frequent-



ly made possible because records of exposures to which the study cohort have been subjected are kept by employers, unions or regulatory bodies. In the case of laboratory technologists, no such records, either of the particular type of laboratory in which subjects have worked at a given time or particular chemical exposures, exist. The only source of this information is the subjects themselves. In this study, work history, certain exposure information and events will be determined using two separate questionnaires. One questionnaire will determine if subjects have experienced a pregnancy, the other will determine the outcome of pregnancies and exposure to potential hazards.

It must be emphasized that information concerning specific chemical and microbiological exposures experienced in the work place will not be requested. The justification for this decision and a detailed description of the questionnaires and the information to be requested follows in the section Description of Instruments on page 41.

iv a) Ascertainment of Events

The purpose of this study is to determine the risk of abnormal reproductive outcomes for workers in medical laboratories. Abnormal reproductive outcomes include spontaneous miscarriages, stillbirths and the birth of live children with congenital abnormalities.

iv b) Possible Sources of Information Concerning Pregnancy Outcomes

Stillbirths and congenital abnormalities detected at birth are reported on the "notice of live or stillbirth" forms required by law to be completed by the health professional attending the birth. These

forms are sent to provincial registrars. Five provinces routinely and one province sporadically send copies of these forms to the birth defect/stillbirth registry at the Department of National Health and Welfare in Ottawa. Ideally, access to the original forms for each subject in this study would greatly facilitate its execution. Unfortunately the Provincial registrars' records are not made available under any circumstances and the Federal registry while accessible has very incomplete records.

Another possible source of data on pregnancy outcome are the medical records of study subjects. Informed consent would have to be obtained from each subject to permit examination of medical records and it is neither feasible nor efficient to attempt to obtain this information on the 8,500 subjects in this study estimated to have had pregnancies when the great majority of these would have resulted in the birth of normal children.

For these reasons members of both study cohorts will be mailed a questionnaire to determine whether or not they have had a pregnancy during the study period. If they have they will be sent a second questionnaire requesting detailed information about pregnancy outcomes and possible influences on these. The questionnaires are described in detail in the section "Description of Instruments" on page 41.

Information contained in the Federal registry will be used to both detect reporting biases among respondents and non-respondents and also where possible to validate information provided by subjects concerning pregnancy outcomes. Informed consent to examine the appropriate

sections of the medical records of subjects who have experienced stillbirths or the birth of children with congenital abnormalities will also be sought.

Confirmation of the occurrence of spontaneous miscarriages will only be sought for a randomly chosen sample of 10% of subjects reporting this outcome.

Details of the strategies to be used to detect biases in reporting and the determination of events are described in the sections "Data Collection and Strengths and Limitations" on pages 65 and 87.

v) Analyses of Results

The analyses of the results of this study will compare the rates of different abnormal reproductive outcomes between laboratory technologists and physiotherapists. Subjects will be stratified by age, parity and exposure to potentially confounding exposures. Separate analyses will compare laboratory technologists who did and did not work during pregnancy and also the rates of different abnormal reproductive outcomes among workers in different types of laboratory. Details of the analyses to be performed are described in the section "Statistical Analysis" on page 73.

## CHAPTER IV

### DESCRIPTION OF INSTRUMENTS

#### A. Initial Questionnaire

Two questionnaires have been developed for this study. The initial questionnaire (see Appendices 1 and 2) will obtain demographic information and information on health effects which may be related to the two occupations of laboratory technology and physiotherapy. This information will be used for separate studies of the health hazards of the two occupations to be conducted by the Canadian Society of Laboratory Technologists and the Canadian Physiotherapy Association. Initial questionnaires for the two organizations will be similar except for questions related to work performed.

The principal use of the initial questionnaire in this study is to determine whether or not subjects have experienced pregnancies. By combining questions relating to pregnancy with a multitude of others it is expected that the overall purpose of this study will remain concealed so as to avoid any bias in the over or under reporting of abnormal pregnancy outcomes by subjects. An additional purpose of the initial questionnaire will be to determine the particular laboratory type or practice setting that subjects have worked in for each year of the study period. Answers to identical questions in the follow-up or pregnancy questionnaire will be compared to answers in the initial questionnaire for subjects who do and do not experience events of interest to assess the reliability of responses.

The initial questionnaire and accompanying letters from the

presidents of the participating organizations and researchers (see Appendix 3 and 4) will be sent by first class mail to each of the 20,000 members and ex-members of the Canadian Society of Laboratory Technologists and 6,000 members and ex-members of the Canadian Physiotherapy Association.

#### B. Pregnancy Questionnaire

The pregnancy questionnaire (see Appendix 5) has been designed to determine the outcome of all pregnancies experienced by study subjects, their working environment and potentially harmful exposures experienced during pregnancy.

Male members of the two organizations will be asked to answer questions regarding pregnancy experience in relation to their spouses because of the possibility that environmental or occupational exposure of the male to mutagens may manifest itself in abnormal reproductive outcomes in their spouse. For the same reason, female subjects will be asked to supply information about their husband's occupation at the time of conception. While it is likely that the numbers of male subjects in the two cohorts will be too small for the hypothesized relative risk to be detected, the inclusion of male subjects was a prerequisite for the cooperation of the participating organizations.

Subjects will be asked the years in which their pregnancies occurred and the years in which they terminated. Those subjects who report having children with congenital abnormalities will be asked to classify the abnormalities into one of:-

Down's syndrome, brain or spinal cord defect, heart or blood vessel defect, limb or musculoskeletal abnormality, cleft lip or palate, disorder of the gastrointestinal tract, multiple malformations or other.

Accuracy of a report of stillbirth or child born with a congenital abnormality and its specific nature will later be sought from medical records and the federal government registry of stillbirth/congenital abnormalities for all subjects providing informed consent (see Appendices 6 and 7).

Stillbirths and congenital abnormalities reported by subjects who later decline to provide informed consent to search medical records will be treated as a separate group of events in the analyses.

The pregnancy questionnaire will be mailed to all those subjects who have experienced pregnancies in the last five years. It will be accompanied by a letter explaining the reasons for this follow-up and thanking the subjects for their cooperation in returning the initial questionnaire (see Appendices 8 and 9).

### C. Exposures

#### 1) Occupations

Subjects will be asked what type of laboratory or practice setting they were working in during the five years of the study period and specifically at the time their pregnancies began.

In the case of laboratory technologists the occupation is divided into 14 sub specialties:- Clinical chemistry, Haematology, Microbiology, Immunohaematology, Histopathology, research, general lab (all disciplines), virology, teaching, immunology, cytology, electron

microscopy, cytogenetics and other. Physiotherapists will be divided into subjects working in general teaching hospitals, independent rehabilitation hospitals, private practice, non-teaching hospitals and home care. In addition to their own work experience, subjects will be asked the occupation of their spouse at the time the pregnancy began.

i b) Reliability of Information About Occupation

All subjects responding to the pregnancy questionnaire will have previously completed the initial questionnaire. Responses to the identical questions about occupation during each year of the study period will be compared. In addition, the pretest of the initial questionnaire will provide an estimate of the reliability of information provided about occupational history.

ii) Solvents and Specific Chemical Exposures

Subjects in this study will not be asked to recall specific chemicals and solvents encountered during the study period. Despite the possibility, supported by some epidemiologic and other evidence, that chemical exposure may be fundamental in relation to the excess risk for abnormal reproductive outcomes observed in laboratory technologists, such information has not been requested for the following reasons:-

- 1) In many instances subjects would be unaware that they had been exposed to a particular substance;
- 2) Accurate recollection of specific exposures is unlikely given the large number of chemicals in routine use in laboratories;
- 3) Subjective estimates of exposure (which cannot be verified) could vary from subject to subject depending on sensory ability; and

- 4) The results could be biased since subjects who have had an abnormal reproductive outcome may search their memory more diligently for culpable exposures than those who have not.

iii) Cigarette Smoking

Subjects will be asked if they smoked cigarettes, if so, the quantity smoked and also whether they smoked cigarettes during their pregnancies.

iii a) Reliability and Accuracy of Information Concerning Cigarette Smoking

A potential concern in attempting to determine maternal smoking habits is the accuracy of self reporting of cigarette use. This question has been examined in two different ways: 1) the quantity of cigarettes reported to have been consumed by subjects has been compared with production and sales quantities (Warren 1978). In 1975 self reported consumption was 2/3 of actual consumption. 2) The quantity of cigarettes reported to have been consumed by subjects has been compared to measurements of either exhaled carbon monoxide, levels of salivary or serum thiocyanate or both (Vogt et.al. 1977). While the operating characteristics of these biochemical tests were not satisfactorily examined, the smoking status reported by subjects in the study was determined to be accurate for all but 1 of 139 (45 non-smokers, 94 smokers). Unfortunately subjects were aware that their reported smoking would be subject to confirmatory tests in this study which tends to diminish the generalizability of the results.

Another study by Vogt (1977) administered a smoking questionnaire



twice to the same subjects one hour apart. Twenty-two per cent of subjects gave different answers when asked how many cigarettes they smoked in a day.

It has been concluded (Stewart et.al. 1979) that while self reported cigarette consumption is frequently inaccurate and unreliable, there is no evidence of systematic differences between groups of adults and that self-report is a suitable measure for the purposes of group comparisons.

iii c) Reliability of Smoking History

Studies which have examined the relationship of cigarette smoking to abnormal reproductive outcomes (8,20,24) have not used standardized questions to determine smoking status or consumption levels. During the pretest of the pregnancy questionnaire the response to the question will be compared to information in the patients medical record since smoking status is routinely obtained during pre-natal work-ups. This will enable an approximate measurement to be made of the probable reliability of self-reporting during the full survey.

iv) Alcohol Use

Because of the possibility that even moderate alcohol use during pregnancy may be related to abnormal reproductive outcomes, subjects will be asked to estimate their levels of consumption during pregnancy.

iv a) Reliability and Accuracy of Information Concerning Alcohol Use

As in the case of cigarette use, the accuracy and reliability of self-reporting of alcohol use is a potential concern.

iv a1) Reliability of Self Reporting

Two independent samples of problem drinkers interviewed two weeks apart about their level and duration of alcohol use achieved test/retest correlation coefficients of .98/.97 and .91/.90 (Rohon 1976).

In a study of 17 "normal" college students, Khavari and Farber (1978) found a test/retest correlation coefficient of .92 when these subjects were given the same questionnaire concerning alcohol use two weeks apart.

iv a2) Accuracy of Self Reporting

While self reports of alcohol use appear to be reliable, their accuracy has been suggested to be poor (Osborne 1980). A study of the patrons of bars whose drinking behaviour was observed surreptitiously over a period of 7 days (Harford et.al. 1976) found that of those consenting to be questioned only 54% could recall the amount they drank daily. When biochemical estimates of alcohol consumption (urinary ethanol) have been compared with self reported alcohol use in alcoholics only 50% of self reports were accurate. It has been concluded that the accuracy of self reports of alcohol use should be treated with great circumspection (Skinner, H., personal communication).

Patients in the McMaster University Health Sciences Centre Family Practice Unit are routinely asked about alcohol use in pre-natal work-ups. Self reported consumption obtained in the pretest will therefore be compared to amounts recorded in the medical record to assess the reliability of this information in the study.

iv b) Accuracy of Questions

Questions relating to alcohol use in previous studies of abnormal reproductive outcomes have not been standardized. The comparison of pretest answers with medical records will thus be used as a measure of the questions ability to elicit information concerning alcohol use.

v) Infection

Subjects will be asked if they had any infections during their pregnancies and if so the nature of the infection since certain infectious agents have been associated with abnormal reproductive outcomes (see Literature Review page 3). While the response to this question relies to some extent on the perceptions of the subject and nature of infection it is felt that over-reporting of infection is unlikely to occur in subjects who have had abnormal reproductive outcomes and in some cases may be validated by subjects medical records. Under reporting is also possible, but there is no reason to expect different rates of reporting between the two cohorts.

v a) Reliability of Information Concerning Infection

Studies which have examined the reliability and accuracy of subjects self reporting of chronic morbidity and hospital visits concur in their findings that such events are usually under reported and that the tendency to under-report increases with time since the event (Cannell 1977).

Studies which have examined self reporting of infectious episodes and particularly those occurring in pregnancy could not be found.

Episodes of infection for which patients sought medical care or which were reported to health care workers will have been recorded in subjects medical records. The ability of subjects to recall infections suffered during pregnancy will be estimated during the pretest of the pregnancy questionnaire when responses to questions will be compared to information recorded in subjects medical records.

vi) Drugs

A variety of prescription drugs have been associated with the genesis of congenital abnormalities (Berry 1976). Subjects will be asked if they were prescribed medication during pregnancy and if so the nature of the medication. Accuracy of this information will be determined from the medical records of subjects who have had either a stillborn or congenitally abnormal child and who provide informed consent. Subjects who have been prescribed androgenic hormones, folate antagonists or anti-convulsants during pregnancy will be separated from those who have not in the analyses since these drugs have been associated with congenital abnormalities (Klingberg 1977).

vi b) Reliability of Information Concerning Drug Use

Studies which have specifically examined the reliability and accuracy of subjects self reporting of prescription drug use were not found. A recent study of maternal drug use and congenital malformations (Weatherall and Greenberg 1979) chose not to rely on information provided by mothers because based on the authors experience it would be completely unreliable. These authors used information on drug prescriptions recorded in medical records.

The ability of subjects in this study to remember and the ability of the pregnancy information questionnaire to obtain information concerning prescription drug use will be examined during the pretest when responses to the questionnaire will be compared to medical record information.

vii) X-rays and Ionising Radiation

Exposure of the fetus to high levels of X-rays has been associated with the genesis of congenital abnormalities (see Literature Review).

While no relationship of diagnostic X-ray exposure or contemporary working levels of ionising radiation to abnormal reproductive outcomes has ever been reported the possibility of a relationship must be considered. Subjects of this study will therefore be asked if they received any X-rays during their pregnancies or recorded any other ionising radiation exposure.

Studies of the accuracy and reliability of radiation exposure self-reporting have not been located. If subjects can recall exposure, the dose they received would be unknown.

Subjects who report exposure to X-rays during pregnancy and an outcome of stillbirth or congenital abnormality will have exposure verified from medical records. Exposure to ionising radiation which occurred because of their occupation will have been determined by the film badge dosimeters which all workers exposed to radiation are required to wear. Copies of these records are available from the Federal Health Protection Branch.

While studies have been attempted to assess the relationship of occupational exposure to radiation to the genesis of congenital abnormalities none have used standardized questions or assessed the accuracy of responses to questions with actual exposure records.

viii) A number of other factors have been suggested to be related to an increased risk of bearing children with congenital abnormalities. These include socio economic status, poor emotional health, low quality and quantity of pre-natal care and season of conception (McKeown 1976). The sources of information concerning the effect of these factors are descriptive studies and in the absence of reference populations and adjustment for possible confounding factors the evidence for their inclusion as variables in this study is inadequate.

It is unlikely that a difference of any magnitude will exist for any of the above factors between the two cohorts in this study as their incomes, education levels and particularly health awareness are believed to be similar (executive directors Canadian Physiotherapy Association and Canadian Society of Laboratory Technologists and Personal Communication).

The inclusion of the questions necessary to obtain information concerning these factors and its personal nature may also tend to diminish the response rates to the questionnaire.

#### D. Events

This study seeks to compare the incidence of spontaneous miscarriages, stillbirths and the birth of live children with congenital abnormalities among the members of the Canadian Society of Laboratory Tech-

nologists and the Canadian Physiotherapy Association.

1) Congenital Abnormalities

Subjects will be asked in the pregnancy questionnaire to state whether and, if so, when they have had a child or children with a congenital abnormality. They will be asked to classify the particular abnormality as one of:- Down's syndrome/mongolism, brain or spinal cord defect, heart or blood vessel defect, limb abnormality, cleft lip or palate, disorder of the gastrointestinal tract, multiple malformations or if none of these to write in a description.

i a) Accuracy of Congenital Abnormality Reporting

All congenital abnormalities reported by subjects of the pregnancy information questionnaire pretest will be compared to information in their medical records.

Descriptions of congenital abnormalities reported by all subjects of the full survey will be compared to information in the medical record of the subjects provided that informed consent is obtained. Confirmatory information will also be sought from the federal stillbirth/congenital abnormality registry. Subjects who do not provide informed consent to confirm reported abnormalities will be treated as a separate stratum in the analyses.

Diagnoses of congenital abnormalities will be defined using the criteria of the International Classification of Diseases Association (1977 edition) numbers 740-7599 inclusive.

ii) Stillbirth

Subjects will be asked how many of their pregnancies experienced during the study period have ended in stillbirth and when the event occurred.

ii a) Accuracy of Stillbirth Reporting

All stillbirths reported by subjects of the pregnancy information questionnaire pretest will be compared to diagnostic information in their medical records.

Stillbirths reported by all subjects of the full survey will be verified from information in the medical record of subjects who provide informed consent. Confirmatory information will also be sought from the federal stillbirth/congenital abnormality registry. Subjects who do not provide informed consent to confirm reported stillbirths will be treated as a separate stratum in the analyses.

A stillbirth will be defined using the International Classification of Diseases (1977 edition) numbers 27.3, 27.4, 27.6, and 27.7.

iii) Miscarriage

Subjects will be asked if any of their pregnancies have terminated in a spontaneous miscarriage which began between 8 and 20 weeks after their last menstrual period.

iii a) Accuracy of Miscarriage Reporting

During the pretest of the pregnancy questionnaire, a group of subjects known to have had spontaneous miscarriages will complete the



pregnancy questionnaire. Their answers will be compared to information recorded in their medical records.

Confirmation of miscarriages will be sought in a randomly chosen sample of 10% of those reported. The large numbers of miscarriages expected as pregnancy outcomes (10% of all pregnancies experienced, Lortie Monette F. Personal Communication) precludes confirmation of all such outcomes from medical records and no central registry for miscarriages exists.

iv) Accuracy of Normal Pregnancy Outcome Reporting

Ideally a randomly selected sample of subjects reporting normal pregnancy outcomes would be requested to provide informed consent to obtain confirming information from medical records. It is likely however that those who have stated that they have had a normal pregnancy outcome when this is not the case are unlikely to provide such consent.

## CHAPTER V

### STUDY POPULATION

All members of the Canadian Society of Laboratory Technologists (n 16,000) and the Canadian Physiotherapy Association (n6,000) who were registered as members between 1975 and 1980 will be eligible for inclusion in this study. Members who have lapsed memberships as well as presently registered members will be included. The outcomes of all pregnancies experienced by the study population between 1976 and 1980 inclusive will be assessed.

#### A. Description of Study Population

##### i) Laboratory Technologists

The Canadian Society of Laboratory Technologists is an organization incorporated under Canadian Federal Government charter. It is responsible for setting curricula for the training of medical laboratory technologists of all disciplines, the accreditation of training programs in hospitals and the examination and licensing of medical technologists. The current membership is 16,000 of whom approximately 80% are female (Canadian Society of Laboratory Technologists Annual Report 1980). A further estimated 4,000 were members between 1976 and 1980, but allowed their membership to lapse. Local laboratory administrators and the executive director of the Canadian Society of Laboratory Technologists have estimated that approximately 40% of laboratory technologists have had at least one pregnancy in the last 5 years.

Members of the Society work in a number of types of laboratory

and the exposures they are subject to vary accordingly. The five principal areas are clinical chemistry, microbiology, hematology, histopathology and immunohaematology with a minority in such specialized labs as immunology and electron-microscopy. Whilst all are characterized by exposure to infectious agents and a variety of chemical hazards, two in particular, (microbiology/virology) and histopathology are distinct in their potential for insult to the reproductive system or fetus: microbiology by virtue of the potential for viral and other infection and histopathology for continuously high exposure to organic solvents.

ii) Physiotherapists

The Canadian Physiotherapy Association is the parent organization for all active physiotherapists in Canada. The organization has approximately 5,000 members of whom 90% are female (Personal Communication Executive Director Canadian Physiotherapy Association). A further 1,200 people have been members since 1975, but have allowed their membership to lapse. It is estimated that 40% of members and ex-members have had pregnancies in the last five years.

B. Characteristics of Both Groups

The laboratory technologists and physiotherapists both have a high median level of education (approximately three years post secondary). The sex distribution of the members of the two organizations is similar as is their geographic distribution throughout Canada which reflects the distribution of the national population (Canadian Society of Laboratory Technologists Annual Report 1980). By virtue of their professions members of these organizations can be expected to be more aware

of health issues than the general population. Both professional organizations have given formal permission to conduct this study (see letters Appendices 10 and 11).

#### C. Dissimilarities of the Two Cohorts

It is not known at present if members of the Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association are similar in either parity, age at which pregnancies have occurred, smoking or alcohol use and health care related exposures. For this reason and because these factors may be related to the outcomes of interest, differences in the two cohorts will be adjusted for in the analyses (see Statistical Analysis).

#### D. Sample Size Considerations

The three outcomes of interest in this study are as follows: spontaneous miscarriage, stillbirth, and the birth of live children with congenital abnormalities.

All sample size and power calculations assume that 80% of subjects who are or have been members of one of the participating organizations and who have had pregnancies will complete and return questionnaires. Given this assumption, it is expected that 2,000 pregnancies among physiotherapists and 6,500 among laboratory technologists will be reported in the survey for the five year period referred to in the questionnaire.

##### 1) Congenital Abnormalities

Previous cohort analytic studies suggest that laboratory technologists will have at least double the number of children with congenital abnormalities as unexposed populations (Meirik et.al. 1979, Hansson et.al. 1980). Assuming that 1.5% of children born to unexposed

mothers will have a defect apparent at birth (see Appendix 12), it can be estimated that 3.0% of children born to the cohort of laboratory technologists or a total of 195 will have congenital abnormalities.

i b) Power of Study to Detect an Increased Risk of Bearing a Child

With a Congenital Abnormality

With alpha (the risk of falsely rejecting the null hypothesis) set at .05 (two sided) and assuming rates of congenital abnormalities of 10/1000 live births or 15/1000 live births in the reference population of physiotherapists, power curves have been drawn (see Appendix 13). Given sample sizes of 6,500 births among laboratory technologists and 2,000 among physiotherapists this study would have an 80% chance of detecting a relative risk of 1.56 for congenital abnormality in laboratory technologists assuming a rate of 10/1000 live births in physiotherapists. If the rate in physiotherapists is as high as 15/1000 live births, the study would have an 80% chance of detecting a relative risk of 1.47 for laboratory technologists.

ii) Miscarriage

Only one previous study (Hansson et.al. 1980) has examined the incidence of spontaneous miscarriage among laboratory workers. Those authors found a relative risk of 1.8 (180/1000 compared to 100/1000) for chemical exposed compared to non-chemical exposed laboratory workers. If the same relative risk existed for members of the Canadian Society of Laboratory Technologists one would expect that approximately 1,200 of their pregnancies would have terminated in spontaneous miscarriage.

ii b) Power of Study to Detect Increased Relative Risk for Miscarriage

It has been estimated that 10% of all recognized pregnancies terminate in spontaneous abortion in Canada (Lortie-Monette F. Personal Communication). No evidence exists to suggest that physiotherapists have a higher or lower rate than this. With alpha set at .05 this study will have an 80% chance of detecting a relative risk of 1.25 for spontaneous miscarriage among laboratory technologists.

iii) Stillbirth

One study (Hansson et.al. 1980) has examined the risk of stillbirth for chemical compared to non-chemical exposed laboratory workers. These authors found a relative risk of 17.0 which result certainly demands confirmation. The reported rate of stillbirths in Canada is 4/1000 live births (Lortie-Monette F. Personal Communication).

iii a) Power of Study to Detect Increased Relative Risk for Stillbirth

Given that there is no evidence to suggest that physiotherapists are at higher risk than the general population of delivering stillborn children and assuming therefore a rate of 4/1000 live births, a power curve has been drawn (see Appendix 14). This shows that this study will have an 80% chance of detecting a relative risk of 1.75 for stillbirth as a pregnancy outcome among laboratory technologists (with alpha set at .05, two sided).

E. Male Subjects

The two organizations whose members are the subjects of this study have requested that male members of the organizations be included in the cohorts.

If males exposed to a laboratory environment are at risk of abnormal reproductive outcomes the mechanism involved is clearly different to that in female subjects.

Any increase in abnormal reproductive outcomes occurring in the spouses of male laboratory workers may also be due to some factor common to their being married to medical technologists rather than exposure of their husband to a laboratory environment.

The power of this study to detect the hypothesized doubling of the risk of abnormal reproductive outcomes in males will be extremely low because while 15-20% of the membership of the Canadian Society of Laboratory Technologists is male only 5-10% of the Canadian Physiotherapy Association is male.

Because of the probable differences in biologic mechanisms of abnormal reproductive outcomes and possible spousal factors which cannot be measured events occurring among male subjects in this study will be treated separately in the analyses.

## CHAPTER VI

### PRETEST OF STUDY INSTRUMENTS

#### A) Introduction and questions to be addressed in pretest studies

Two different instruments have been developed for this study. One will obtain health, demographic and occupational information and determine whether or not the subject has experienced a pregnancy (see Appendices 1 and 2). The second instrument to be mailed after the return of the first will seek to determine the outcomes of pregnancies experienced and information concerning possible influences on those outcomes (see Appendix 5). Both questionnaires will be labelled with the study subjects unique identification number.

Prior to the use of these instruments in the actual study the following must be determined in pretest studies.

- (1) Is the content of the questionnaires appropriate to obtain the information required?
- (2) When the initial questionnaire is applied to members of the study population will it obtain the information required reliably?
- (3) Is the pregnancy information questionnaire capable of obtaining information which is both reliable and accurate?

#### B) Initial questionnaire pretests

##### (i) Quality of questionnaire content

Both questionnaires have been examined by members of the executive committees of the two participating organizations to detect factual errors. In addition, both questionnaires have been examined by other in-



investigators experienced in the design of such instruments.

(ii) Feasibility of initial questionnaire

A convenience sample of ten local laboratory technologists and ten physiotherapists will be asked to complete and return the initial questionnaire. After the return of the questionnaires the subjects will all be interviewed in person by one interviewer. At the end of the interview the respondents will be asked for suggestions about the questionnaire. In particular, the clarity of the questions and their feasibility for detecting the required information will be discussed. Any changes deemed necessary as a result of this pretest will be incorporated into the questionnaire which will be further pretested using a different convenience sample of laboratory technologists and physiotherapists. Subjects of this pretest will be asked not to discuss the study with their colleagues.

(iii) Retest reliability of initial questionnaire

After the content validity of the initial questionnaire has been established, its ability to obtain precise answers will be evaluated.

A quota sample of 50 laboratory technologists and 50 physiotherapists will be selected from the current Canadian Society of Laboratory Technologists and Canadian Physiotherapy membership lists. A sample of 100 subjects for this pretest will be both feasible and permit a high degree of confidence to be placed in the estimate of agreement among subjects (see section on Statistical Analysis). Subjects will be selected who broadly represent the wide variation in age and time since initial certification of the members. Those selected will be sent a copy of the

initial questionnaire together with a letter requesting their cooperation in completing it and requesting written consent for them to be telephoned for follow-up. Any of this group of 100 who do not return the questionnaire will be sent another by special delivery with an additional letter emphasizing the importance of their cooperation.

Three weeks after the questionnaires have been returned, the subjects will be telephoned by an interviewer. It will be explained that as part of the pretest process we are interested in discerning the ability of the questionnaire to obtain reliable information and that we wish to verify the written answers. The questionnaires will then be administered by the clerk and answers recorded by him. Questions to which disagreement occurs between answers in a significant number of subjects will be examined and if necessary modified.

The results of the two different applications of the questionnaire will be compared by a statistical analysis of intra-subject agreement to each question (see Analysis section) which will have to be 90% before a question will be acceptable.

(iv) Ability of pregnancy questionnaire to detect exposures and events accurately

For the purpose of this pretest a spontaneous miscarriage will be defined as the spontaneous loss of (or spontaneous initiation of loss of) the products of conception between 8 and 20 weeks after the last menstrual period. A stillbirth will be defined as the spontaneous delivery

of a fetus having a gestational age of greater than 20 weeks and which is dead at the time of delivery. Congenital abnormalities will be accepted as diagnosed and recorded in the subject's medical records by the physicians.

A quota sample of 120 patients of the McMaster University Health Sciences Centre Family Practice Unit will be selected as subjects for this pretest. Thirty will be selected who have had children with a variety of congenital abnormalities, 30 who have had stillborn children, 30 who have had pregnancies which terminated in spontaneous abortion and 30 who have had normal deliveries and children, but not at any time had an abnormal reproductive outcome. These subjects will first be sent a letter explaining the purpose of the pretest study and requesting their consent to participate (see Appendix 14 and 15).

The assumption has been made that 15-20% of these subjects will not wish to participate leaving approximately 100 who will. As in the case of the pretest of the initial questionnaire this number of subjects has been selected as being feasible and permitting a high degree of confidence to be placed in the results of the study.

These subjects will be mailed the pregnancy questionnaire with a covering letter explaining that a study of the relationship of occupation to abnormal reproductive outcomes is about to be conducted and requesting them to complete and return the questionnaire.

For this pretest question 9 which asks specifically about laboratory or physiotherapy work will be modified to ask about all occupations. Subjects who do not return the first mailed questionnaire will be sent

another by special delivery.

Answers to questions will be compared to existing medical records and a statistical analysis of the agreement between reported outcomes and exposures and medical record information performed for each subject (see Analysis section).

## CHAPTER VII

### RESEARCH QUESTIONS

1. Are medical laboratory technologists more likely to have spontaneous miscarriages, stillbirths or living children with congenital abnormalities (abnormal reproductive outcomes) than physiotherapists?
2. Is the incidence of abnormal reproductive outcomes among female laboratory technologists who worked during pregnancy higher than the incidence of such events among those who did not work during pregnancy?
3. Is the rate of abnormal reproductive outcomes among laboratory technologists associated with the type of laboratory worked in and, in particular, with the performance of work associated with a greater potential for exposure to organic solvents and microbiologic agents?

## CHAPTER VIII

### DATA COLLECTION

#### A. December 1981 (Notification of Survey)

An announcement will be made in the journals of the Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association that a health survey of the professions is about to be conducted. The importance to the successful completion of the study of completing and returning the questionnaires will be emphasized.

#### B. January 1982 (Initial Questionnaire Mailed Out)

The initial questionnaire (see Appendices 1 and 2) will be mailed to all 20,000 current and ex-members of the Canadian Society of Laboratory Technologists and all 7,500 current and ex-members of the Canadian Physiotherapy Association whose names appear in any register of members since 1976.

Ten days after the initial mailing all subjects will be sent a postcard reminding them to complete the questionnaire and thanking them for their cooperation.

Subjects who do not return the questionnaire within three weeks will be sent a second copy with a covering letter explaining the importance to the study of their cooperation (see Appendix 4). This second questionnaire will be clearly coded to enable it to be identified in case subjects fill in and return both first and second copies. After another two weeks pass, non-respondents will be sent another copy of the questionnaire by special delivery which will also be labelled for the investigators to identify.

### C. Justification of Three Mailings

A review of the results of 98 separate mailed surveys (Heberlein and Baumgarten 1978) has found that two factors, the number of mailings and the salience of the questionnaire to the subject are the two factors which principally affect return rates.

The average response rate for studies with one mailing was 46.1% but for studies with three mailings 80.6%. Questionnaires judged by respondents to be non-salient achieved an average of a 42% response rate whereas questionnaires judged to be salient achieved an average return rate of 77%. In addition, special mailing techniques such as registered mail or special delivery were found to "significantly" improve response rates when used in conjunction with repeat mailings.

### D. Execution of Study

The timetable for this study is summarized in Table VIII. Clearly the largest volume of work is during the preparation of the mailings and the return of questionnaires. For this reason temporary staff will be hired to assist the project manager during this period (approximately 6 months)

### E. Collection of Data from Initial Questionnaire

Returned questionnaires will be collected and study I.D. numbers of those subjects who have experienced one or more pregnancies in the last five years will be abstracted. Pre-coded information on the questionnaires will be keypunched in preparation for analysis.

Table VIII: Execution of Study

Year Month	1981 4 5 6 7 8 9 10 11 12	1982 1 2 3 4 5 6 7 8 9 10 11 12	1983 1 2 3 4 5 6 7 8 9 10 11 12	1984 1 2 3 4
	<p>PRETEST OF INSTRUMENTS</p> <p>PRINTING OF INSTRUMENTS</p> <p>HIRING OF STAFF</p> <p>ANNOUNCEMENT OF STUDY</p> <p>FIRST MAILOUT OF INITIAL QUESTIONNAIRE</p> <p>SECOND MAILOUT OF INITIAL QUESTIONNAIRE</p> <p>THIRD MAILOUT OF INITIAL QUESTIONNAIRE</p> <p>IDENTIFICATION OF SUBJECTS WHO HAVE HAD PREGNANCIES</p> <p>1ST PREG Q MAILOUT</p> <p>F/UP MAILING PREG Q</p> <p>CODING + KEYPUNCHING</p> <p>INFORMED CONSENT OBTAINED</p> <p>PHYSICIAN VERIFICATION</p> <p>STATISTICAL ANALYSIS</p> <p>PREPARATION OF REPORTS</p>			



F. Detection and Follow-up of Subjects Whose Memberships Have Lapsed

A principle reason for either laboratory technologists or physiotherapists to leave their profession and membership in their professional organization might be the birth of children.

Review of membership records has indicated that approximately 85% of women using the title Mrs. and 80% of men who were members of the Canadian Society of Laboratory Technologists in 1976 are still members in 1980. The current address of 4,000 laboratory technologists and 1,200 physiotherapists are not known to be up to date.

Since it is quite possible that these lapsed members would be more likely to have had children than the majority who have maintained their membership it is imperative that they be included in the study.

A copy of the initial questionnaire will be sent to the last address recorded by the Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association for all lapsed members. Since the questionnaire will be sent by first class mail they will automatically be forwarded to new addresses if the changes are recent and if non-deliverable will be returned to the study centre. (Possible bias introduced by an inability to contact lapsed members is discussed in the section Strength and Limitations on page 89).

G. April 1982 (Pregnancy Questionnaire Mail-Out)

The pregnancy questionnaire will be mailed to all subjects who state that they have had a pregnancy within the last five years. A letter of explanation will accompany the questionnaire. (see Appendix 8).

Ten days after the initial mailing of the pregnancy questionnaire a reminder postcard will be sent to all subjects.

Subjects who have had pregnancies but who do not return the questionnaire will be mailed a second questionnaire with a covering letter explaining the importance of their cooperation (see Appendix 9).

Subjects known to have had pregnancies (based on responses to the initial questionnaire) but who do not respond to either the first or second mailings will be sent a further questionnaire by special delivery.

#### H. September 1982 (Pregnancy Outcome Verification)

All subjects who report having had stillborn children or children with congenital abnormalities and a random sample of 10% of subjects reporting miscarriages will be sent a consent form and explanatory letter by special delivery (see Appendices 6 and 7). These will request consent for information contained in their medical records concerning their pregnancies and pregnancy outcomes to be released to the investigators.

The subjects' physician will be contacted by mail and confirmation of both exposure and outcome information reported in the pregnancy questionnaire by the subject will be requested (see Appendices 17 and 18 for letter and questionnaire respectively). If no reply from the physician is received after one mailing a second copy of the documents will be sent. In the event that no reply is received by mail, subjects' physicians will be contacted directly by telephone. In addition to confirmation from medical records, reported pregnancy outcome will be verified by seeking diagnostic information from the federal government stillbirths/birth defects

registry. While not all cases will have been recorded in the registry, it will provide a second confirmation of reported events for those subjects living in provinces which provide information to the registry. The section Strengths and Limitations on page 89 provides a discussion of the possible problems of confirming events.

It is anticipated that there will be a total of approximately 300 stillbirths and congenital abnormalities as pregnancy outcomes occurring during the study period in both cohorts.

This relatively low number makes intensive follow-up to confirm events feasible both in terms of cost and time required.

Conversely, the number of miscarriages expected to have occurred in both cohorts during the five year study period is so large (1400) that confirmation of all of them is not feasible. For this reason a randomly selected sample of 10% of subjects reporting miscarriage will have the event confirmed. Since no central registry for miscarriages exists, subject's medical records will be the only source of confirming information.

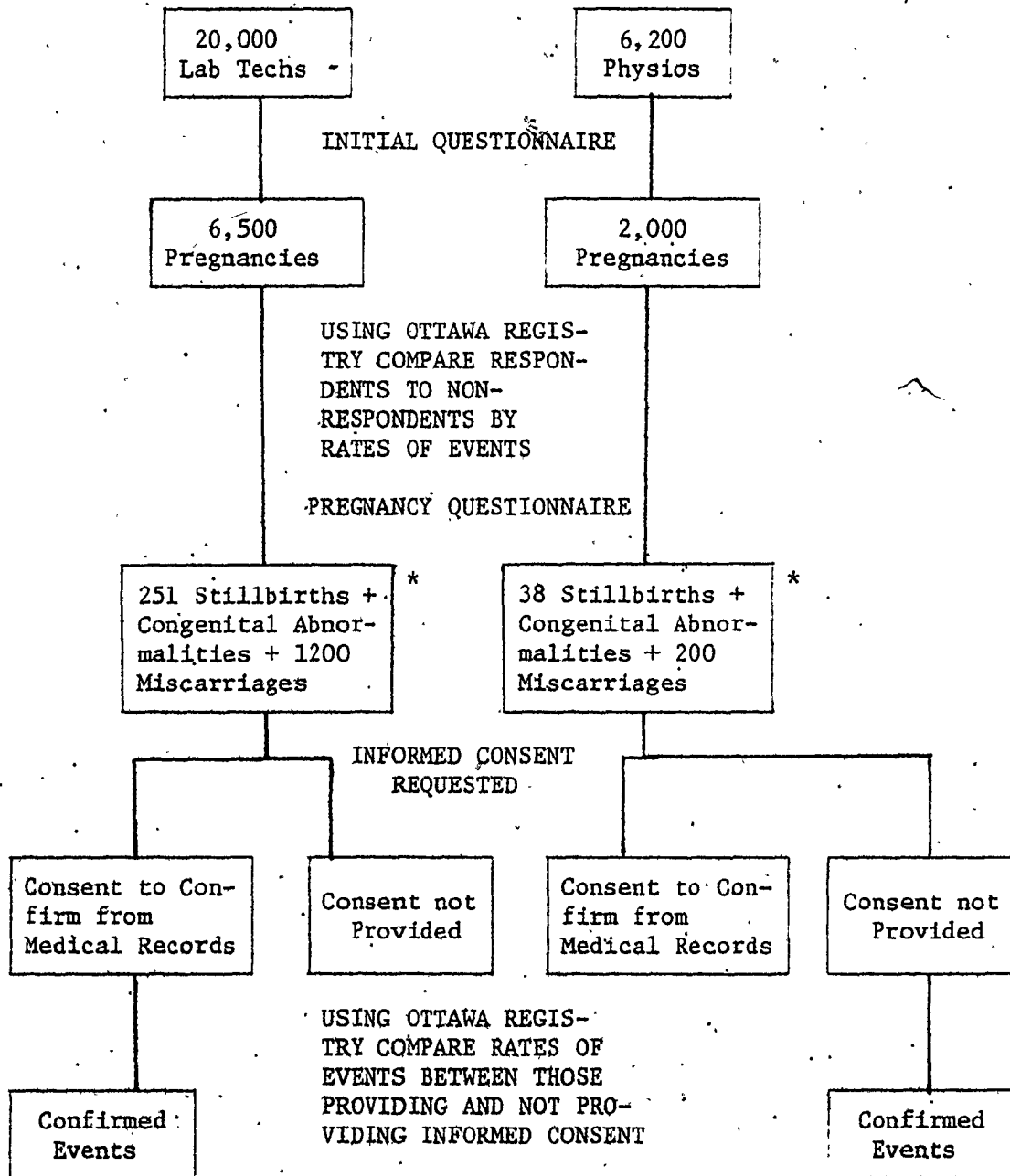
#### I. Informed Consent not Provided

Subjects who report in the pregnancy information questionnaire that they have had either a stillbirth or a child with a congenital abnormality but decline to provide consent to obtain confirmatory information will be treated as a separate stratum in the analyses.

The possibilities of under-reporting of events is discussed in the section Strengths and Limitations (page 89).

The means of data collection and confirmation are summarized in Table IX.

Table IX: Event Detection Reporting and Confirmation



\* Estimate of the number of events based on relative risks of 1.8 for miscarriage and 2.0 for stillbirth and congenital abnormality for laboratory technologists (see page 56 for discussion).

## CHAPTER IX

### STATISTICAL ANALYSIS

#### A. Analysis of Pretests

##### i) Methods of Analysis

Cohen's kappa statistic (Cohen 1960) unlike the more normally used co-efficient of correlation takes into account the contribution of chance agreements.

Kappa can be thought of as observed agreement over and above chance divided by possible agreement not accounted for by chance. As in the case of the correlation coefficient, kappa varies from -1.0 to +1.0 with -1.0 being complete disagreement, 0 chance agreement and +1.0 complete agreement.

##### i b) Calculation of Kappa

$$K = \frac{(P_o - P_c)}{1 - P_c}$$

where  $P_o$  is the observed agreement and  $P_c$  is agreement expected by chance.

##### ii) Initial Questionnaire Reliability

Answers to the initial questionnaire completed by subjects of the pretest will be compared to the answers that they give when the questionnaire is applied 3 weeks later by telephone. The quota sample for this pretest will consist of 100 subjects chosen to be representative of the two study cohorts. This pretest in addition to detecting questions which may obtain unreliable information will also provide an indication of the quality of the information to be obtained when the full survey is con-

ducted.

Answers to each dichotomous question will be analysed in the following way:-

A kappa statistic will be calculated based on the responses to the question at initial testing and at retesting. Any question for which a kappa of less than 0.8 is calculated will be examined for possible rephrasing.

When kappa equals 0.8, 90 of 100 subjects will have given the same answers at test and retest.

By calculating the standard error of kappa given 90% agreement and with 100 subjects in the pretest, confidence limits around kappa can be calculated.

$$\text{S.E. Kappa} = \frac{\sqrt{O(1-O)}}{N(1-E)^2}$$

substituting the hypothetical values in the pretest

$$O \text{ (observed agreement)} = 0.9$$

$$E \text{ (expected agreement)} = 0.5$$

$$N \text{ (number of observations)} = 200$$

$$\text{Kappa} = \frac{0.9 - 0.5}{0.5} = 0.80$$

$$\therefore \text{S.E. Kappa} = \frac{\sqrt{.9(.1)}}{200(.5)^2} = .042$$

95% confidence interval around kappa will be .72 - .88.

Thus a sample size of 100 subjects will enable considerable con-

confidence to be placed in conclusions drawn from this pretest about the reliability of answers to questions.

iii) Ability of Pregnancy Questionnaire to Obtain Accurate Information

The pregnancy questionnaire will be pre-tested using 100 subjects selected from the patients of the McMaster University Health Sciences Centre Family Practice Unit. These subjects will be formed of 4 sub-groups, 3 of which will each have experienced one of the events of interest and 1 which has had only normal reproductive outcomes. Answers to questions provided by these subjects will be compared to their existing medical records.

The kappa statistic will again be used to evaluate the reliability of responses to the questionnaire. The value of the statistic required will be 0.8 and if this level is not reached for any question it will either be rephrased or deleted.

For this analysis the results from each of the three groups of 25 with abnormal pregnancy outcomes and 25 with normal outcomes will be pooled. An initial analysis using the chi squared statistic to test for homogeneity will be conducted before pooling subjects for the calculation of kappa.

As in the case of the retest reliability of the initial questionnaire with a sample of 100 and a specified agreement requirement of 90% the confidence limits around the required kappa value of 0.8 will be 0.72 - 0.88.



## B. Analysis of Primary Research Questions

1) Are medical laboratory technologists more likely to have spontaneous miscarriages, stillbirths or living children with congenital abnormalities?

2) Is the incidence of abnormal reproductive outcomes among female laboratory technologists or physiotherapists who worked during pregnancy higher than the incidence of such events among those who did not work during pregnancy?

3) Does the rate of abnormal reproductive outcomes among laboratory technologists vary by the type of laboratory they work in and in particular with the performance of work associated with a greater potential for exposure to organic solvents or microbiologic agents?

## C. Variables to be Considered in the Analysis

### 1) Outcomes of interest

There are 3 outcomes of interest in this study. These are the termination of a pregnancy in spontaneous miscarriage, stillbirth or the birth of a live child with a congenital abnormality.

### 2) Main explanatory variable

The two occupations of medical laboratory technology and physiotherapy are the principle explanatory variable in this study. These two occupations are sub-divided into groups which may vary in their potential for exposures which may be hazardous to the reproductive process.

These sub-categories are as follows:-

Laboratory Technologists

clinical chemistry  
 microbiology  
 haematology  
 immunohaematology  
 histopathology  
 research  
 general lab all disciplines  
 virology  
 teaching  
 immunology  
 cytology  
 electron microscopy  
 cytogenetics

Physiotherapists

general teaching hospital  
 independent rehabilitation hospital  
 private practice  
 non-teaching hospital  
 home care

## D. Units of Analysis

Two possibilities occur for the analysis of the primary research questions. These are:- 1) Pregnant females counting only the first abnormal pregnancy outcome during the study period; 2) All pregnancy outcomes occurring during the study period.

Apart from the extrinsic factors hypothesized to be associated with abnormal reproductive outcomes in this study there are possible intrinsic factors which may influence the likelihood of such events.

If a subject has had one abnormal pregnancy outcome it is possible that she is less likely to initiate further pregnancies. Converse-

ly those subjects who have had one abnormal pregnancy outcome may be at increased risk of having further such events because of inherited characteristics or other pathopoesis.

If pregnant females were used as the unit of analysis dichotomised to either event or no event during the study period all events subsequent to the first in subjects would not be included. If all events are the units of analysis it is possible that if multiple events occur in the same subjects that a misleading conclusion would be drawn from the analyses.

Accordingly it has been decided to analyze the data both using all events and separately for the first and each subsequent event occurring during the study period.

f) Males

Since events occurring as the reproductive outcomes of male subjects will have occurred as the result of a different gonadopathic process to those of females a separate analysis will be performed for these events.

The numbers of male subjects will be small relative to the number of females (see section on Study Population). For this reason it is likely that the strata proposed for the analysis of events among female subjects will have to be extensively collapsed to obtain a test statistic. Additionally the power of the study to detect an increased relative risk for males will be low because of the paucity of these subjects.

## E. Confounding Variables

### 1) Definition

A confounding variable is that which is associated with the outcome of interest and which is unequally distributed among cases and controls or among the two study cohorts.

### ii) Age

The age of the subject at the time the event occurred will be adjusted for in the analysis by classification into three strata: 20-30, 31-40, and 41-50.

### iii) Parity

Parity will be divided into four strata for the purposes of analysis, no children, one child, two to four children or five or more children.

### iv) Cigarette Smoking

Cigarette smoking will be divided into three levels for adjustment, no smoking during pregnancy, smoking up to one small pack per day during pregnancy and smoking over one small pack per day during pregnancy.

### v) Alcohol

Alcohol use during pregnancy will be divided into three levels for adjustment, no alcohol use during pregnancy, up to the equivalent of two ounces of pure alcohol per day and over two ounces of pure alcohol per day.

### vi) Infection

Subjects will be divided into two groups, those who have and have not had an infection during pregnancy.

## vii) Drugs

Subjects who have been prescribed any of folate antagonists, androgenic hormones or anti-convulsants will be treated as a separate strata in the analysis.

## viii) Ionising Radiation

Subjects will be divided into two strata depending on whether or not they have received diagnostic X-rays or other measureable ionising radiation during pregnancy.

## F. Method of Analysis

The Mantel-Haenzel procedure (Mantel and Haenzel 1959) is a method for calculating a summary relative risk for a particular outcome between two groups of subjects while simultaneously adjusting for confounding variables. In addition a summary chi square statistic may be calculated for all groups. It is also possible to examine components of the total chi square to determine if significant differences exist between sub-groups. The Mantel-Haenzel chi square estimate eliminates the need to analyze each sub-group separately while permitting examination of such sub-groups when this is required.

## G. Logic of the Analysis

Estimates of relative risk from data arranged in four fold tables depend upon the rarity of the outcome of interest for their calculation. The two methods of calculating relative risk can be illustrated in the following way:

	STILLBIRTH	NO STILLBIRTH	
Lab Techs	a	b	a + b
Physios	c	d	c + d
	a + c	b + d	a + b + c + d

The proportion of laboratory technologists having stillbirths is  $\frac{a}{a+b}$  and that of physiotherapists having stillbirths is  $\frac{c}{c+d}$ .

The relative risk for stillbirth for laboratory technologists compared to physiotherapists is thus  $\frac{\frac{a}{a+b}}{\frac{c}{c+d}}$

When the outcome of interest, in this example stillbirth, is rare, that is when the numbers in cells a and c are small compared to those in cells b and d, an estimate of the relative risk is provided by  $\frac{a d}{b c}$ . This estimate is often referred to as the odds ratio.

Both of the above estimates of relative risk assume that the distribution of other factors which may be related to outcomes in both cases and controls are equally distributed. Clearly this is unlikely to happen in practice and cannot be assumed to be the case. The Mantel-Haenzel procedure (Mantel and Haenzel 1959) provides a method of estimating the odds ratio  $\frac{a d}{b c}$  by summarizing the odds ratio for each strata created to classify subjects by confounding variables.

If a large number of factors are being adjusted for and if the number of strata within a factor is large, a high number of cells can be generated. If the distribution of a factor between cases and controls is radically different, it may be possible to generate cells with no subjects in them. For example, if all cases were aged 30 - 45 and all controls 20 - 29, the mutually exclusive nature of the age distribution would create at least two cells in which there were no subjects. The data must thus be inspected to ensure that this condition has not occurred.

#### H. Calculation of Summary Relative Risk and Chi Square Statistic Using the Mantel-Haenzel Method

Strata	Lab Tochs		Physios		Total	Odds Ratio
	Still-birth	No Still-birth	Still-birth	No Still-birth		
1	$a_1$	$b_1$	$c_1$	$d_1$	$n_1$	$R_1 = \frac{a_1 d_1}{b_1 c_1}$
2	$a_2$	$b_2$	$c_2$	$d_2$	$n_2$	$R_2 = \frac{a_2 d_2}{b_2 c_2}$
i	$a_i$	$b_i$	$c_i$	$d_i$	$n_i$	$R_i = \frac{a_i d_i}{b_i c_i}$
k	$a_k$	$b_k$	$c_k$	$d_k$	$n_k$	$R_k = \frac{a_k d_k}{b_k c_k}$
Total	A	B	C	D	N	

i) Crude relative risk (odds ratio) =  $\frac{AD}{BC}$

ii) Adjusted relative risk =  $\frac{\sum \frac{a_i d_i}{n_i}}{\sum \frac{b_i c_i}{n_i}}$

$$\text{iii) } Z = \frac{(\sum A - E(A) \cdot 1 - \frac{1}{2})^2}{VA}$$

$$\text{iv) } \text{where } E(A) = \frac{\sum (a_i + b_i)(a_i + c_i)}{n_i} \quad (\text{the expected value of } A)$$

$$\text{v) } \text{and } V(A) = \frac{\sum (a_i + b_i)(a_i + c_i)(b_i + d_i)(c_i + d_i)}{n_i^2(n_i - 1)} \quad (\text{the variance of } A)$$

The correction factor of  $\frac{1}{2}$  used in expression (iii) leads to a very conservative estimate of the  $X^2$  statistic (Haybittle and Freeman 1979). For this reason in the analysis of data in this study it will not be used.

#### I. Conduct of Analysis to Answer Research Questions

i) Are medical laboratory technologists who worked during pregnancy more likely to have spontaneous miscarriages, stillbirths, or living children with congenital abnormalities (abnormal reproductive outcomes) than physiotherapists who worked during pregnancy?

Separate analyses using the Mantel-Haenzel technique will be performed for each of the three outcomes of interest stratifying subjects by age, parity, smoking status, alcohol use, prescribed drug use and X-ray or other ionizing radiation exposure.

Additionally separate analyses will be performed for all events occurring in the study period and for first, second or subsequent events. That is for example a separate analysis will be performed to compare the proportions of subjects in each cohort suffering three miscarriages within the study period.



ii) Is the incidence of abnormal reproductive outcomes among female laboratory technologists and physiotherapists who worked during pregnancy higher than the incidence of such events among those who did not work during pregnancy.

Separate analyses will be performed using the Mantel-Haenzel technique for each of the outcomes of interest stratifying subjects by occupational group, age, parity, smoking status, alcohol use, prescribed drug use and X-ray exposure.

It is realized that this analysis will provide two separate estimates of relative risk, one for laboratory technologists and one for physiotherapists which will not be capable of statistical comparison, however, the research question relates to the risk within each of the two professions.

iii) Does the rate of abnormal reproductive outcomes among laboratory technologists vary by the type of laboratory they work in and particularly with the frequency with which organic solvents and or microbiologic agents are encountered.

The working hypothesis in this study is that within laboratory work exposure to either microbiologic agents, organic solvents or both are associated with an increased risk of abnormal reproductive outcomes. Accordingly the analyses for this research question will be as follows:-

Because of their possible high exposure to organic solvents and microbiologic agents subjects employed in microbiology, virology or histopathology during pregnancy will be compared to both laboratory technologists in other sub-specialities and physiotherapists. Laboratory tech-

nologists employed in sub-specialities other than microbiology, virology or histopathology will also be compared to physiotherapists.

For each of the three outcomes of interest a Mantel-Haenzel analysis will be performed comparing laboratory technologists by the sub-speciality in which they were employed during their pregnancies stratifying subjects by age, parity, smoking status, alcohol use, prescribed drug use and X-ray exposure.

#### J. Empty Cells

A problem which may occur in the Mantel-Haenzel procedure is that cells will be created in which there are no subjects. The effect of this will be to render the calculation of either an odds ratio but not a chi square statistic impossible for that stratum.

This is illustrated in the following example:

	STILLBIRTH		NO STILLBIRTH	
	LAB TECH	PHYSIO	LAB TECH	PHYSIO
Age Group I	2	0	20	20
Age Group II	4	2	50	50

$$\text{Relative Risk for stratum I} = \frac{2.20}{0.20} = \infty$$

$$\text{Relative Risk for stratum II} = \frac{4.50}{2.50} = 2.0$$

If upon inspection of the data the above situation occurs, and it is desired to determine an odds ratio, strata will be collapsed until all cells contain subjects.

In the above hypothetical example this would lead to the following:

	STILLBIRTH		NO STILLBIRTH	
	LAB		LAB	
	TECH	PHYSIO	TECH	PHYSIO
Age Groups I and II	6	2	70	40

$$\text{Odds ratio} = \frac{6.40}{2.70} = 1.71$$

## CHAPTER X

### STRENGTHS AND LIMITATIONS

#### A. Detection of Abnormal Reproductive Outcomes

This study relies on a mailed self administered questionnaire for the detection of abnormal reproductive outcomes. The ability of this instrument to detect abnormal reproductive outcomes will have been examined in a pretest and events which are reported during the actual survey will be subject to verification from either the subjects medical record or in some instances official registries.

It is possible that events will be over or under reported. In order to measure the size of this problem the federal government still-birth/birth defect registry will be asked to provide the number of these outcomes recorded for the study population by type of abnormality and province which will be compared with the data received during the survey.

#### B. Survey Methods and the Detection of Outcomes

##### 1) Rate of Return

If too few questionnaires were to be returned, the accuracy and credibility of the study results would be questioned.

As stated in the section on data collection this possibility will be addressed by a concerted follow-up of all subjects using additional conventional mailings and one by special delivery. A previous health survey of all members of the Canadian Society of Laboratory Technologists to investigate the possibility of eye ailments related to the occupation

obtained an 80% response rate after one mailing (Personal Communication with the Executive Director Canadian Society of Laboratory Technologists).

ii) Bias in Response to the Initial Questionnaire

Respondents and non-respondents to the initial questionnaire may have had different pregnancy outcomes. This possibility will be examined in the following way:-

Respondents to the initial questionnaire will be compared to non-respondents by sex, province of residence, membership classification and length of time since certification to detect differences between the two groups. Information needed to make this comparison is available from the participating organizations. A list of the names of respondents and non-respondents to the initial questionnaire will be given to the federal government birth defect/stillbirth registry which will be asked to provide the number and diagnoses of children born to members of each group. This will establish if any systematic difference exists in the numbers of congenital abnormalities or stillbirths as pregnancy outcomes in respondents compared to non-respondents. While information provided by the registry is subject to the quality of reporting to itself and this is believed to be incomplete, there is no evidence of reporting being inadequate enough to prevent a comparison such as that above being made.

iii) Contamination

The underlying hypothesis for this study is that laboratory technologists will have a higher incidence of abnormal reproductive outcomes than the reference population of physiotherapists.

If both groups were at an elevated risk due to some common exposure or risk factor this might not be detected if the groups were compared to each other. For this reason rates of individual abnormalities and stillbirths will be compared by province of residence for both physiotherapists and laboratory technologists using vital statistics assembled by the birth defects registry of Health and Welfare Canada for each of the five years of the study period. While this data may be incomplete and only drawn from six provinces it will permit the detection of unusual patterns of abnormality occurrence (see Appendix 12 for sample data summary).

iv) Bias Due to Lapsed Members

Subjects of this study who have had children will be more likely to have let their memberships in the two professional organizations lapse as they are more likely to have stopped working than those without children. In particular, those subjects who have had abnormal children may be strongly over-represented in the "lapsed membership" group. Since current addresses may not be available for lapsed members, the study may underestimate the true incidence of congenital abnormalities.

The names of current and lapsed members of both participating organizations will be given to the Health and Welfare Canada birth defects/stillbirth registry which will be asked for the number and diagnoses of these outcomes occurring among both groups.

While as stated previously it is thought that reporting to this registry may be incomplete there is no reason to suspect that differ-

ences will exist in the extent of reporting for current and lapsed members of the organizations participating in this study.

Additionally there is no evidence to suggest that both laboratory technologists and physiotherapists will not be subject to the same pattern of return to work. While there may be some underestimate of the total numbers of events, the internal validity of the study in comparing the risk for the two groups will not be affected.

In the event that proportionately many more subjects having either stillbirths or children with congenital abnormalities were found to be unreachable because their current addresses were not available, more strenuous procedures would be used to locate them. These might include surveys of local telephone and other directories and the placement of newspaper advertisements.

#### C. Reporting of Exposures

##### 1) Occupation

Subjects of this study will be asked what sub-specialty of their occupation they were employed in for each year of the study period. It is possible that this information may be subject to errors of recall. This possibility will be examined during the pretest of the initial questionnaire when subjects will be tested and retested one month later to establish reliability of reporting. In addition, sub-specialty of occupation during the study period will be determined in both the initial and the pregnancy questionnaires. All subjects who complete a pregnancy questionnaire will have previously completed the initial questionnaire

thus permitting an examination of the reliability of the reporting of work history.

ii) Specific Chemical and Microbiologic Exposures

This study does not seek to determine specific exposures which may have been causally associated with abnormal reproductive outcomes in literature reports.

While information on specific exposures would be of great value in determining courses of action in the event that laboratory workers are bound to be at increased risk of abnormal reproductive outcomes, the inability to validate specific exposures and possible biases in their reporting are considered strong reasons not to request such information.

Specifically reporting of exposures may be subject to the following sources of bias and error.

- 1) Errors of recall:- The ability of subjects to recall exposures may change with the time since exposure. Since this study is examining a five year period, there may be differences in exposures reported depending on the individual capacity of subjects to recall them.
- 2) Exposure Suspicion:- Subjects who have had an abnormal reproductive outcome or other illness may search their memory more diligently for plausible exposures which may explain the outcome.
- 3) Obsequiousness:- The act of including questions about specific occupational exposures in survey questionnaires may suggest to subjects that the investigators are particularly interested in such



information.

- 4) Errors of Awareness:- Subjects may be unaware that they have been exposed to hazardous substances because of sensory ability, changes which may have occurred in the definition of hazardous exposures and/or increased concern for the possible effect of extrinsic factors on the unborn.

Accordingly, information concerning specific occupation related exposures will not be asked in this study. Specific exposures would more reasonably be the subject of a later study if sub-populations of subjects in this study for whom particular exposures were probable were shown to have an elevated risk of abnormal reproductive outcomes.

### iii) Lifestyle and Health Care Related Exposures

#### a) Cigarette and Alcohol Use

Cigarette and alcohol use are both subject to a number of potential reporting errors (see section on Description of Instrument), however, this information will be requested because it is frequently recorded in medical records and is thus subject to a check for reliability.

Any biases or errors in reporting which do occur are likely to be of equal magnitude in both cohorts thus not affecting their comparability

#### b) Ionising Radiation, Drugs and Specific Infection

Exposure to X-rays during pregnancy, prescription drugs and infections recognized by subjects will have been recorded in medical records and are thus subject to validation.

Exposure to ionising radiation experienced occupationally may be verified from film dosimetry records maintained by the Radiation Protection Branch of Health and Welfare Canada.

The pretest of the pregnancy information questionnaire will provide a measure of its ability to obtain valid information concerning the above exposures since answers provided by subjects will be verified from medical records.

iv) ~~Confirmation~~ of Exposures in Subjects with Normal Pregnancy Outcomes

Subjects who report normal pregnancy outcomes will not be requested to provide consent to obtain confirmatory information concerning these outcomes as discussed in the section Description of Instruments. A random sample of such subjects will however be requested to provide consent to request confirmatory medical record information from their physician in order to examine the reliability of information concerning exposures in the pregnancy information questionnaire.

## CHAPTER XI

### ETHICAL CONSIDERATIONS

A principle concern in a study of this nature is that while it is non-invasive in a physical sense, the psychologic or social well being of those subjects who may have had abnormal reproductive outcomes may be adversely affected. Clearly the birth of a stillborn or abnormal child is an event that will in most cases have an emotionally scarring effect which may well last years.

The act of sending a questionnaire which requests information of a personal nature may be perceived as an intervention which may if only transiently have an adverse effect on the subjects of this study.

The nature of this study is such that assurances of confidentiality must be both made and adhered to.

#### A. Pretests

##### i) Retest Reliability of Initial Questionnaire

Consent will be obtained from subjects of the reliability pretest of the initial questionnaire prior to their being contacted directly by study personnel.

##### ii) Pretest of Pregnancy Questionnaire

Because no benefit will accrue either directly or indirectly to subjects of the pretest of the pregnancy questionnaire who will all be patients of the McMaster University Health Sciences Centre Family Practice Unit, formal informed consent will be obtained prior to their being mailed a questionnaire. This consent form (see Appendix 14) will

advise subjects of the purpose of the pretest, that is the ability of the pregnancy questionnaire to accurately obtain information concerning pregnancy outcomes and the long term purposes of the study.

Questionnaires will be mailed to subjects who consent to participate and will be pre-coded with the Family Practice Unit patient identification number. Returned questionnaires will not contain names and addresses of subjects.

#### B. Study Data Collection

##### i) Initial Questionnaire

All initial questionnaires sent to members of the Canadian Society of Laboratory Technologists or Canadian Physiotherapy Association will bear unique study identification numbers. Lists of names and addresses of subjects matched to the identification numbers will be held centrally for reference but no names or addresses will appear on returned questionnaires.

While prior consent will not be obtained from subjects, consent to participate will be implicit in the return of a completed questionnaire. In addition, the boards of directors of the two organizations representing the participating laboratory technologists and physiotherapists are elected democratically and have formally considered and approved the aims and objectives of this study.

##### ii) Pregnancy Questionnaire

As in the case of the initial questionnaire, no names or addresses will appear on returned pregnancy questionnaires and completion

and return will imply consent to participate in the study.

A possible concern with this questionnaire is that those subjects who have had abnormal reproductive outcomes may experience some distress at being asked detailed questions about these experiences.

This is probably unavoidable, but given the nature of the study population, it is to be hoped that their awareness of health issues will in conjunction with explanatory letters reassure them of the potential benefit to others of the investigation.

#### C. Diagnostic Confirmation of Congenital Abnormalities and Stillbirths

Informed consent (see Appendices 6 and 7) will be obtained from those subjects who have had stillbirths or children with congenital abnormalities to request detailed diagnostic information from their attending physician. In addition to a written explanation of the need for this information, a collect telephone facility will be installed for subjects to request any further information anonymously which may assist them in deciding whether or not to provide consent.

## CHAPTER XII

### BENEFITS OF STUDY

#### A. Benefits to Study Groups

At present evidence exists which suggests that laboratory work may pose a threat to the unborn children of its practitioners. The study that is proposed will clarify and measure the extent of this risk and indeed whether or not it is present. Specific sub-groups of laboratory workers exposed to particular hazards will be examined and any excess risk of abnormal reproductive outcome will be measured.

This study will thus provide information to enable working exposure standards to be modified and where necessary set to alleviate any risk which may be found.

#### B. Benefit to Others

Exposures which are common to laboratory work are found in many other occupations and laboratories other than those in hospitals. The results of this study may well be generalizable to other groups of laboratory workers both nationally and internationally and may well generate hypotheses which can be tested in other non-laboratory work environments to identify and measure presently unsuspected hazards.

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## APPENDIX 1

STUDY OF THE HEALTH OF LABORATORY TECHNOLOGISTSQUESTIONNAIREBACKGROUND INFORMATION

1. What is your sex?

1 MALE

2 FEMALE

2. When were you born?                             
Day Month Year3. Where do you now live:                                                                    
City ProvinceOCCUPATIONAL ENVIRONMENT4. Which of the following types of laboratory best describes the type you were working in between 1975 and 1980? Indicate with a ✓ only one type for each year.

1976 1977 1978 1979 1980

CLINICAL CHEMISTRY

MICROBIOLOGY

HAEMATOLOGY

IMMUNOHAEMATOLOGY

HISTOPATHOLOGY

RESEARCH

GENERAL LAB  
ALL DISCIPLINES

VIROLOGY

TEACHING

IMMUNOLOGY

CYTOLOGY

## APPENDIX 1 (continued)

	1976	1977	1978	1979	1980
ELECTRON MICROSCOPY					
CYTOGENETICS					
OTHER					

QUESTIONS ABOUT YOUR FAMILY

5. Have you (or in the case of males your spouse) had a pregnancy in the last five years?

1 NO

2 YES

6. Do you have children?

1 NO

2 YES

QUESTIONS CONCERNING YOUR HEALTH

7. Have you ever had hepatitis?

1 NO

2 YES----7a. When was that? \_\_\_\_\_  
Year

7b. What type of laboratory were you working in at that time?

\_\_\_\_\_  
Type of Laboratory

8. Do you have migraine headaches?

1 NO

2 YES----8a. How often do you have migraine headaches?

1 MORE THAN ONCE A WEEK

2 WEEKLY

3 MONTHLY

4 LESS FREQUENTLY THAN MONTHLY

APPENDIX 1 (continued)

9. Do you suffer from dermatitis?

1 NO

2 YES

10. Do you suffer from asthma?

1 NO

2 YES

11. Are you allergic to any substances that you work with?

1 NO

2 YES---11a. What substances are these? (Please list below)

- 1 \_\_\_\_\_
- 2 \_\_\_\_\_
- 3 \_\_\_\_\_
- 4 \_\_\_\_\_

12. Have you ever suffered from low back pain which required medical treatment?

1 NO

2 YES---12a. Was this the result of a work related event?

1 NO

2 YES---12b. Please briefly describe the event

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

APPENDIX 1 (continued)

13. Do you now smoke cigarettes?

1 NO

2 YES----13a. How many cigarettes do you smoke daily?  
(Circle the number that applies)

1 LESS THAN TEN

2 MORE THAN TEN BUT LESS THAN TWENTY

3 BETWEEN ONE AND TWO SMALL PACKS

4 MORE THAN TWO SMALL PACKS

14. Have you ever had an illness that required you to miss more than one month at work?

1 NO

2 YES----14a. Please describe the illness below.

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---

15. Have you ever had an infection (other than hepatitis) that you acquired at work?

1 NO

2 YES----15a. Please describe the infection below.

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16. Please describe any other job related health problems that you have had.

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THANK YOU FOR YOUR COOPERATION

## APPENDIX 2

STUDY OF THE HEALTH OF PHYSIOTHERAPISTSQUESTIONNAIREBACKGROUND INFORMATION

1. What is your sex?

1 MALE

2 FEMALE

2. When were you born?                                            
  Day      Month      Year

3. Where do you now live?                  
  City      Province

OCCUPATIONAL ENVIRONMENT

4. Which of the following types of facility best describes the type you were working in between 1976 and 1980? Indicate with a ✓ only one type of facility for each year.

1976      1977      1978      1979      1980

GENERAL TEACHING HOSPITAL

INDEPENDENT REHABILITATION  
HOSPITAL

NON-TEACHING HOSPITAL

PRIVATE PRACTICE

HOME CARE

QUESTIONS ABOUT YOUR FAMILY

5. Have you (or in the case of males your spouse) had a pregnancy in the last ten years?

1 NO

2 YES



APPENDIX 2 (continued)

6. Do you have children?

1 NO

2 YES

QUESTIONS CONCERNING YOUR HEALTH

7. Have you ever had hepatitis?

1 NO

2 YES----7a. When was that? \_\_\_\_\_  
Year

7b. What type of facility were you working in  
at that time?

\_\_\_\_\_  
Type of Facility

8. Do you suffer from dermatitis?

1 NO

2 YES

9. Are you allergic to any substances that you work with?

1 NO

2 YES----9a. What substances are these? (please list  
below)

- 1 \_\_\_\_\_
- 2 \_\_\_\_\_
- 3 \_\_\_\_\_
- 4 \_\_\_\_\_

APPENDIX 2 (continued)

10. Have you ever suffered from low back pain which required medical treatment?

1 NO

2 YES----10a. Was this the result of a work related event?

1 NO

2 YES----10b. Please briefly describe the event.

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11. Do you now smoke cigarettes?

1 NO

2 YES----11a. How many cigarettes do you smoke daily?  
(circle the number that applies)

1 LESS THAN TEN

2 MORE THAN TEN BUT LESS THAN TWENTY

3 BETWEEN ONE AND TWO SMALL PACKS

4 MORE THAN TWO SMALL PACKS

12. Have you ever had an illness that required you to miss more than one month at work?

1 NO

2 YES----12a. Please describe the illness below.

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APPENDIX 2 (continued)

13. Have you ever had an infection (other than hepatitis) that you acquired at work?

1 NO

2 YES----13a. Please describe the infection below.

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14. Please describe any other job related health problems that you have had.

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THANK YOU FOR YOUR COOPERATION

## APPENDIX 3

INTRODUCTORY LETTER TO INITIAL QUESTIONNAIRE

Dear Member

As announced in the December issue of the Canadian Journal of Medical Technology and Canadian Physiotherapy Association Journal, a study is being conducted jointly by the Canadian Society of Laboratory Technologists, Canadian Physiotherapy Association and the Department of Clinical Epidemiology and Biostatistics at McMaster University of the health of members of the two professions.

At the present time little is known about whether our professions pose any particular health risks. We are sending questionnaires to all members of the two participating organizations and it is important if the study is to be accurate that every questionnaire is completed and returned.

You are assured of complete confidentiality. The questionnaire has an identification number for coding purposes only and at no time will your name be released by the Canadian Society of Laboratory Technicians or Canadian Physiotherapy Association to the research personnel.

The results of this study will, when completed, be published in the Canadian Journal of Medical Technology and Canadian Physiotherapy Association Journal. Unfortunately our budget will not permit the mailing of individual copies of the results.

Thank you for your assistance.

## APPENDIX 4

FOLLOW-UP LETTER TO INITIAL QUESTIONNAIRE

Dear Member

As announced in the December issues of the Canadian Journal of Medical Technology and Canadian Physiotherapy Journal, a study is being conducted jointly by the Canadian Society of Laboratory Technologists, Canadian Physiotherapy Association and the Department of Clinical Epidemiology and Biostatistics at McMaster University of the health of members of the two professions.

At present little is known about whether our professions pose any particular health risks. We are sending questionnaires to all members of the two participating organizations and it is important if the study is to be accurate that every questionnaire be completed and returned.

Two or three weeks ago you were mailed a questionnaire concerning your health and occupational history. We have not yet received a completed questionnaire from you and are enclosing another copy in the event that the last one we sent did not arrive.

If you have already completed and returned a questionnaire, please accept our apologies for sending you this extra copy.

It is of vital importance to the success of this study that the highest possible number of Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association members participate in this survey so that we can identify health problems which may affect our two professions.

## APPENDIX 4 (continued)

Please be assured that as your name does not appear on the questionnaire and code lists are held by the Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association the information that you provide will remain anonymous.

## APPENDIX 5

STUDY OF THE HEALTH OF LABORATORY TECHNOLOGISTS AND PHYSIOTHERAPISTSPREGNANCY INFORMATION QUESTIONNAIREBACKGROUND INFORMATION

1. What is your sex?

1 MALE

2 FEMALE

2. When were you born?

\_\_\_\_\_  
Day\_\_\_\_\_  
Month\_\_\_\_\_  
Year

3. Where do you now live?

\_\_\_\_\_  
City\_\_\_\_\_  
ProvincePREGNANCY INFORMATION

*If you are male, please answer these questions based on your spouses pregnancy experience.*

4. Have you had a pregnancy in the last five years? (Circle your answer)

1 NO

2 YES----4a.

How many pregnancies have you had in the  
the last five years?\_\_\_\_\_  
number of pregnancies4b. In which years did your pregnancies begin?  
(Circle all the years below which apply)

1976

1977

1978

1979

1980

## APPENDIX 5 (continued)

5. Have you had a pregnancy or pregnancies in the last five years which ended in spontaneous miscarriage between the 8th and 20th week after the previous menstrual period? (Circle your answer below)

1 NO

2 YES----5a. How many of your pregnancies have ended in miscarriage? (Please write number below)

\_\_\_\_\_ number of miscarriages

5b. In which years did you have miscarriages? (Circle all the years below which apply)

1977

1978

1979

1980

1981

6. Were any children born to you in the last five years stillborn?

1 NO

2 YES----6a. How many of your children born in the last five years have been stillborn? (Please write the number below)

\_\_\_\_\_ number of stillbirths

6b. In which years did you have stillborn children? (Circle all the years below which apply)

1977

1978

1979

1980

1981



## APPENDIX 5 (continued)

7. Have you had any children born alive in the last five years who suffered from any congenital defect or birth abnormality?

1 NO

- 2 YES-----7a. How many of your children born in the last five years have had congenital defects or birth abnormalities? (Please write the number below)

       number of abnormal children

- 7b. In which years did you have children with congenital defects or birth abnormalities? (Circle all the years below which apply)

1977

1978

1979

1980

1981

- 7c. Which of the following categories of congenital abnormality was your child (children) born with? *Please write the year of birth of the child in the box beside each description.*

       DOWN'S SYNDROME/MONGOLISM

       DISORDER OF THE BRAIN OR SPINAL CORD

       HEART OR BLOOD VESSEL DEFECT

       LIMB ABNORMALITY

       CLEFT LIP OR PALATE

       DISORDER OF THE GASTROINTESTINAL TRACT

       SKIN ABNORMALITY

       MULTIPLE MALFORMATIONS

APPENDIX 5 (continued)

\_\_\_\_\_ OTHER (PLEASE SPECIFY BELOW)

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

OCCUPATIONAL HISTORY

8. Did you work as a laboratory technologist or physiotherapist at any time during your pregnancies?

1 NO

2 YES-----8a. What type of laboratory or practice setting did you work in during your pregnancies in the last five years? *Please fill in the approximate date that your pregnancy began and mark one box opposite the laboratory type or practice setting you worked in during each pregnancy with a ✓*

PREGNANCY NUMBER	1	2	3	4	5
DATE BEGAN	<u>        </u>	<u>        </u>	<u>        </u>	<u>        </u>	<u>        </u>
	Day Mo Yr	Day Mo Yr	Day Mo Yr	Day Mo Yr	Day Mo Yr

Type of Laboratory  
or Practice Setting

CLINICAL CHEMISTRY

MICROBIOLOGY

HAEMATOLOGY

IMMUNOHAEMATOLOGY

HISTOPATHOLOGY

RESEARCH

GENERAL LAB/  
ALL DISCIPLINES

VIROLOGY

APPENDIX 5 (continued)

PREGNANCY NUMBER	1	2	3	4	5										
DATE BEGAN	<u>Day</u>	<u>Mo</u>	<u>Yr</u>	<u>Day</u>	<u>Mo</u>	<u>Yr</u>	<u>Day</u>	<u>Mo</u>	<u>Yr</u>	<u>Day</u>	<u>Mo</u>	<u>Yr</u>	<u>Day</u>	<u>Mo</u>	<u>Yr</u>

TEACHING

IMMUNOLOGY

CYTOLOGY

ELECTRON MICROSCOPY

CYTOGENETICS

OTHER

GENERAL TEACHING  
HOSPITAL

INDEPENDENT REHAB.  
HOSPITAL

NON-TEACHING  
HOSPITAL

PRIVATE PRACTICE

HOME CARE

9. What was your spouses occupation at the time your pregnancies began during the last five years?

SPOUSES OCCUPATION

FIRST PREGNANCY \_\_\_\_\_

SECOND PREGNANCY \_\_\_\_\_

THIRD PREGNANCY \_\_\_\_\_

FOURTH PREGNANCY \_\_\_\_\_

## APPENDIX 5 (continued)

QUESTIONS ABOUT YOUR LIFESTYLE

10. Did you smoke cigarettes during any part of your pregnancies in the last five years?

1 NO

2 YES----10a. About how many cigarettes did you smoke daily during each pregnancy

NUMBER OF CIGARETTES DAILY

FIRST PREGNANCY \_\_\_\_\_

SECOND PREGNANCY \_\_\_\_\_

THIRD PREGNANCY \_\_\_\_\_

FOURTH PREGNANCY \_\_\_\_\_

11. Did you drink alcohol during any part of your pregnancies in the last five years?

1 NO

2 YES----11a. Please mark with a ✓ the box opposite the pregnancy number which best describes the amount of alcohol you consumed.

PREGNANCY	MORE THAN 5 DRINKS DAILY	1 TO 5 DRINKS DAILY	1 TO 5 DRINKS WEEKLY	RARELY	NEVER
FIRST °	_____	_____	_____	_____	_____
SECOND	_____	_____	_____	_____	_____
THIRD	_____	_____	_____	_____	_____
FOURTH	_____	_____	_____	_____	_____

APPENDIX 5 (continued)

12. Did you have any infections during any part of your pregnancies in the last five years?

1 NO

2 YES----12a. What was the infection?  
*Please describe below opposite the pregnancy number.*

TYPE OF INFECTION

FIRST PREGNANCY \_\_\_\_\_

SECOND PREGNANCY \_\_\_\_\_

THIRD PREGNANCY \_\_\_\_\_

FOURTH PREGNANCY \_\_\_\_\_

13. Were you prescribed any medication during any part of your pregnancies in the last five years?

1 NO

2 YES----13a. What was the medication or medications?  
*Please describe below opposite the pregnancy number.*

TYPE OF MEDICATION

FIRST PREGNANCY \_\_\_\_\_

SECOND PREGNANCY \_\_\_\_\_

THIRD PREGNANCY \_\_\_\_\_

FOURTH PREGNANCY \_\_\_\_\_

## APPENDIX 5 (continued)

14. Did you receive any diagnostic X-rays during any part of your pregnancies in the last five years?

1 NO

2 YES----14a. During which pregnancies?  
Please circle either YES or NO  
opposite the pregnancy number below.

FIRST PREGNANCY 1 NO

2 YES

SECOND PREGNANCY 1 NO

2 YES

THIRD PREGNANCY 1 NO

2 YES

FOURTH PREGNANCY 1 NO

2 YES

15. Did you wear a radiation film badge at any time during the last six years?

1 NO

2 YES----15a. Have you been told during the last six years that you have registered an exposure to radiation on your badge?  
Please circle YES or NO below.

1 NO

2 YES----15b. Did this exposure occur during one of your pregnancies? Please circle YES or NO below.

1 NO

2 YES

THANK YOU FOR YOUR COOPERATION IN COMPLETING THIS QUESTIONNAIRE

## APPENDIX 6

LETTER TO ACCOMPANY CONSENT FORM (DIAGNOSTIC INFORMATION)

Dear Member:

You have recently participated in an investigation of the health of laboratory technologists and physiotherapists.

This participation for which we are extremely grateful and which has yielded many valuable results has taken the form of completing two comprehensive questionnaires, the first concerning your own health and the second the outcomes of your pregnancies. As you know all of this information has been obtained and evaluated with your name remaining unknown to the researchers.

You have stated on the pregnancy information form that a child born to you was either stillborn or born with a congenital abnormality.

In order for us to obtain detailed diagnostic information vital to the completion of this study about the birth of your child we would like to ask your consent to request this information from your physician.

This information will only be used for the purposes of this study and will have any identification removed before being used in the study. If you would like to obtain more information anonymously about this study before signing the enclosed consent form please telephone (416) 525-9140, extension 2426, collect and request the information you require without giving your name.

Your contribution to the success of this study will be gratefully appreciated.

## APPENDIX 7

CONSENT FORM FOR DETAILED DIAGNOSTIC INFORMATION

I am asked to provide consent for medical information concerning me or my family to be released to Mr. N.W. Johnston of McMaster University.

I understand that this information will only be used to confirm diagnoses and that my name will not be associated with the information or stored electronically or in any other way.

The information requested relates to my pregnancy and the birth and health of my child and no other information is requested or is to be provided.

I \_\_\_\_\_ hereby give my consent for  
Your Name

Dr. \_\_\_\_\_ of \_\_\_\_\_  
Name of Your Doctor Doctor's Address

\_\_\_\_\_ to provide diagnostic information concerning my pregnancies and child

\_\_\_\_\_ born on \_\_\_\_\_  
Child's Name Child's Date of Birth

\_\_\_\_\_ Your Signature

\_\_\_\_\_ Today's Date



## APPENDIX 8

INTRODUCTORY LETTER TO PREGNANCY QUESTIONNAIRE

Dear Member:

Earlier in the year you very kindly completed and returned a questionnaire concerning your work and health history.

Thanks to you and your colleagues the response to the survey was excellent.

We are now contacting members of the Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association who reported that they or their spouse have had a pregnancy in the last five years to obtain further information to complete our study of the health of laboratory technologists and physiotherapists.

Information about pregnancies was not requested in the initial questionnaire because the majority of Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association members do not currently have children.

A study of this kind will only be accurate if most of the people surveyed respond. Please take the time to fill out and return the questionnaire. A pre-paid envelope has been enclosed for your convenience.

We realize that much of the information requested is of a highly personal nature. The information is however required if the study is to be successful in determining every possible aspect of the health of our professions.

You are assured of complete confidentiality. The questionnaire

## APPENDIX 8 (continued)

has an identification number for coding purposes only and at no time will your name be released by the Canadian Society of Laboratory Technologists or Canadian Physiotherapy Association to the research personnel.

While we would like to mail individual copies of the results of the study to all who participate, our budget will not permit this. The results will be published in the Canadian Journal of Medical Technology and Canadian Physiotherapy Association Journal.

## APPENDIX 9

FOLLOW-UP LETTER FOR SECOND MAILING OF PREGNANCY QUESTIONNAIRE

Dear Member;

Earlier in the year you very kindly completed and returned a questionnaire concerning your work and health history.

Thanks to you and your colleagues the response was excellent.

About three weeks ago we sent you a further health questionnaire relating to your pregnancy history. We have not yet received a completed copy of this questionnaire from you.

Information about pregnancies was not requested in the initial questionnaire because the majority of Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association members do not currently have children.


A study of this kind will only be accurate if as many people as possible respond. Please take the time to fill out and return the questionnaire. In the event that the first copy has been misplaced we are enclosing a replacement.

We realize that much of the information requested is of a highly personal nature. The information is required however if the study is to be successful in determining every aspect of the health of our professions.

You are assured of complete confidentiality. The questionnaire has an identification number for coding purposes only and at no time will your name be released by the Canadian Society of Laboratory Technologists or Canadian Physiotherapists to the research personnel.

## APPENDIX 9 (continued)

While we would like to mail individual copies of the results of the study to all who participate, our budget will not permit this. The results will be published in the Canadian Journal of Medical Technology and Canadian Physiotherapy Association Journal.



Canadian Society of Laboratory Technologists

(INCORPORATED UNDER FEDERAL CHARTER)

Official Registry of Medical Laboratory Technologists (Canada)

Association Canadienne des Technologistes de Laboratoire

(Incorporée en vertu d'une charte fédérale)

Régistre Officiel des Technologistes Médicaux de Laboratoire (Canada)

Mr. Neil Johnston  
Department of Pathology  
McMaster University  
1200 Main Street West  
HAMILTON, ON L8S 4J9

Telephone (416) 528-8642

P.O. Box 830

Hamilton, Ontario L8N 3N8

October 12, 1979

Dear Neil:

Further to our recent telephone conversation concerning your proposed survey of members of the C.S.L.T. concerning laboratory hazards, this will confirm that your proposal was referred to the Board of Directors of the C.S.L.T. for consideration during September 21-23, 1979.

The Board of Directors approved the following motions: "that Mr. Neil W. Johnston be authorized to conduct a survey amongst the C.S.L.T. members concerning some laboratory hazards as long as there is no direct cost involved to the C.S.L.T. Strict confidentiality of mailing lists or other information obtained from the C.S.L.T. must be assured"; and "that when the proposed survey of the C.S.L.T. membership by Mr. Neil Johnston re: occupational hazards on laboratory personnel becomes available that Mr. Neil Johnston be required to report his findings for publication in the Canadian Journal of Medical Technology".

I hope that the above actions will be of some assistance to you with the administrative actions you have to take now, and perhaps you could arrange to meet with Miss Booth and myself at some mutually convenient time during November for further discussions in this regard.

Yours sincerely,

A.R. Shearer  
Executive Director

ARS:mj

Canadian Association  
physiotherapy  
association

l'association  
canadienne de  
physiothérapie

June 18, 1980

Mr. Neil Johnston  
Department of Clinical  
Epidemiology and Bio-Statistics  
McMaster University  
1200 Main Street West  
Hamilton, Ontario  
L8N 3Z5

Dear Mr. Johnston:

I am pleased to advise you that the Executive Committee of the Canadian Physiotherapy Association at its recent meeting in Regina looked favourably upon your request that the membership of the Canadian Physiotherapy Association be utilized as a control group for your study of the relationship between laboratory work, its inherent chemical exposure and the genesis of birth defects.

The Committee did preface its agreement to your request with three conditions:

1. The study must be approved by an ethics committee,
2. There should be no cost to the Canadian Physiotherapy Association, and
3. The confidentiality of membership lists must be retained.

In our earlier telephone conversations, the mechanism whereby the confidentiality of the membership list could be maintained was discussed with you. I believe that I advised at that time we would be prepared to do the mailing to our members of the material with which you provide us.

I would be pleased to discuss this information with you further once the conditions have been accepted and where appropriate met. I look forward to talking with you further in this regard.

Yours truly,



Nancy Christie  
Executive Director

NC/pl

BUREAU OF EPIDEMIOLOGY  
SURVEILLANCE SYSTEM OF CONGENITAL ANOMALIES

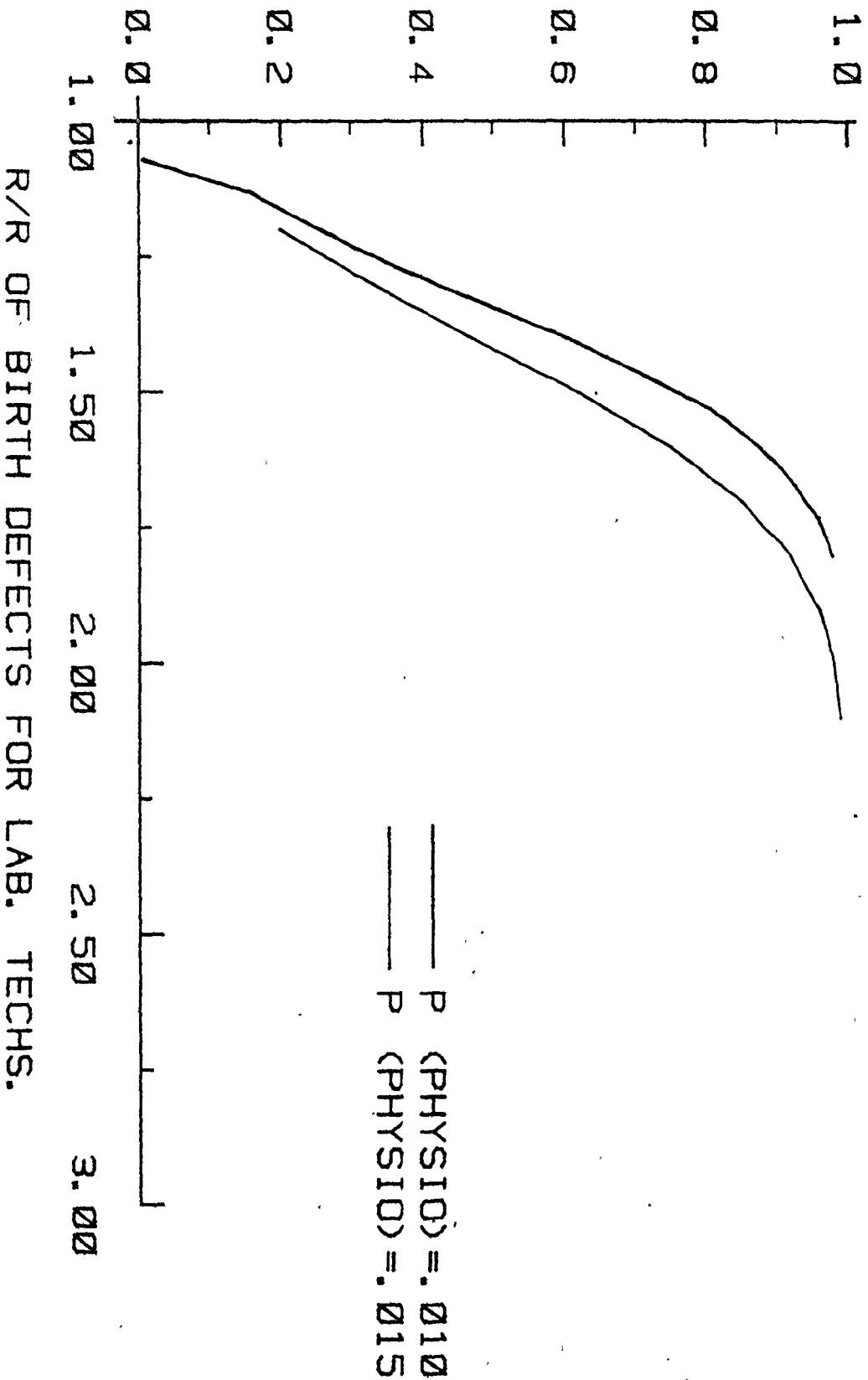
DATE OF PRINTOUT: 17 MAY. / 1979

31 DEC. 1978 TO 31 DEC. 1978  
NUMBER OF CONGENITAL ANOMALIES REPORTED (1), BY MONTH OF BIRTH  
NEW BRUNSWICK, ONTARIO, MANITOBA, ALBERTA, BRITISH COLUMBIA, P.E.I.  
1978

NO. CONGENITAL ANOMALIES (2)	MONTH OF BIRTH												TOTAL	PRCNT	RATE (3)
	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC			
1 HEMANGIOMA (OF SKIN)	11	12	17	18	20	10	10	15	18	12	12	167	3.0	7.5	
2 LYMPHANGIOMA	0	0	1	1	0	0	0	1	0	0	0	3	0.1	0.1	
3 PHENYLKETONURIA	0	1	0	0	0	0	0	0	0	0	0	2	0.0	0.1	
4 CONG DISORDERS AMINO-ACID METABOL	1	1	0	1	2	0	1	0	1	0	0	7	0.1	0.3	
5 CYSTIC FIBROSIS	0	0	0	0	0	0	1	0	0	0	1	3	0.1	0.1	
6 DISORDERS TOOTH DEVELOP & ERUPTION	0	0	0	0	0	1	1	0	0	0	0	2	0.0	0.1	
7 DENTO-FACIAL ANOMALIES	5	3	3	2	7	1	5	0	2	0	1	33	0.6	1.5	
8 INGUINAL HERNIA	5	4	2	1	2	3	3	4	0	0	1	3	28	0.5	1.3
9 UMBILICAL HERNIA & EXOMPHALOS	9	12	10	8	8	9	11	6	8	9	6	101	1.8	4.5	
10 VENTRAL HERNIA	2	0	0	1	0	1	1	1	0	1	0	7	0.1	0.3	
11 DIAPHRAGMATIC HERNIA	3	5	3	6	4	6	4	6	3	3	1	49	0.9	2.2	
12 HERNIA OF OTHER SITES	0	0	0	0	0	0	0	0	0	2	0	3	0.1	0.1	
13 PHIMOSIS	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	
14 ANENCEPHALUS	9	12	23	15	15	14	13	14	10	8	14	156	2.8	7.0	
15 SPINA BIFIDA WITH HYDROCEPHALUS	5	4	8	3	4	2	3	3	3	3	1	42	0.7	1.9	
16 SPINA BIFIDA	11	11	18	10	10	7	8	10	10	9	8	119	2.1	5.3	
17 CONGENITAL HYDROCEPHALUS	7	13	13	5	6	8	7	7	10	5	10	98	1.7	4.4	
18 ENCEPHALOCELE	2	1	3	0	1	0	2	1	2	3	1	17	0.3	0.8	
19 MICROCEPHALUS	7	3	1	2	1	2	1	1	1	0	1	24	0.4	1.1	
20 OTHER ANOM OF NERVOUS SYSTEM	2	1	0	1	2	0	0	0	1	3	2	12	0.2	0.5	
21 ANOPHTHALMOS & MICROPHthalmos	1	0	6	2	0	0	1	0	1	1	1	14	0.2	0.6	

POWER (1-B)

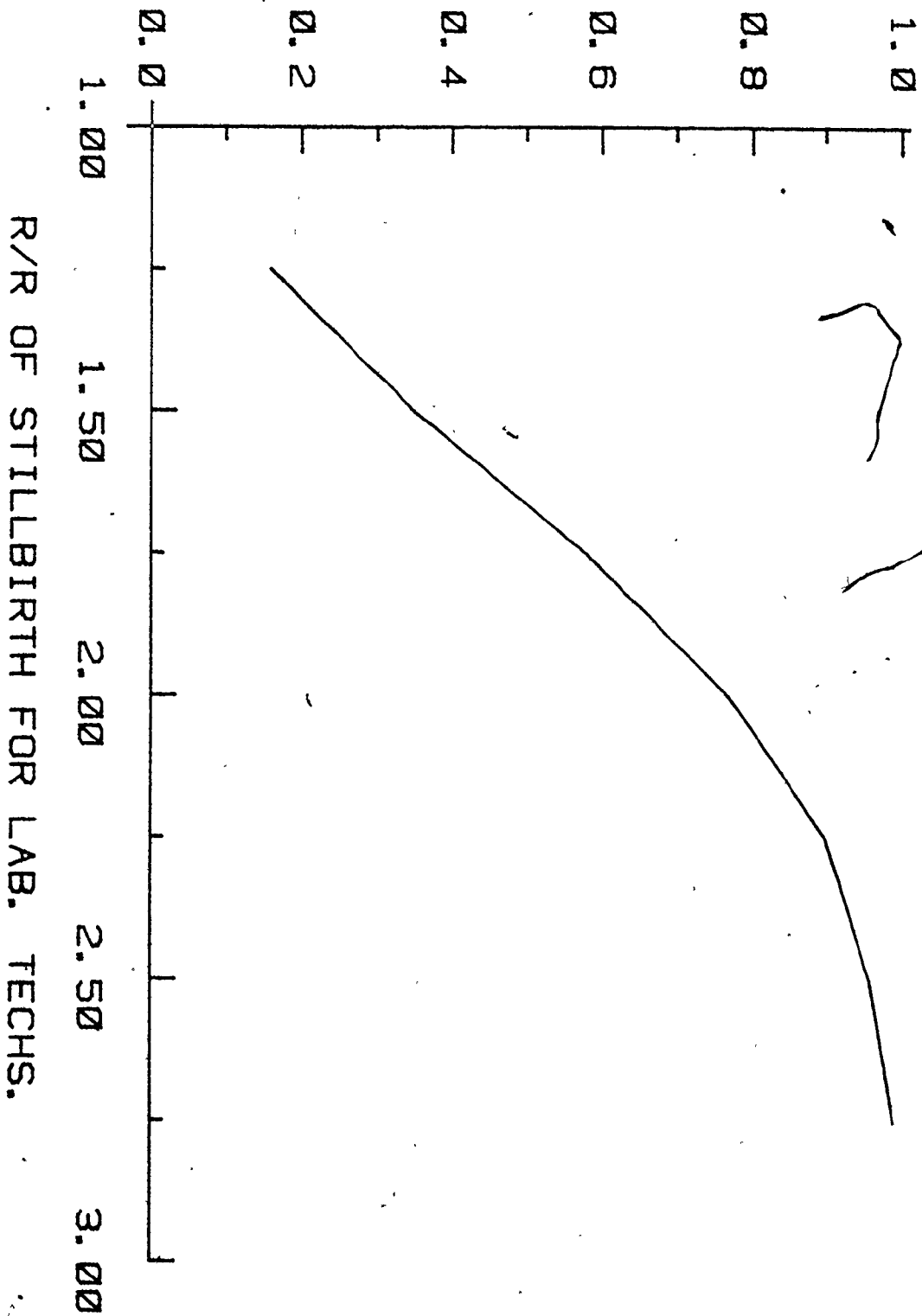
POWER OF STUDY TO DETECT DIFFERENT  
RELATIVE RISKS OF BIRTH DEFECTS





POWER (1-B)

POWER OF STUDY TO DETECT DIFFERENT  
RELATIVE RISKS OF STILLBIRTH



## APPENDIX 15

LETTER TO F.P.U. PATIENTS REGARDING PREGNANCY QUESTIONNAIRE PRE-TEST

Dear

We would like to ask your help in a study which is about to be conducted. This study will be examining the risks posed by certain occupations to the reproductive system and unborn children and will not be conducted by the Family Practice Unit but by a separate group of researchers in the McMaster University Health Sciences Centre.

One thing which is very important to find out before the study actually begins and the reason we are asking your help is to find out if the questionnaires that will be used in the study are clear and understandable.

In order to find this out, the questionnaire must be filled out by a group of people who have had pregnancies with many different results.

The reason that we are sending you this letter is to ask if you will help by completing one of the questionnaires.

We realize that this may evoke some painful memories for you and therefore if you do not wish to participate do not return the enclosed consent form and we will not send you a questionnaire. If however you are willing to help, please sign and return the consent form enclosed and we will send you the questionnaire shortly.

Under no circumstances will your name or address be released to the researchers and you will not be contacted at all except by mail.

## APPENDIX 16

CONSENT TO PARTICIPATE IN PREGNANCY QUESTIONNAIRE PRE-TEST

I am asked to take part in a study to find out if a questionnaire will be useful in a study which will take place at a later date.

I realize that I will receive no benefit from taking part in this test and that I am required to do nothing except fill in the questionnaire.

If I wish to change my mind about taking part in this test at any time I am free to do so and this will not be held against me in any way.

Information from my medical record may be used to check on the answers I give in the questionnaire but at no time will I be contacted by anyone except by mail.

PRINT NAME BELOW

I \_\_\_\_\_ hereby give my consent to take part in this test of a questionnaire.

---

YOUR SIGNATURE

TODAY'S DATE

## APPENDIX 17

LETTER TO BE SENT TO SUBJECTS PHYSICIANS TO OBTAIN

## MEDICAL RECORD INFORMATION

Dear Doctor

✓ Your patient \_\_\_\_\_ is currently participating in a study of the relationship of occupation and other factors to reproductive outcomes.

This study is being conducted by the Department of Clinical Epidemiology and Biostatistics at McMaster University and is supported by the Canadian Society of Laboratory Technologists and Canadian Physiotherapy Association whose members form the study population.

Mrs. \_\_\_\_\_ has stated in a questionnaire that a pregnancy or pregnancies of hers terminated in the birth of a stillborn child or child with a congenital abnormality. She has provided consent (copy attached) for us to contact you and request diagnostic information concerning her pregnancy and its outcome.

Would you please help us in completing the study by providing answers to the questions overleaf based on her medical record.

Your cooperation will be greatly appreciated and will greatly improve the likelihood that the study will be able to determine if either of the two occupations of medical technology and physiotherapy pose a threat to the reproductive process.

Thank you for your assistance.

## APPENDIX 18

## MEDICAL RECORD INFORMATION QUESTIONNAIRE

Patient's Name A. Subject Date of Birth 19-7-49

1. What was the outcome of Mrs. Subject's third  
no. of pregnancy  
pregnancy which terminated on date of birth 1977.

Please check one box with a ✓

Normal Child

Stillborn Child

Child with a Congenital Abnormality

- 1a. If a child was born with a congenital abnormality please check with a ✓ the box or boxes below which best describe the abnormality

Down's Syndrome

Disorder of the Brain or Spinal Cord

Cardiovascular Defect

Limb Abnormality

Cleft Lip or Palate

Disorder of the Gastro Intestinal Tract

Skin Abnormality

## APPENDIX 18 (continued)

Multiple Malformations

Other

- 1b. Please would you write below the specific diagnosis of the congenital defect(s) as recorded in Mrs. Subject's medical record.

---



---



---



---



---



---



---



---

Please answer the questions below based on the information recorded during Mrs. Subject's third pregnancy.

2. Did Mrs. Subject smoke cigarettes at any time during her third pregnancy (please check one box with a ✓)?

NO

NOT RECORDED

YES----2a. How many cigarettes did Mrs. Subject smoke per day during her third pregnancy?

\_\_\_\_\_ number of cigarettes smoked daily

## APPENDIX 18 (continued)

3. Was Mrs. Subject prescribed any medication during her third pregnancy?

(please check one box with a ✓)

NO

YES ----3a. What were the medications? (please list below)

---



---



---



---



---



---

4. Was Mrs. Subject given any X-ray examinations during her third pregnancy?

NO

YES

5. Did Mrs. Subject consume alcohol during her third pregnancy? (Please check one box below with a ✓)

NO

NOT RECORDED

YES ----5a. What quantity of alcohol did Mrs. Subject consume daily during her third pregnancy? (Please check one box with a )

AMOUNT CONSUMED NOT RECORDED

APPENDIX 18 (continued)

- UP TO 2 OUNCES OF PURE ALCOHOL/DAY  
(ie. 5 regular shots)
- OVER 2 OUNCES OF PURE ALCOHOL/DAY

6. Did Mrs. Subject suffer from any infection during her third pregnancy? (Please check one box below)

NO

YES ----6a. What was the infection?  
(Please describe below)

---

---

---

---

---

THANK YOU ONCE MORE FOR YOUR COOPERATION.