1970

An Epidemiological Study Of Childhood Cancer With Special Emphasis On Smoking During Pregnancy

Clasina Ineke Neutel

CANADA

NATIONAL LIBRARY OF CANADA

CANADIAN THESES

ON MICROFILM

BIBLIOTHÈQUE NATIONALE DU CANADA

THÈSES CANADIENNES

SUR MICROFILM

No 6349

NL-101(1/66)

A STUDY OF THE EPIDEMIOLOGY OF CHILDHOOD CANCER WITH SPECIAL EMPHASIS ON SMOKING DURING PREGNANCY

by

Clasine Ineke Neutel, M.Sc.
Department of Community Medicine

A thesis submitted in partial fulfillment
of the requirements for the degree of
DOCTOR OF PHILOSOPHY

FACULTY OF GRADUATE STUDIES
THE UNIVERSITY OF WESTERN ONTARIO
LONDON, ONTARIO
MARCH, 1970

This research was supported by a grant from the Ontario Cancer Foundation, which assistance is gratefully acknowledged.

ACKNOWLEDGEMENTS

The writer wishes to express her gratitude to Professor Carol Buck for her invaluable guidance and encouragement; to Miss M. D. Neilson and Dr. Elizabeth MacKay of the Ontario Department of Health, and to Mr. Humphries, Deputy-Registrar of Ontario for providing essential parts in the process of linking cancer cases with the Ontario Perinatal Mortality Study; to the staff of the Ontario Cancer Clinics for their cooperation; to Dr. Eva Alberman and the National Birthday Trust Fund, and the National Study of Physically Handicapped Children of the National Bureau for Cooperation in Child Care for providing the data of the British Perinatal Mortality Survey; to Mrs. Violet Bacsi and Mrs. Jo Brown for technical assistance; to my husband Walter Neutel for unfailing encouragement.

CONTENTS

CONTENTS (Continued)

CONTENTS (Continued)

LIST OF TABLES

LIST OF TABLES (Continued)

LIST OF TABLES (Continued)

ABSTRACT

In this study the development of cancer in childhood was related to events occurring during the relevant pregnancy and delivery of the mother. Of particular interest was the investigation of a possible association between smoking during pregnancy by the mother and an increased risk of cancer in the offspring. Previous studies providing the results which suggested that this hypothesis was a tenable one, were those showing a relation between: smoking and lung cancer because it indicated the carcinogenicity of tobacco smoke for humans; smoking and bladder cancer because it demonstrated that the carcinogen circulates throughout the body; smoking in pregnant women and an increased prematurity rate because it shows a direct effect of smoking on the fetus albeit not carcinogenic; and smoking and an increased activity of 3,4-benzpyrenehydroxylase in human placentas because it suggests that a carcinogen is active in proximity to the fetus.

In addition, many other variables during the pregnancy and delivery of the mothers were investigated for a possible association with increased cancer rate in the offspring. Some of these variables have been examined previously in other studies, while others have not.

For this purpose the data on the 73,099 births of the Ontario Perinatal Mortality Study and the 16,350 births of the British Perinatal Mortality Survey, surviving seven days or more were used. These

populations were followed from birth to seven to nine years and a total of 97 cancer cases were found -- 65 deaths and 32 survivors.

The children of mothers who smoked during the relevant pregnancy did have a somewhat higher cancer rate than children of nonsmokers but this could not be shown to be statistically significant. A tripling in cancer rate for the children of smokers can be excluded, which is important in view of the greater increase of lung cancer risk found among smokers.

Among the other variables investigated the maternal blood group provided the most interesting results. Among the maternal ABO blood groups, B and AB showed the highest childhood cancer rates and when considering Rh factor the mothers with Rh negative blood had the highest cancer risk in their children. The maternal blood group distribution for children with cancer was compared to that found for infants with hemolytic disease of the newborn due to Rh isoimmunization.

A number of suggestions for further research were made on the basis of the other variables investigated.

INTRODUCTION

At present very little is known about the causation of cancer in general, and childhood cancer in particular. Yet cancer has the second highest mortality rate in childhood, behind accidental deaths, now that the mortality due to infectious disease has been reduced so drastically.

A number of previous studies relating childhood cancer with prenatal factors have been executed by various research groups. The most notable result of these was the demonstration of a relation between in utero irradiation and subsequent development of cancer in childhood. In some of these studies the information about irradiation and other variables was obtained from mothers of cancer and control children and therefore the possibility of differential maternal recall existed. A prospective study does not have this disadvantage since the information is recorded prior to the development of cancer.

For the present study, extensive records were available for the 73,099 births, surviving seven days, of the Ontario Perinatal Mortality Study in 1959-60. Later these were supplemented by similar records available for 16,350 survivors of the British Perinatal Mortality Survey, recorded in 1958. Among the information recorded on these births, the data on the smoking habits of the mothers during pregnancy were supplied. Since similar information has not been avail-

able elsewhere, this was a unique opportunity for a prospective study of smoking during pregnancy in relation to childhood cancer. In addition many other prenatal variables not previously studied, could be related to the childhood cancer risk as well.

LITERATURE SURVEY

I. The Possibility of Increasing the Risk of Childhood Cancer through Smoking during Pregnancy

A. Carcinogenicity of Tobacco Smoke:

The study of the carcinogenic properties of tobacco smoke or its components has benefitted greatly by various types of animal experiments. Most of these have been summarized in Wynder & Hoffmann's book Tobacco and Tobacco Smoke (1967, p. 258-315), showing in a table the pertinent data from studies performed between 1928 and 1963. Those with the most consistent results were published since 1953 and in these cancer was produced either by painting tobacco smoke condensate on the shaved skin of mice, or by subcutaneous injection of the condensate. Many of the components found to be carcinogenic are listed in the Report to the Surgeon General of the U.S. (1962) on Smoking and Health which rates the polycyclic hydrocarbons isolated from tobacco smoke as being among the most potent of carcinogens known. Yet the total tumorigenic potency of the smoke condensate is many times that of even these potent carcinogens. This could be explained by supposing that some of the components, not themselves carcinogenic, may potentiate the effect of the carcinogens present in the tobacco smoke.

The importance of the animal experiments lies in showing consistently that tobacco smoke is carcinogenic and in identifying those components which are the most powerful in this respect. Examples of the

latter are benzo(a)pyrene, dibenzo(a,i) pyrene. In spite of the usefulness of the animal experiments, the effect on humans can only be inferred from studying humans exposed to tobacco. Obviously, an entirely different approach has to be used and epidemiological studies are one answer to the problem.

The relation between the smoking of tobacco and the increased risk of cancer has been shown most spectacularly by the excess of lung cancer among chronic smokers. In spite of some continued controversy among proponents and opponents of the theory, sufficient reliable studies have been conducted to establish the relation between habitual smoking and subsequent development of lung cancer with reasonable certainty (e.g., Wynder & Graham, 1950, Doll & Hill, 1956, Hammond & Horn, 1958). Much has been written about this relation and for this reason it is not necessary to elaborate here.

The development of lung cancer after prolonged smoking could possibly be explained by the direct contact, including some degree of mechanical irritation, of the components of tobacco smoke with pulmonary tissue. However, if smoking by a pregnant woman is to affect the offspring at a later age, compounds originating in the tobacco smoke or metabolites of such compounds would have to circulate within the body in order to travel from the lungs to the placenta as well as be able to penetrate the placental barrier.

The probability of the circulation of tobacco components throughout the body is supported by the likely association of cancer of the bladder with smoking. In 1964, Lilienfeld reviewed four retrospective and three prospective studies, of which all but one prospective study

showed such a relation. The latter (Doll & Hill, 1956) included cancer of the bladder in the category "cancer of other sites". Thus if the other cancers included bore no relation to tobacco smoking they might well have obscured a relation between cancer of the bladder and smoking. Lilienfeld concluded that although the evidence was not sufficiently strong to prove a causal relationship between smoking and cancer of the bladder, additional research would probably show this to be the case. This hypothesis is strengthened by the extremely high rate of bladder cancer among workers occupationally exposed to certain chemicals such as some of the aromatic amines. In this case the development of cancer seems to be induced by excretion of the metabolites of the chemical compounds to which the worker is exposed. The same mechanism could occur in smokers and further work in analysing and identifying chemicals present in the urine of smokers but not in the urine of nonsmokers would be very useful. Differences such as the presence of acetonitrile, an increase in polonium 210 (Wynder & Hoffmann, 1967) and different end products in tryptophan metabolism have already been found (Kerr, Barkin, Levers, Woo & Menczyk, 1965).

Evidence from a different approach to the problem was supplied by Fraumeni (1968). He examined the sales of cigarettes as estimated from state tax receipts in the various states of the U.S.A. and compared this to the mortality of bladder cancer in the same states. Per capita cigarette sales correlated highly with bladder cancer rates in the area. Although this does not prove a direct relation it does help to strengthen the case in providing additional evidence.

B. The Effect of Smoking in Pregnancy:

Recent papers brought the evidence closer to the fetus (Welch, Harrison & Conney, 1962, Welch, Harrison, Gommi, Poppers, Finster & Conney, 1969). They described a study in which they examined placentas of smokers and those of nonsmokers for the presence of 3,4-benzpyrene hydroxylase, an enzyme which hydrolyses the potent carcinogen 3,4 benzpyrene. The placentas of 17 smokers and 17 nonsmokers were either tested immediately or placed in a freezer and assayed for 3,4-benzpyrene hydroxylase activity within 48 hours. It could be shown that the freezing process did not affect the results. None of the placentas of the nonsmokers showed any detectable 3,4-benzpyrene hydroxylase activity while all the placentas of the smokers did. A consistent dose-response curve could not be shown since variations in enzyme activity were present even among women smoking the same number of cigarettes per day. Welch pointed out that this could be explained by (i) different amounts of 3,4-benzpyrene and other polycyclic hydrocarbons present in the different brands of cigarettes, (ii) different habits of inhaling smoke, (iii) individual differences in response. The repetition of this study by giving known amounts of 3,4-benzpyrene orally to pregnant rats did give a consistent dose-response of increased 3,4-benzpyrene hydroxylase activity with increased amounts of 3,4-benzpyrene.

Thus cigarette smoke is capable of inducing a placental enzyme which will metabolize a potent carcinogen. This might be expected to act as a protection of the fetus since the metabolic products have been shown by Berenblum & Schoental (1943) to be less carcinogenic than the original compound. Nevertheless, as Welch et al (1969) assert, a complete

protection is not necessarily afforded since possibly not all the 3,4-benzpyrene is removed from the body before doing any harm. For our purposes this study is strong evidence that a potent carcinogen does invade the placenta and could reach the fetus.

Whether the carcinogen itself crosses the placenta and affects the fetus has not been shown explicitly but that the fetus is affected in some ways by the smoking of the mother is becoming increasingly clear. A number of studies have been published which demonstrate a significantly lower average birth weight for infants of smokers than for infants of nonsmokers. A few of these studies will be mentioned here. In 1963 O'Lane published a study of 1031 Caucasian women with single, vaginal deliveries, showing that the 465 women who were smokers had a prematurity rate double that of the 566 women who did not smoke. Also of interest are factors for which no significant differences were found between smokers and nonsmokers: maternal weight gain during pregnancy, placental weight, or length of gestation. Thus the lighter weight of infants of smokers cannot be explained by a decreased maternal food intake, or by a shorter gestational period.

Comstock & Lundin (1967) studied all perinatal deaths and 3% of all live births in Washington County, Maryland. The birth weights of live infants of smoking mothers varied with the amount smoked but were on the average 200 grams lighter than that of the infants of nonsmoking mothers. The excess deaths that could be demonstrated among infants of smoking mothers disappeared on adjusting for birth weight. Still Comstock & Lundin hesitated to postulate a causative effect between smoking in pregnancy and a direct effect on the fetus and suggested a common

association with another factor, e.g., adequacy of medical care.

MacMahon, Alpert & Salber (1965) investigated 16,741 single white births and detected a mean decrease of 10 ounces in the weight of babies born of smoking mothers when compared to the offspring of non-smoking mothers. Those mothers who smoked before, but not during the pregnancy, had infants of weight similar to infants of nonsmokers, implying that the effect is on the fetus itself rather than the parental germ cells or the maternal constitution.

Among others who have found a decreased birth weight for offspring of smokers are: Savel & Roth (1962), Ravenholt, Levinsky, Nellist & Takenga (1966), Yerushalmy (1964), Jarvinnen & Osterlund (1963), Zabriskie (1963), Lowe (1959). Zabriskie suggested that the vasoconstrictor effect of smoking which has been shown in the extremities of smokers could also alter the blood supply to the placenta and thus decrease the supply of nutrition to the fetus. Another possibility is a toxic effect of the components of tobacco smoke or their metabolites crossing the placenta and retarding the growth of the fetus even in the presence of sufficient nutrition.

This section may be summarized by concluding that tobacco smoke does have carcinogenic components which circulate throughout the body and may cause cancer in parts of the body other than the lung. In addition the fetus is affected directly or indirectly by components of tobacco smoke. That prenatal factors are able to increase the risk of childhood cancer has been suggested in various studies, especially those showing a relation between X-radiation in utero and a higher rate of cancer in children. These studies will be discussed in more detail below.

Therefore it is reasonable to postulate that smoking in pregnancy might increase the risk of childhood cancer.

II. Other Factors in the Epidemiology of Childhood Cancer

Many environmental and genetic factors have been studied and discussed in connection with the epidemiology of childhood cancer. However, this literature survey will be confined mainly to prenatal and other factors which can be recorded at birth, in order to include only material relevant to the present study.

In order to eliminate some repetitive statements, most of the studies mentioned have been summarized in Table I with respect to the sources of their data.

A. Sex Distribution:

As will be seen in this section most investigators have found an excess of male children when studying childhood cancer. This relation holds for the most common childhood cancers - leukemia and cancer of the nervous system - and for the overall cancer rates. No such consistent results have been found for other types of cancers. These other cancers are often grouped together under one heading, and a fair amount of variation probably exists from one study to another in the proportion of children with the more specific diagnoses. Most studies dealing with the epidemiology of childhood cancer give the number of male and female children among their cancer cases. Not all studies will be mentioned here but still sufficient to show the most common sex distribution and some studies showing differences in either direction.

One of the most informative and best executed of such studies is

TABLE I

Some Previously Published Studies on the Epidemiology of Childhood Cancer

Authors	Year Published	Total Number of Cases	Age Range	Geographic Area of Study	Diagnosis	Control Group
Ager et al	1965	112	0 - 4	Minnesota	Leukemia	(i) Matched Siblings (ii) Neighbourhood Child
Ederer et al	1965	39,235	0 -14	U.S.A.	Any cancer	All U.S. of same age
Elliott et al	1961	258	Children	Colorado	Leukemia	All U.S.
Ford et al	1959	152	0 - 9	Louisiana	Any cancer	306 died of other causes
Fraumeni et al	1968	21,659	Newborn	U.S.A.	Any cancer	All births in U.S.A.
Gibson et al	1968	170	1 - 4	Minnesota, New York, Maryland	Leukemia	236 stratified random sample
Graham et al	1966	319	0 -14	Minnesota, New York, Maryland	Leukemia	884 stratified random sample
Hernandez & Tokuhata	1966	133	0 -19	Tennessee	Leukemia Lymphsarcoma	Per population

Table I (Continued)

Authors	Year Published	Total Number of Cases	Age Range	Geographic Area of Study	Diagnosis	Control Group
Iverson	1965	628	0 -14	Denmark	Leukemia	Per population
Knox	1964	185	0 -14	Northumberland and Durham	Leukemia	Per population
MacMahon	1962	566	0 -13	9 Northeast U.S.A. States	All cancer	Prospective study 7,242 births
MacMahon & Newill	1962	4,198	0 -11	Northeast States	All cancer	All births
Manning & Carroll	1957	323	0 -14	Boston, Mass.	All cancer	50 patients at an orthopedic clinic
Miller et al	1968	1,362	0 -14	All U.S.A.		Per population
Pinkel et al	1963	206	0 -16	Buffalo, N.Y.	Solid Tumours	97 traffic fatalities - same age
Pinkel & Nefzger	1959	137	0 -15	Buffalo, N.Y.	Leukemia	Per population
Sessions et al	1964	761	0 -20	Tennessee	All cancer	
Stewart, Webb & Hewitt	1958	1,416	0 - 9	England and Wales	Any cancer	1,416 matched controls

a prospective study by MacMahon (1962). Among his base population he found 50.7% males while among the cancer cases 58.0% males. When divided into smaller ranges of diagnoses, 58.2% of leukemia patients and 58.3% of patients with tumours of the central nervous system were males. Others finding 58% and 59% of males among their youthful cancer patients were the following: Knox (1964), studying leukemia patients in Northumberland and Durham counties in England; Iversen (1965), among leukemia children in Denmark; Sessions, McSwain, Stephenson (1964), among 761 cases with all types of cancer in Nashville, Tenn.; Pinkel, Dowd & Bross (1963) among 206 children with solid malignant tumours in Buffalo area.

A somewhat lower percentage of males but still significantly higher than expected was found by Graham, Levin, Lilienfeld, Schuman, Gibson, Dowd & Hempelman (1966) in whose study 56.7% males were present and by Ederer, Miller & Scotto (1965) who examined 39,235 death certificates of children who died of any cancer and found 55.5% males.

Two papers giving figures on either side of the 55-60% range are Pinkel & Nefzger (1959) who found 51.1% males among young leukemia patients in Buffalo, and Hernandez & Tokuhata with 62.4% males among 133 cases of leukemia and lymphosarcoma.

A variation in the proportion of males within one study was found by Miller, Fraumeni & Hill (1968) who studied death certificates of children who died of neuroblastoma in the years 1960-1964 and noticed that the sex ratio for children under 5 years shifted from 1.68 (approximately 63% males) in 1960 to 1.11 (approximately 53% males) in 1964. This trend was found to be statistically significant at $p < 0.02$.

As an explanation for this, he postulated a possible selective response by sex to a new treatment, or to a new oncogenic agent in the environment.

From the above it may be concluded that males have a higher risk of childhood cancer than females of the same age. This is not surprising since males are known to have an increased risk of many other diseases as well.

B. Birth Order Effect:

The effect of birth order on childhood cancer risk is not easy to evaluate because of the difficulty in obtaining a representative control group in a retrospective study. In the study of sex distribution and childhood cancer risk, national birth statistics can often be used as a norm. However, when studying birth order, the use of the birth statistics may be misleading. The proportion of first-born among all births may vary from one year to the next. This is especially true when the scope of the study includes births in the 1940's and 1950's and is complicated by the fact that cancer mortality shows a peak in the third and fourth year of life. This may be one reason for the variation in proportion of first born from one study to another (in addition to geographic and ethnic variations).

Another problem is the definition of birth order. It may be defined either as the number of older living siblings, or, at the other extreme, as the number of all previous pregnancies including abortions. Most commonly, birth order refers either to previous live births, or to all previous pregnancies which progressed past a certain stage. The

published papers do not always mention the particular meaning used especially when birth order is not their primary interest. As will be discussed in another section, some evidence has been accumulated that mothers of children with cancer have an increased rate of previous stillbirths and abortions and thus the decision as to counting these in determining birth order may change the results.

The majority of studies dealing with the relation of birth order and childhood cancers indicate an excess of first-born when compared to a control group. Stewart, Webb & Hewitt (1958) found 39.3% first-born among all cancer deaths while only 32.9% among controls. However, they concluded that the control group was deficient in first-born since the national average for that time period was about 38.5% first-born. The reason given was that the control group was selected in such a way that a smaller number of mobile families was included than in the families of cases. Since the smallest families are more likely to be mobile, the control group would have larger families than expected and therefore the control child is less likely to be the oldest. Even when compared with the population at large, a 70% excess in first-born was found among children who died of lymphatic and blast cell leukemia and a 10% increase for other leukemia.

An excess of first-born was also obtained among cancer cases in MacMahon's prospective study (1962). The study population consisted of all children born in, and discharged from 37 hospitals in 1947 to 1954. The cancer group consisted of all subsequently identified cancer deaths born in these hospitals within the specified years while the control

group used in the analysis was a 1% random sample of the study population. The control had 36.2% first-born while the cancer group had 42.8%. When subdivided into narrower ranges of diagnoses 44.4% of leukemia patients and 44.1% of children with cancer of the nervous system were first-born.

Two other studies may be mentioned in which was found a decreasing cancer risk with increasing birth order. Stark and Mantel (1966) found an excess of first-born among their leukemia cases, while Ford, Paterson & Treuting (1959) noted 39.1% first-born among leukemia cases, 31.5% among other cancers and only 25.2% among controls.

However, not everyone has obtained results in agreement with the above. Graham et al (1966) found an excess of first-born among his leukemia cases but only among those born prior to 1950 and an excess of first-born among controls of those born after that date. For the latter excess they blamed an unrepresentatively large proportion of first-born in their control group which was larger than expected when compared to New York birth statistics.

A few others also found a smaller percentage of first-born among children with cancer. Manning & Carrol (1957) had 36.7% first-born among leukemia, 35.6% among lymphoma patients and 39.7% among those with other cancers, as opposed to 43% first-born among the 50 controls. But this control group could be criticized, firstly, because it was a small group, and, secondly, because the members of the control group were all patients of an orthopedic clinic and thus may have had characteristics peculiar to their illness. Ager, Schuman, Wallace, Rosenfield & Gullen (1965) studied children who had died of leukemia in Minnesota and found

25.0% were first-born as opposed to 30.4% of neighbourhood controls, matched for sex and age. On studying the birth statistics for Minnesota, they decided that the proportion of first-born among their controls was abnormally high and should be about 24.0%, which is very near, and even slightly below that of the leukemia patients in their study.

The above summary of some of the epidemiological studies of the effect of birth order on the risk of childhood cancer seems to favour an excess of first-born in the cancer group. However, before any definite conclusions can be drawn, the effect of maternal age has to be considered.

C. Maternal Age:

Results of studies of the effect of maternal age on the risk of childhood cancer have varied from finding an increased risk with increasing maternal age to finding no effect of maternal age. As with birth order, a major problem is a representative control group for comparison. Stewart et al (1958) made no attempt to use their control group but compared the age of the mothers of leukemic children with the ages of mothers of children with other cancers. The mothers of leukemic children were on the average 25 weeks older than the mothers of children with other cancers, in spite of the fact that the latter group included a smaller proportion of first-born children. This effect persisted when mothers of children with Down's syndrome were removed from the analysis. Further examination of the data revealed that the effect was due mainly to a small group of mothers over forty.

A similar excess of older women among mothers of leukemic children

was found by Manning & Carroll (1957) but they also found an excess of younger women among mothers of children with other cancers when compared with their control group. However, as mentioned above, their control group was small and unrepresentative. A higher average age was also demonstrated for mothers of Minnesota pre-schoolers who died of leukemia (Ager et al, 1965) when compared with their neighbourhood controls. Again the effect persisted after removing mothers of children with Down's syndrome.

Opposed to the studies detecting an increased risk of childhood leukemia with increasing maternal age, are several others which did not show any significant change. MacMahon (1962) found no statistically significant increase of risk with increasing maternal age, nor did Graham et al (1966) in the tristate leukemia survey. In these studies the average maternal age was not calculated as in the others mentioned above, and the main reason for considering maternal age at all was to ascertain whether it would affect other results. MacMahon & Newill (1962) working with larger numbers did find a 40% higher risk for women over forty than for those under twenty, this effect being independent of birth order.

The best conclusion after considering the literature seems to be that there is a relatively small increase in the risk of childhood cancer, and in particular of leukemia, with increasing maternal age. It is obvious that birth order and maternal age are closely related but their effects on cancer rate appear to be separate, not only because several studies have standardized for one and found the effect of the other to persist but also because the effects of the two variables are in opposite

directions, and one would thus serve only to diminish that of the other.

D. Birth Weight:

Birth weight has been mentioned in only a few epidemiological studies of childhood cancer. Ager et al (1965) mentioned it in their study of Minnesota childhood leukemia deaths. Among their leukemia deaths three out of 112 children were under 2500 gms at birth while two out of 113 matched neighbourhood controls and none of the sibling controls were premature at birth. The smallness of these numbers prevents the drawing of any conclusions. More definite results were obtained by MacMahon & Newill (1962) who found that the birth weight of the cancer patients was on the average slightly higher than that of the comparison births which consisted of the next birth on file after the birth certificate of the cancer death. This difference occurred for all diagnostic categories and on computation was found to be statistically significant. MacMahon & Newill explained this result by pointing out that the cancer victims had survived sufficiently long to develop cancer while the comparison group only needed to be live-born. Some of the latter probably died of conditions associated with prematurity, thus in effect removing them from the population at risk of developing childhood cancer. After removal of these low-weight infants, the remainder of the population would have a higher average birth weight.

Thus no general conclusion can be drawn on the presence of a relation between birth weight and childhood cancer risk.

E. Socioeconomic Class:

The study of socioeconomic levels in conjunction with childhood cancer is significant in that a relation might indicate the importance of environmental, rather than prenatal, or genetic, factors. A difficult problem in the execution of such a study is a consistent definition of socioeconomic class. The lack of such consistency is probably an important cause of variation in results from one study to another.

Stewart et al (1958) based their index of social class on occupation and income. They found no difference between the leukemia cases and their matched controls, nor between the children with other cancers and their controls. Since the families of the control children moved less often than the families of the cancer patients and since mobility may be related to socioeconomic class, they made a separate comparison of the cancer cases who had moved since birth with their controls, but the same results ensued.

In the tristate leukemia survey Graham et al (1966) also used occupation and income as a measure of socioeconomic class. Like Stewart et al, they found no difference between the cancer group and the control group. In this study the controls had been chosen by stratified random sampling from census tracts which were representative of the areas from which the leukemia patients originated (Graham, Levin, Lilienfeld, Dowd, Schuman, Gibson, Hempelman & Gerhardt, 1963).

A different method of obtaining a distinction between a higher and lower level of socioeconomic class was to use pay status in the hospital at delivery, assuming that the more affluent mothers would tend to be private patients. This method was used by MacMahon (1962) and he was

able to show a significantly increased risk for children of the private patients when compared to children of the clinic patients.

The most frequently used method of measuring socioeconomic class when analysing its effect on childhood cancer risk has been the grouping of census tracts with respect to average income, standard of housing, etc. This was the method used by Elliott, Githens & Saunders (1961) in their investigation of childhood leukemia deaths in Colorado. They calculated rates for the different census tracts by using Colorado statistics for the base population. In general they found that the more favourable the conditions in the census tracts, the greater the risk of leukemia: the highest income tracts had double the rate of the lower income tracts; those census tracts in which the least crowding occurred had triple the rates of those in which the most crowding occurred; the census tracts with the best sanitation system had double the rates of census tracts with worse sanitation. All these factors are closely related to one another and give only a general indication of increased leukemia risk with higher socioeconomic level.

Two other papers have demonstrated the same relation. Hernandex & Tokuhata (1966) used the census tracts in Memphis and found a greater risk of cancer in the better census tracts. Pinkel et al (1963) discovered that the upper economic half of the Buffalo population had double the risk of childhood neuroblastoma than did the lower half and in 1959 he showed the same relationship for leukemia deaths in Buffalo (Pinkel & Nefzger, 1959).

It is interesting to note that the two studies which did not find a relation between cancer risk and socioeconomic class are the ones that

used occupation and income of father as an index of socioeconomic class, while the studies that found a definite relation used census tracts differences, or hospital pay status. A variation in accuracy of diagnosis from one socioeconomic level to another should be considered. It is quite possible that medical care and thus accuracy of diagnosis is of a better quality in the better census tracts than in the poorer tracts. Thus some of the leukemia, or other cancer cases, could be missed in the poorer areas causing a difference in rates among the classes. However, if this were the sole explanation for the difference in rates between census tracts, it is difficult to account for the fact that there is no difference in rates when socioeconomic class is based on the father's occupation and income. The difference in rates between census tracts appears to indicate that the environment as such is more important in determining cancer risk than factors such as education and income by themselves.

F. Clustering in Space and/or Time:

In spite of the data available for the present study not being suitable for studying a possible clustering of cases, a short discussion of a few typical studies which have been published will be useful, and may be related to the distribution of cases among social classes and among urban and rural areas. Clustering has been studied by two main approaches: (i) by studying unusual aggregations of cancer cases; (ii) by taking a defined area, e.g., a large city, or a county, or a state, and pairing cases according to proximity in space (or time) and then deciding whether the pairs are closer in time (or space) than can be expected

by chance.

A study using the first method is that of Heath & Hasterlik (1963). This is the often quoted study in Niles, Illinois, in which 8 cases of leukemia were diagnosed within a few years, all attending, or being closely connected to, the same elementary school. The authors could not find a common factor to explain this occurrence but did suggest that epidemiologic characteristics hinted at an infectious process.

In evaluating the type of situation described above, several possibilities must be considered: (i) such situations attract attention because they are unusual; (ii) the numbers are often small and slightly different treatment, e.g., different boundary lines, might give entirely different results; (iii) if these are legitimate clusters, the cause of this grouping of cases may not be representative of all childhood leukemia.

The second approach which is probably more indicative of clustering as a generally occurring phenomenon, investigates the childhood cancer cases in a predefined area. The cases are then paired according to proximity and a variety of statistical methods have been used to decide if the time and space distances are less than expected. Pinkel et al (1963) and Pinkel & Nefzger (1959) found an excess of pairs less than 1/8 mile apart in Buffalo, N.Y. The first paper dealt with solid tumours and the second with leukemia. The same method when applied to 97 traffic deaths did not show any evidence of clustering. Ederer, Myers & Mantel (1964) criticized the methods used in the above papers and developed a method which did show clustering for polio and infectious hepatitis but not for leukemia. However, this included leukemia cases

of all ages and not only children.

Knox (1964) studied childhood leukemia in Northumberland and Durham counties in England and found an excess of pairs of children under six years with onset up to two months apart at a distance of less than two kilometers. An excess of pairs of children less than 250 days and four kilometers apart was found in the state of Oregon by Meighen & Knox (1964).

The above summary does suggest the possibility of some cancer cases occurring closer together than is to be expected by chance, although controversy continues over the method. Just how to interpret such an excess of pairs is an additional problem. There is no apparent connection between the cases in spite of their proximity. In the papers mentioned, no attempt is made to distinguish this so-called clustering from increased childhood cancer rates in some census tracts when compared with others in the discussion of socioeconomic class. Perhaps the reason should be sought in environmental conditions, such as exposure to chemicals or certain refined foods.

A study conducted in California by Klauber (1968) has a more direct significance for the present study. He investigated the possibility of a clustering of childhood cases by hospital of birth. Of 1,000,000 children born in California hospitals in 1958-1960, 234 children developed leukemia before age five. No statistically significant clustering by hospital of birth was found.

G. Urban-Rural Distribution:

In studies examining the urban-rural distribution of childhood leukemia, the consensus is an increase in risk of leukemia in urban

areas. Meadors (1956) listed U.S. urban and rural leukemia mortality rates for five-year age groups for both males and females and in all age groups the urban rates were substantially higher than the rural rates. In England, Stewart et al (1958) found the lowest leukemia mortality rates among the children in the rural areas while the highest rate occurred in the medium-sized towns. The occurrence of other cancers could not be shown to have any significantly different distribution in urban, or rural areas.

Knox (1964) obtained a doubling of rates for myeloblastic leukemia for children under 15 in towns over 50,000 and a lesser increase for lymphoblastic leukemia. A doubling of rates was found by Elliott et al (1961) on comparing leukemia in urban areas with that in rural areas. Stark and Oleinich (1966) found a higher rate of leukemia for white urban children compared to white rural children but did not find the same relation for nonwhite children. They suggested that perhaps the nonwhites are either not exposed to, or are protected from the agents causing this relation. This suggestion is especially plausible when one considers the differences in socioeconomic class between the white and nonwhite in the U.S.A., which might expose these groups to quite different environmental agents.

H. Preconception Radiation:

The only studies paying a significant amount of attention to preconception radiation and childhood cancer are the survey conducted by Stewart et al (1958) in England and Wales and the tristate leukemia survey in the United States (Graham et al, 1966, Gibson, Bross, Graham,

Lilienfeld, Schuman, Levin & Dowd (1968). Stewart et al acquired information on the number of abdominal x-rays reported before marriage of the mother and those between marriage and the relevant conception for both cases and controls. Surprisingly enough, an excess of cases was found among those whose mother had received x-rays prior to marriage but no effect of abdominal radiation could be shown between the time of marriage and the relevant conception. The latter result remained when differences in birth order between cases and controls were taken into consideration. Stewart et al could not find a satisfactory explanation for this but suggested that damage of the gonads may account for the influence of x-rays prior to marriage.

In the tristate leukemia survey, preconception irradiation included all types of diagnostic radiation at any time prior to conception. Among mothers of cases, ages 0 - 15, a consistent excess of women with a history of preconception radiation was found when compared to mothers of controls of the same age (Graham et al, 1966). This excess was highly significant even when standardized for factors such as year of birth, age of mother, birth order, previous miscarriages or stillbirths. The mothers who had received radiation to the abdomen, pelvis, spine, or femur only, were considered separately although it was not possible to standardize for other factors because of the small numbers involved. Such pelvic irradiation was experienced by 12.1% of mothers of cases and 6.1% of mothers of controls. This was highly significant at $p < 0.001$ and the estimated relative risks of cancer among children of irradiated mothers compared to children of nonirradiated mothers was 2.1.

Gibson et al (1968) considered separately the children of ages zero to four years from the same study. Preconception irradiation was not only considered as a factor by itself but also in combination with three other risk factors: history of reproductive wastage, in utero irradiation, and childhood virus diseases. Reproductive wastage and childhood virus diseases were considered pathologic factors as opposed to the radiologic factors, consisting of preconception or in utero irradiation. Gibson et al found that each of these four factors separately was not associated with a greater risk for leukemia in children under four. But children who had been exposed to a combination of factors, especially if both pathologic and radiologic factors were involved, showed a significantly greater risk than children who were not so exposed. The highest risk was for children exposed to all four factors. Gibson et al view irradiation, both preconception and in utero, as a " triggering agent of a sequence of events that increases a child's risk for leukemia".

The above presents evidence for the importance of preconception radiation. Further study of this, especially in combination with other factors as was done in the tristate leukemia survey, will be very informative.

I. In Utero Radiation:

A number of studies have been published to date, which consider a relation between radiation of the pregnant woman and an increased risk of childhood cancer in her offspring. Although some of the studies show no increase, the majority show an excess of childhood cancer cases after

in utero radiation. In 1962, MacMahon and Hutchison listed eleven studies, of which six showed such an excess (Ager et al, 1962, Court Brown, Doll & Hill, 1960, Kjelsberg, 1957, Lewis, 1960, Murray, Heckel & Hempelman, 1959 and Wells & Steer, 1961). When MacMahon & Hutchison weighted the relative risks of the eleven studies according to number of children included and combined them, the result was a statistically significant increase in cancer risk for children who had been irradiated before birth. The reason for the overall excess if that the remaining five studies showed statistical significance or near statistical significance (Fort et al, 1959, Kaplan, 1958, MacMahon, 1962, Polhemus & Koch, 1959, Stewart et al 1958). Of these studies, those of MacMahon (1962) and Stewart et al (1958) can be considered major studies by virtue of size and comprehensive scope and will be discussed in more detail.

Stewart et al compared 1299 matched pairs of leukemia cases and controls and found the case/control ratio of 1.91 for abdominal x-ray during the relevant pregnancy to be different from one at p 0.001. This excess remained when adjustments were made for possible over-reporting by mothers of cases and x-rays associated with ill health.

MacMahon (1962) described his prospective study of 556 cancer cases resulting from approximately 730,000 pregnancies. In this study, 7.2% of mothers of controls and 15.3% of mothers of cancer cases had received radiation during the relevant pregnancy. Overreporting for mothers of cancer patients could not have been a factor since all the information had been recorded at birth. The increase in cancer mortality was most marked at ages five to seven years at which time the

relative risk was double that of non-irradiated children. For all ages a 40% increase in cancer risk was estimated after x-ray in utero.

In the tristate leukemia survey Graham et al (1966) found a significant increase in leukemia cases for the children of women who had received abdominal x-rays during pregnancy. Gibson et al (1968) studying the under five age group of the same study noticed that the cancer risk increased particularly if a pathologic factor such as reproductive wastage in the mother, or a childhood virus disease was also present. This effect of a combination of radiologic and pathologic factors was described also in the previous section.

Leukemic children under five were also considered by Ager et al (1965) in a study in which leukemia patients were compared with neighbourhood controls. The mothers of the children suffering from leukemia could not be shown to have had a more frequent history of radiation during the relevant pregnancy than the mothers of the controls. Since MacMahon pointed out that the greatest effect of in utero irradiation occurred in the five to seven year age range, this may be part of the reason why Ager et al did not find a significant association.

From the above the conclusion may be drawn that in utero irradiation is followed by an increase in childhood cancer risk. However, whether the x-ray initiates cancer, or promotes cancer in individuals susceptible for other reasons, or whether a common factor, such as poorer health of the mother, is involved, is difficult to decide from the available evidence.

J. Miscellaneous Conditions and Abnormalities:

1. Maternal smoking

Only two published studies of the epidemiology of childhood cancer mention smoking of the parents. Stewart et al (1958) placed the parents of cases and controls into smoking categories, presumably according to smoking habits at the time of interview rather than during the relevant pregnancy. The proportion of smokers among fathers of cases was 82.9% and among mothers of cases 47.8% as opposed to 80.9% for fathers of controls and 43.8% for mothers of controls. For the mothers the difference was significant at $p < 0.04$ but as Stewart et al indicate the difference is small and no attempt was made to relate it to other pertinent factors such as age, number of children, etc. Even if the difference persisted after such analysis the effect may have been precipitated by exposure of the children to smoke after birth rather than prenatally. This is, of course, difficult to separate but of the smoking mothers in Stewart's survey a number may not have smoked during pregnancy and this would weaken any relation which might exist between childhood cancer and prenatal smoking.

One other study mentioned smoking in relation to childhood cancer. Manning & Carroll (1957) included a question on smoking, "as a device for reliability" although it is not quite clear what is meant by this, nor is it clear whether the question referred to smoking at the time of the interview or at the time of birth of the child in question. In any case a very similar percentage of women smoking

10 cigarettes per day or more was obtained for control and cancer groups.

2. Abnormalities of pregnancy

MacMahon (1962) in his prospective study found no increase in childhood cancer after the occurrence of abnormal conditions in pregnancy and delivery such as: breech, caesarean or forceps delivery, or various types of abnormal placentae. Stewart et al (1958) did find an excess of threatened abortions and virus infections during the relevant pregnancy of mothers of cancer cases when compared to controls, although the numbers involved were small.

3. Congenital malformations

The large increase in leukemia risk for children with Down's syndrome is generally accepted. The investigations by Ager et al (1965) and by Stewart et al (1958) may be mentioned as examples of studies in which a much larger number of children with Down's syndrome appeared in the leukemia group than expected. Stewart et al also found an excess of children with naevi among those with cancer - 34 out of 1299, as opposed to 21 out of 1297 controls. Miller et al (1968) scrutinized 504 cases with neuroblastoma and published a list of congenital malformations found among these children. Since they did not have a control group it was difficult to decide whether any particular type of malformation occurred with greater frequency than expected. They concluded that it did not seem likely that any specific defect clearly exceeded normal expectations. Miller, Fraumeni & Manning (1964) were able to show an excess of aniridia, congenital hemihypertrophy

and defects of the genitourinary tract among children with Wilms's tumour.

4. Previous fetal wastage

The presence of an above average rate of abortions and stillbirths among mothers of children who develop cancer might indicate a less favourable prenatal environment for the child.

Some indications of an association between fetal wastage and an increased risk of cancer have been found in a number of studies.

Stewart et al (1958) noted an excess number of abortions among mothers of leukemic children. On the other hand, MacMahon (1962) could detect no difference in history of stillbirths among mothers of cancer patients.

Graham et al (1966) in the tristate leukemia survey found an increase of previous stillbirths in mothers of leukemic children after standardization for such factors as year of birth, age of mother and birth order. Gibson et al (1968) studied the under five age group of the same study more intensively. In this paper fetal wastage was considered one of two pathologic factors and it could be shown that when a pathologic factor was combined with a radiologic factor the risk of cancer in childhood increased greatly. This phenomenon was described in greater detail in the section on preconception radiation.

5. Blood groups

A possible association between blood group phenotypes and an increased susceptibility to certain diseases has been a controversial subject for many years. Wiener (1965) opposes such an idea vehemently

and yet review papers (e.g., Marcus 1969, Muschel, 1966) are able to collect a fair amount of evidence that blood groups are not unrelated to the frequency of various diseases, e.g., peptic ulcer, gastric carcinoma, pernicious anemia.

A relation between childhood cancer and ABO blood groups has been investigated a number of times. Cordone & Tavella (1963) found a statistically significant increase in the proportion of children with blood groups 0 among 102 children with leukemia. However, he also quoted a number of papers with conflicting results. Campbell (1961) showed blood group frequencies among children under 15 years suffering from all types of cancer but no association between a particular blood group and a type of cancer was found, except for an excess of blood group A among children with gliomas.

In relating blood groups to leukemia, it should be noted that the suppression of A_1 antigen has been observed in some patients with leukemia. At the same time an increase in reactivity with anti-H reagents occurred so that the red blood cells reacted like 0 cells (Marcus, 1969). Thus if blood groups are determined when patients are known to have leukemia, an increase in blood group 0 could be explained by the suppression of the A_1 antigen.

Another factor which has to be considered is the possibility of ethnic variations, both in susceptibility to cancer and in blood group frequencies. MacMahon & Folusiak (1958) showed a deficiency of group 0 patients among 1387 leukemia patients, of all ages, when compared to a systematic sample of blood donors. A second control group was then

selected, matched with the leukemia patients for surname on the assumption that this would match the two groups for ethnic background - particularly with respect to the high proportion of those of Jewish background. The second control group did not differ significantly in distribution of ABO blood group. In this case, therefore, the initial deficiency in blood group 0 in the leukemia series was secondary to ethnic differences in susceptibility to leukemia.

The importance of maternal-fetal incompatibility both with respect to ABO blood group and Rh factor is well established and the knowledge of this has saved many infants. A fact which is not clearly explained is the interaction of ABO incompatibility and Rh incompatibility in that the presence of the former appears to reduce the probability of hemolytic disease of the newborn due to Rh incompatibility. The most likely explanation is that the ABO incompatible fetal cells are removed from maternal circulation before reaching sites of maternal antibody formation (Muschel, 1966).

Of interest would be a study of the relation between maternal blood group and occurrence of childhood cancer. This, however, does not appear to have been investigated.

K. Conclusion

The first section in this literature survey described why it is reasonable to suspect that smoking in pregnancy might influence the occurrence of childhood cancer. In short, smoking is strongly implicated in the causation of lung cancer, suspected in the development of cancer of the bladder and known to affect the birth weight of infants.

Therefore it is known that the fetus is affected directly, or indirectly, by some components of tobacco smoke, and it is not impossible that the fetus is also affected by the carcinogenic components of smoke, resulting in an increase in childhood cancer risk.

The second section describes many other factors which have previously been studied in the epidemiology of childhood cancer, emphasizing those which occur before,or at birth of the infant and affect the child's cancer risk. The present study was initiated because of the availability of extensive records on approximately 75,000 births in the hope that a worthwhile contribution could be made to the epidemiology of childhood cancer.

PROCEDURE

1. Base Population

A. Source:

The population on which this prospective study is based was originally collected for the Ontario Perinatal Mortality Study. In 1959, 1960 and 1961 detailed medical histories were taken for all deliveries in ten teaching hospitals in the province of Ontario. Of these hospitals, five were in Toronto (St. Michael's Hospital, Toronto General Hospital, Toronto Western Hospital, Wellesley Hospital, Women's College Hospital), three were in London (St. Joseph's Hospital, Victoria Hospital and Bethesda Hospital) and one each in Kingston and Ottawa (Hotel Dieu Hospital and Ottawa General Hospital).

The data recorded included information on the past obstetrical history of the mother, the events of the present pregnancy and the condition of the infant at birth. A recording clerk gathered the data from information supplied by the attending doctor, the intern, the mother and the hospital records.

The accuracy of the information on the record has been investigated and discussed in a previous study (Buck, Gregg, Stavraky, Subrahmaniam, Brown, 1969, Stavraky, 1963). They took a sample of 152 deliveries performed by ten London physicians. When the information on complications of pregnancy on the physician's office record was compared with that recorded on the perinatal form, the differences were minor and mainly in the direction of omissions from the perinatal form. Such conditions

as mild spotting in pregnancy not necessitating bed-rest, or an occasional blood pressure elevation to 140/80 were recorded on the physician's records but not on the perinatal form. Since it is very unlikely that the proportion and type of inaccuracies would be different for the children who subsequently developed cancer than for the remainder of the population, it is improbable that the inaccuracies would bias the results of the present study. Only in one case does the possibility exist that the presence of the cancer could have influenced the accuracy of the data on the perinatal record. In this case an infant was born with bilateral Wilms's tumour to a mother with terminal carcinoma of the bowel. No other child in the study developed cancer until after the completion of the perinatal record.

B. Format of the Individual Perinatal Record:

The medical histories were recorded on one standard form for 1959 (Appendix A) and another standard form for 1960 and 1961 (Appendix A), each of which contained similar information. Both formats were such that IBM cards could easily be punched from them. However, the very different format of the 1959 cards caused a major difficulty in handling the data.

In 1959 the information on each birth occupied two 80-column punch cards, while in 1960 and 1961 most of this information was condensed to one 80-column punch card by means of split fields and multiple punch columns. In the former case the making of cross-classifications of variables on one card with variables on the other card was virtually impossible with a simple IBM sorter. Fortunately such cross-classifica-

tions were not essential. In the case of split fields and multiple punches, many extra sorts on an IBM sorter were needed in order to determine the different combinations of attributes. Initially an IBM sorter was used but later in the study all 1960 and 1961 cards were recorded on a computer tape using a binary code for each possible combination of punches in a column. The programme written especially for this study made certain types of group counts easier to obtain, although still expensive in computer time.

C. Total Births in the Base Population:

For use in the present study a set of punched cards was obtained from the Ontario Department of Health for all single births in 1959, 1960 and 1961, surviving at least seven days. The availability of this set of cards allowed the making of any group counts necessary. However, many tabulations of the base population had already been published in two reports (Ontario Perinatal Mortality Study Committee, 1961 and 1967) and these were used whenever possible. According to these reports, 22,965 infants survived at least seven days in 1959, while 50,134 infants survived at least this time in 1960 and 1961. When comparing the total number of cards in the available deck with the published number, three cards were missing from the deck but this discrepancy is not sufficient to alter any cancer rates which were calculated with either number as base population.

II. Expected Number of Childhood Cancer Deaths

Before collecting the cancer deaths, calculations were made to predict the number of deaths that would occur in a population of 75,000

children, born in 1959, 1960 and 1961. Table II shows the computation of such an estimate using the Ontario Vital Statistics for the calculation of the expected yearly rates. For the under five age group the cancer deaths were available for each year of age. Other figures were available for four or five year intervals only and were divided by the number of years in the interval to give an average yearly rate. According to Table II, 54 children in the Perinatal Study would be expected to die of cancer before the end of 1968.

A number of adjustments are needed to make this expected number more realistic. A proportion of the children from the base population who developed cancer in childhood may be expected to have moved away from Ontario and died of cancer elsewhere. A subsequent section has been devoted to the problem of mobility.

Another necessary adjustment concerns a difference between the base population and the general population of Ontario. The base population is almost exclusively from urban centres of the province while the general population of the province contains both rural and urban portions. According to the 1961 census 22.7% of Ontario's population lived in rural areas, defined as towns with a population of 1,000, or less. As was pointed out in the literature survey, childhood cancer death rates are substantially higher for urban areas than for rural areas, and a 50% increase in cancer deaths in urban areas is not an unreasonable estimate. Therefore the 54 deaths estimated using Ontario rates consist of an urban and rural component.

TABLE II

Expected Cancer Deaths

	1959 Births		1960 Births		1961 Births	
Year of Death	Age in Year of Death	Expected No. of Deaths in 25,000 Births	Age in Year of Death	Expected No. of Deaths in 25,000 Births	Age in Year of Death	Expected No. of Deaths in 25,000 Births
1959	0					
1960	Under 1	1.6				
1961	1 - 2	1.9	Under 1	2.7		
1962	2 - 3	2.7	1 - 2	2.0	Under 1	0.8
1963	3 - 4	3.3	2 - 3	2.0	1 - 2	1.7
1964	4 - 5	4.3	3 - 4	3.1	2 - 3	2.1
1965	5 - 6	1.7	4 - 5	2.8	3 - 4	3.3
1966	6 - 7	1.8	5 - 6	1.8	4 - 5	2.7
1967	7 - 8	2.0	6 - 7	2.0	5 - 6	2.0
1968	8 - 9	2.0	7 - 8	2.0	6 - 7	2.0
Total		21.3		18.4		14.6
					Total expected cancer deaths	54.3

Note: The expected number of deaths were calculated using the Ontario Vital Statistics for the years indicated.

$54 = xU + yR$

where x is the urban childhood cancer rate

y is the rural childhood cancer rate

thus $y = \frac{2}{3} x$

if T is the number in the base population then:

U is the urban component of T

R is the rural component of T

thus $U + R = T$

$U = 0.773T$

$R = 0.227T$

Substituting:

$54 = 0.773xT + 0.227\ (2/3)\ xT$

solving for xT

$xT = 58$, which is the number of deaths which would occur at an entirely urban rate.

Still another adjustment can be made since the cancer deaths obtained in the present study are all those with cancer mentioned on the death certificates and not only those with deaths ascribed to cancer. Only the latter are considered in the calculation of the provincial mortality rates. A correction factor for Ontario was calculated by dividing the number of deaths ascribed to cancer by the number of deaths with cancer mentioned (Ontario Department of Health, 1967). However, this correction factor, 0.88, is for all ages and could not be determined for childhood cancer cases. Some cancers, such as skin cancer, are more common at older ages, and are less likely to be lethal. For this reason the correction factor for childhood cancer is probably nearer one. Using

0.88 as correction factor, the expected number of deaths increases from 58 to 66. Arbitrarily choosing 0.95 as correction factor (which is possibly more nearly correct for children) results in 61 expected deaths.

III. Mobility of the Base Population

In this context, mobility will refer to children born in Ontario in 1959 to 1961 who left the province prior to the end of 1968. Early in the study it was feared that the mobility of the population might cause a drastic reduction in the number of cancer deaths traced. The possibility of tracing such migrant children was explored with the Dominion Bureau of Statistics but no arrangements could be made.

In addition to the loss of deaths per se, it should be considered whether such loss could be selective for the characteristics under investigation, such as smoking habits of the mother. Some information on this could be gleaned from data collected for a previous study (Buck et al, 1969). A group of children, born in 1959 and 1960 in St. Joseph's Hospital and Victoria Hospital in London, were given periodic examination until school age. At age 5-1/3 years old, 584 children were seen in this context while an additional 52 had been in the study previously but had moved out of Ontario prior to this age. Since the perinatal forms were available, the two groups could be compared on maternal smoking habits during pregnancy (Table III).

Because the number of migrants is rather small (52) this table has limited reliability but some comparison between migrants and non-migrants can be made. If the proportion of heavy smokers among migrant mothers were 3.4%, i.e., the same as for non-migrant mothers, then of 52

TABLE III

Smoking Habits of Migrant Mothers
as Compared to Non-Migrant Mothers

	Year of Birth	Smoking Habits: None		>1 pack per day		1 pack per day & over		Unknown		Total	
		N	%	N	%	N	%	N	%	N	%
Non-migrant mothers	1960	171	59.2	93	32.2	8	2.8	17	5.9	289	100.0
Migrant mothers		9	40.9	13	59.1	0	0	0	0	22	100.0
		None and > 1 Pack									
		N		%							
Non-migrant mothers	1959	277		93.9		12	4.1	6	2.0	295	100.0
Migrant mothers		28		93.3		1	3.3	1	3.3	30	99.9
Non-migrant mothers	1959)	541		92.6		20	3.4	23	3.9	584	100.0
Migrant mothers	1960)	50		96.2		1	1.9	1	1.9	52	100.0

Note: Migrant mothers are those moving out of Ontario after the birth of the relevant child.

mothers two should be heavy smokers, with 95% confidence limits of 0.2 to 7 (Table 40, Pearson and Hartley, 1966). These limits include one (the actual number of heavy smokers among migrants) and therefore from the available data it cannot be concluded that the migrant mothers differ significantly in proportion of heavy smokers.

The data from the same study (Buck et al, 1969) can be used to estimate the percentage of the cancer population likely to have moved. The study began with 749 children of which at age 5-1/3, 584 remained, 113 had moved within Ontario and 52 (i.e. 7.5% of the total) had moved out of Ontario. If the cancer cases were exposed to moving for a similar time period (a more exact time is difficult to determine since the cancer deaths would no longer be exposed to moving after death) then 7.5% of the previous estimate of 61, i.e. 5 deaths, might move out of Ontario resulting in an estimate of 56 cancer deaths which could be traced within Ontario.

IV. The Linking of Cancer Cases with Perinatal Records

A. Deaths:

The initial lists of names of children of the appropriate ages with cancer mentioned on their death certificates were received from Dr. Elizabeth MacKay of the Cancer Statistics Section, in the Research and Planning Branch of the Ontario Department of Health. For each name, information sufficient to locate the birth certificate was sent to the Deputy Registrar of Ontario, who supplied the date of birth, the hospital of birth and the mother's first name from the birth certificate. From this, the deaths relating to the base population of births could be iden-

tified and the necessary information was sent to Miss M. D. Neilson of the Maternal and Child Health Division of the Ontario Department of Health for linkage with the original perinatal mortality records. The flow of information through this system was of necessity slow but because of the excellent cooperation of everyone involved, no major problems were encountered.

By these methods, 54 deaths occurring before the end of 1968 were obtained. This number is not far from the number of deaths estimated (56, see previous sections).

B. Survivors:

In addition to lists of childhood cancer deaths, Dr. MacKay sent lists of names, or cancer clinic case numbers of children who had been diagnosed as having cancer by one of the Ontario Cancer Clinics. For these cases no identifying numbers, such as the death certificate number, was available and further information was needed before the Deputy Registrar's staff could locate the birth certificate. Therefore all the cancer clinics in Ontario, as well as the Princess Margaret Hospital and the Hospital for Sick Children in Toronto, were visited in order to find for the children on the list as well as any other children of the right age, sufficient information to lead back to the birth certificate.

Whenever possible the date of birth was obtained; if this was not possible other information was noted, such as Christian names of parents, address, etc. Subsequent steps in the linkage process were the same as those described for the deaths.

From these sources an additional 28 childhood cancer cases were

obtained who survived at least until the end of 1968. One of the children died in 1969, and another had died earlier of a motor vehicle accident but at autopsy no trace remained of the Wilms's tumour for which he was previously treated. Both of these children will be considered survivors whenever a distinction is made between deaths and survivors.

To what extent the collection of survivors is complete is difficult to assess. Age-specific morbidity figures of the same accuracy as the mortality figures are not available and thus this method cannot be used to estimate loss. However, since all the hospitals participating in the perinatal mortality study were in cities with cancer clinics, the children most likely to be lost to the study would be those who had moved to more remote parts of Ontario. These children might be treated in local hospitals rather than travelling great distances to the nearest clinic. An opportunity to estimate the number of these children was supplied by the 1964 Ontario cancer prevalence survey.

The 1964 cancer prevalence survey was conducted by the Ontario Department of Health and went beyond the cases listed in the cancer clinics, the most important extension being the Ontario Hospital Service Commission separation forms. Table IV shows the details of information received through the 1964 Cancer Survey. For the 35 cases with a hospital but no cancer clinic mentioned, letters were sent to the hospitals asking for discharge diagnoses and dates of birth. Of these cases only 3 had a final diagnosis of cancer and were born in 1959, 1960 or 1961 (11 were not born in these years, while 21 did not have a final diagnosis of cancer regardless of year of birth). Not one of these three cases was born in a hospital participating in the Ontario Perinatal Mortality Study.

TABLE IV

1964 Cancer Prevalence Survey of the Ontario Department of Health

Number of cases within age range 1-6 years (i.e., could be born in 1959, 1960, 1961)	172	
A. Cases linked to the Ont. PMS population		8
B. Cases that could have been ascertained from Ontario cancer clinics*		
(i) Those born in 1959, 1960, 1961		69
(ii) Those born before 1959 or after 1961		47
(iii) Untraced (Hospital for Sick Children mentioned but not found in H.S.C. registry		6
C. Cases that could not have been ascertained from Ontario Cancer clinics*		
(i) From other hospitals only		35
(ii) Biopsy and Drug Service		7
		172

*Includes Hospital for Sick Children and Princess Margaret Hospital, both in Toronto.

The fact that only three cases of the required age and with a diagnosis of cancer were found for 1964 through a more extensive survey, suggests that not many cases were lost by concentrating mainly on the cancer clinics and the two Toronto hospitals. How many cases were lost is difficult to estimate since it is probably not accurate to extrapolate this result to other years. The possibility of selective loss does not differ from the situation as discussed previously with respect to mortality. For either mortality or morbidity there is no a priori reason for suspecting that possibly incomplete collection of data will bias the results.

V. Source of Additional Data

Perinatal records similar to those collected for the Ontario Perinatal Mortality Study, were completed in 1958 for the British Perinatal Mortality Survey under the auspices of the National Birthday Trust Fund (Butler & Bonham, 1963, Butler & Alberman, 1969). During the week of March 3rd to March 9th, 1958, an extensive record was kept of every birth in England and Wales. In this week, 16,350 infants were born who survived at least seven days. All possible cooperation was provided through Dr. Eva Alberman, to the extent that the same group counts were received for the English population as were available for the Ontario population for some of the basic characteristics. The children in the English population were followed until past age seven and within this population 13 cancer cases occurred - eleven deaths and two survivors.

The 13 cases in a population of 16,350 provided a cancer rate of

8.0 per 10,000 which does not differ greatly from the rate of 9.4 per 10,000 for cancer cases up to the same age limit in the Ontario population. The somewhat lower rate in the English population may be due to the fact that both urban and rural areas are included as opposed to the almost exclusively urban composition of the population in the Ontario Study.

RESULTS

I. Composition of the Cancer Population by Diagnostic Subdivision and Age Distribution

Table 1 shows the cancer deaths and survivors by diagnostic subdivisions. The survivors are those cancer cases still living at the time of the cut-off point for collecting data, i.e., the end of 1968, while the deaths are all those who died prior to this date. Thus the survivors would include those who contracted cancer early in life and may be considered cured, as well as those who were diagnosed as having cancer shortly before the cut-off point and were still being treated for this condition. The two largest diagnostic subdivisions are leukemia and cancer of the central nervous system, with Wilms's tumour a distant third. The 30 remaining children are spread over eleven different diagnoses. The study most like the present one (MacMahon, 1962) found a larger proportion of leukemia deaths, 55% as compared to 37% in the present study. However, the two studies are difficult to compare in this respect because of the different age distribution. In MacMahon's study the births occurred in 1947 to 1954 and the deaths were traced until 1960 - thus the population was followed from birth to age 6 to 13 years depending on year of birth. In the present study this age range was from birth to age seven to nine years.

Table 2 shows the cancer deaths by age of child at death as well as by the three major diagnostic subdivisions - leukemia, cancer of the central nervous system and other cancers. The numbers in the subdivisions

TABLE 1

Cancer Deaths and Survivors by Diagnostic Subdivisions

	Brit. PMS +		Ont. PMS +		Total		
Type of Cancer	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Both
Leukemia	5	0	19	5	24	5	29
Hodgkin's disease	0	1	0	3	0	4	4
Lymphosarcoma	1	0	2	0	3	0	3
Central nervous system	2	0	15	8	17	8	25
Other nervous tissue	0	0	0	3	0	3	3
Retinoblastoma	0	0	3	1	3	1	4
Wilms's tumour	3	1	4	5	7	6	13
Endocrine glands	0	0	4	0	4	0	4
Other* & unspecified	0	0	7	5	7	5	12
Total	11	2	54	30	65	32	97

*Other cancers include: cancer of prostate, connective tissue, bone, mediastinum, testes and left orbit.

+ Brit. PMS is the abbreviation for British Perinatal Mortality Survey
Ont. PMS is the abbreviation for Ontario Perinatal Mortality Study

These abbreviations will be used in all future tables.

TABLE 2

Cancer Deaths by Age at Death for Several Diagnostic Groups

Age at Death (in Years)	Brit. P.M.S.				Ont. P.M.S.				Total			
	Leukemia	C.N.S.*	Other Cancer	Total	Leukemia	C.N.S.*	Other Cancer	Total	Leukemia	C.N.S.*	Other Cancer	Total
0 - 1	1	1	2	4	1	1	5	7	2	2	7	11
1 - 2	0	0	1	1	0	3	1	4	0	4	1	5
2 - 3	1	0	0	1	4	0	1	5	5	0	1	6
3 - 4	0	0	0	0	0	3	4	7	0	3	4	7
4 - 5	1	0	0	1	3	1	6	10	4	2	5	11
5 - 6	0	0	1	1	5	2	3	10	5	3	3	11
6 - 7	0	1	0	1	1	0	0	1	1	1	0	2
7 - 8	2	0	0	2	5	1	3	9	7	1	3	11
8 - 9	0	0	0	0	0	1	0	1	0	1	0	1
Total	5	2	4	11	19	15	23	54	24	17	24	65

Note: The youngest children in the Ontario Perinatal Mortality Study were born in December 1961 and would reach age seven by the end of 1968. The children in the British Perinatal Mortality Study were checked between ages seven and eight.

* C.N.S. refers to cancer of the central nervous system.

of the table are rather small and for this reason do not show a consistent trend by age. Leukemia deaths usually show a peak for the age group from three to five years, as can be seen, for example, in the Canadian mortality statistics (Canada, Dominion Bureau of Statistics, 1960-1968). In Table 2 the leukemia deaths do not show such a trend.

The age of the children at death could be calculated accurately since both the date of birth and the date of death became available during the process of linking the cancer deaths with the perinatal mortality forms. The estimation of a corresponding age for the survivors was a more difficult matter. In the subsequent tables in which the cancer cases (including both deaths and survivors) are divided into age groups, the age for the survivors was derived from the first year the child was treated for cancer as this was the only information available for most cases. Although this age does not correspond to age of death for those who died of cancer, it is the best available and the only alternative to discarding the survivors in all situations where the age of the child is considered.

II. Factors Affecting the Composition of the Base Population

There are a number of factors which might affect the cancer rates by affecting the base population:

a. In a few of the tables the cancer rates for age group zero to seven do not show precisely the same trend as the overall rates, since the latter include a number of children who were followed to the age of eight or nine years. In these situations the rates will also be calculated per person-years in order to compensate for the different

years of exposure to the risk of cancer in the various sections of the base population.

b. The total number of births in the population is not always identical from one table to another, in spite of the fact that the base population used is the same. The reason is that more than one method was used to obtain the population counts. For many variables the numbers provided in the reports (Ontario Perinatal Mortality Study Committee, 1961, 1967) are used, while for other variables, or a combination of variables, special counts were made. In the special sorts, unknowns in sex, birth weight and birth order were generally excluded. In no case is the base population sufficiently different to alter even the first decimal place of the cancer rates calculated.

c. Since the cancer rates are calculated using the original base population as a denominator without considering other causes of death, the possibility exists that the base population may be depleted selectively for levels of certain variables. For instance, suppose that the total death rate (excluding cancer deaths) for children of heavy smokers were three times that of the average death rate. On applying the age-specific death rates of the province of Ontario to the children of the heavy smokers according to the above assumption, it may be calculated that the failure to deplete the base population of children of heavy smokers causes the cancer rate to appear 0.2 per 10,000 births lower than the actual rate. This difference is not sufficient to affect any discussion of this variable with respect to the childhood cancer rates. The same discussion applies to other variables as well and the selective depletion of the base population with respect

to certain variables may be considered negligible.

III. Maternal Smoking Habits during Pregnancy

The childhood cancer rates are shown in Table 3 by maternal smoking habits during the relevant pregnancy. The various sections of the table show the parts of the base population for which different perinatal questionnaires were used. Thus the forms for the Ontario Perinatal Mortality Study in 1959 divided smoking habits into two categories: (i) less than one pack per day, including nonsmokers; (ii) one pack per day or more. The 1960 and 1961 Ontario Perinatal Mortality forms separated the women into three groups: (i) nonsmokers; (ii) those smoking less than one pack per day; (iii) those smoking one pack per day or more. The British Perinatal Mortality forms asked how many cigarettes per day the woman smoked during this pregnancy. For the purpose of the present study, the British data were divided into three groups: (i) nonsmokers; (ii) those smoking less than 20 cigarettes per day, i.e., corresponding to one pack; (iii) those smoking 20 cigarettes per day or more, i.e., corresponding to one pack per day or more. This division made it possible to amalgamate the results of the British Perinatal Mortality Survey with the Ontario study, as is shown in sections (v) and (vi) of Table 3.

The third column in Table 3 shows the rate of cancer cases per 10,000 single live births surviving seven days or more. For the 1960 and 1961 Ontario data combined with the British data, the nonsmokers show a childhood cancer rate of 8.8 per 10,000 among their offspring, while all smokers have a cancer rate of 11.7 per 10,000 among their

TABLE 3

Cancer Rates by Maternal Smoking Habits during the Relevant Pregnancy for Various Sections of the Base Population

Maternal Smoking Habits	Base Population	Cancer Cases N	Rate/10,000	(deaths and survivors)
(i) Ont. PMS 1959				
None or < 1 pack/day	19,481	28	14.4	
1 pack/day and over	1,314	2	15.2	
Unknown	2,051	2	9.8	
Total	22,846	32	13.9	
(ii) Ont. PMS, 1960 and 1961				
None	27,684	28	10.1	
< 1 pack/day	14,899	18	12.1	
1 pack/day and over	6,359	5	7.9	
Unknown	1,164	1	8.6	
Total	50,106	52	10.4	
(iii) Ont. PMS 1959, 1960, 1961 births				
None, or < pack/day	62,064	74	11.9	
1 pack/day and over	7,673	7	9.1	
Unknown	3,215	3	9.3	
Total	72,952	84	11.5	
(iv) Brit. PMS				
None	10,802	6	5.6	
< 1 pack/day	4,110	7	17.0	
1 pack/day or more	298	0		
Unknown	1,140			
Total	16,350	13	8.0	

TABLE 3 (Continued)

Maternal Smoking Habits	Base Population	Cancer Cases (deaths & N	Rate/10,000 survivors)	
(v) Ont. PMS 1960, 1961, Brit. PMS				
None	38,486	34	8.8	
< 1 pack/day	19,009	25	13.2	) Rate for all smokers
1 pack/day or more	6,657	5	7.5	) combined is 11.7
Unknown	2,304	1	4.3	
Total	66,456	65	9.8	
(vi) Ont. PMS 1959, 1960, 1961, Brit. PMS				
None or < 1 pack/day	76,976	87	11.3	
1 pack/day or more	7,971	7	8.8	
Unknown	4,355	3	6.9	
Total	89,302	97	10.9	

children (Table 3 (v)). The relative risk for children of smokers compared with children of nonsmokers is 1.33. To test whether this relative risk is significantly different from one, the method described by Woolf (1954) was used. Using this method, 95% confidence limits around the relative risk 1.33 were computed to be 0.81 to 2.2. (The confidence limits were calculated by using a slight modification of Woolf's method as described in Appendix B.) Although the lower confidence limit indicates that the two rates cannot be considered significantly different, the upper limit suggests that the difference between cancer rates for smokers and nonsmokers could be as much as a doubling. What can be concluded here is that it is extremely improbable for the real situation to be a tripling of cancer risk for the children of smokers, since a tripling is well outside the confidence limits.

For the same population (Ontario 1960 and 1961, and British P.M.S.), Table 3(v) divides the smokers into light smokers, i.e., less than one pack per day, and heavy smokers, i.e., one pack per day or more. The childhood cancer rate among offspring of light smokers shows a 50% increase over that of nonsmokers, while the offspring of heavy smokers show no increase, but even a numerically lower cancer rate than for nonsmokers. Although the lower cancer risk among children of the heavy smokers is not significant at the 5% level, the lack of a dose-response relation casts further doubt on the hypothesis that smoking during pregnancy increases the risk of childhood cancer in the offspring. For lung cancer an increase in amount smoked could be shown to cause an increase in cancer rate, and it would not be unreasonable to expect such a relation here also. However, the low cancer rate for the offspring of the heavy smokers is the least reliable of the rates given since it

is based on the smallest number of births. This is evident from the 95% confidence limits of the relative risk of heavy smokers over non-smokers (0.33 to 2.2) which shows that the possibility of the rate of heavy smokers being double that of nonsmokers remains, in spite of the fact that the rate for heavy smokers is numerically lower in this study.

Another reason for lower reliability of the cancer rate of heavy smokers is the following. The most likely error in reporting smoking habits would be that women smoking over one pack per day would not admit to this and instead classify themselves with the light smokers. This would tend to increase the cancer rate in the light smokers (if a relation does exist) and to make the rate of the heavy smokers less reliable because of smaller numbers.

Table 3 (vi) shows the childhood cancer rates by maternal smoking habits for all the data combined. Because of the format of the 1959 Ontario data, only two divisions are possible: the light smokers combined with nonsmokers, and the heavy smokers. These data show the same trend as that discussed above, with the childhood cancer rate for the offspring of heavy smokers being lower than that for the offspring of light and nonsmokers combined.

The childhood cancer rates by maternal smoking habits during the relevant pregnancy are given in Table 4 for the major diagnostic divisions. In none of the diagnostic divisions could a statistically significant difference be shown between the rates for the children of the different smoking groups. The most divergent rates are for the "other cancers" category with a rate of 2.6 per 10,000 for children of non-smokers and 5.1 per 10,000 for children of smoking mothers. The ratio

TABLE 4

Cancer Rates for

Maternal Smoking Habits by Diagnostic Groups

(i) Ont. PMS, 1960, 1961, Brit. PMS

Maternal Smoking Habits	Base Population	All Cancer Cases N	All Cancer Cases Rate	Leukemia N	Leukemia Rate	CNS Cancer N	CNS Cancer Rate	Other Cancers N	Other Cancers Rate
None	38,486	34	8.8	10	2.6	14	3.6	10	2.6
< 1 pack/day	19,009	25	13.2	10	5.3	4	2.1	11	5.8
1 pack/day or more	6,657	5	7.5	2	3.0	1	1.5	2	3.0
Unknown	2,304	1	4.3	0		0		1.	4.3
Total	66,456	65	9.8	22	3.3	19	2.9	24	3.5

(ii) Ont. PMS, 1959, 1960, 1961, Brit. PMS

None or < 1 pack/day	76,976	87	11.3	28	3.6	22	2.9	37	4.8
1 pack/day or more	7,971	7	8.8	2	2.5	3	3.8	2	2.5
Unknown	4,355	3	6.9	0		0		3	6.9
Total	89,302	97	10.9	30	3.4	25	2.8	42	4.7

Note: Rates are per 10,000

is not statistically significant. If the difference were significant, it would be difficult to interpret. This category is composed of many types of cancer with the largest single diagnostic group consisting of the children with Wilms's tumour and the other diagnoses have no more than four cases each.

Table 5 shows age-specific cancer rates by maternal smoking habits. Two sets of rates show a statistically significant difference: (i) In the age group under two years the cancer rate for children of mothers smoking one pack per day or more is significantly greater than the cancer rate of children of light and nonsmokers combined (Table 5(ii), relative risk of 3.32 giving 95% confidence limits of 1.21 to 9.2). (ii) In the age group from two to five years, the children of mothers smoking less than one pack per day have a significantly higher rate of cancer than the children of mothers who do not smoke (Table 5 (i), 95% confidence limits 1.1 to 5.6 around the ratio of 2.42).

Some sets of rates differ in the opposite direction of that hypothesized but these lacked statistical significance. Thus in the medium age range the children of heavy smokers show an apparent deficiency in cancer when compared to children of light and nonsmokers combined. Also in the oldest age group, children of all smokers appear to show a lower cancer rate than children of nonsmokers. However, since confidence limits around the ratios of these rates are wide, the children of smokers in the oldest age group could still be from a population with a cancer risk double that of children of nonsmokers.

More than one interpretation of these results is possible:

TABLE 5

Age-Specific Cancer Rates by Maternal Smoking Habits

(i) Ont. PMS 1960, 1961 Births, Brit. PMS

Maternal Smoking Habits	Base Population	All Cancer Cases N	All Cancer Cases Rate/10,000	0 - 24 mos. N	0 - 24 mos. Rate/10,000	25 - 60 mos. N	25 - 60 mos. Rate/10,000	60 mos. and over N	60 mos. and over Rate/10,000
None	38,486	34	8.8	8	2.1	10	2.6	16	4.2
< 1 pack/day	19,009	25	13.2	5	2.6	12	6.3	6	3.2
1 pack/day & over	6,657	5	7.5	4	6.0	0		1	1.5
Unknown	2,304	1	4.3	1	4.3	0		0	
Total	66,456	65	9.8	18	2.7	22	3.3	23	3.4
(ii) Ont. PMS, 1959, 1960, 1961, Brit. PMS									
None or < 1 pack/day	76,976	87	11.3	15	1.9	33	4.3	36	4.7
1 pack/day & over	7,971	7	8.8	5	6.3	1	1.3	1	1.3
Unknown	4,355	3	6.9	2	4.6	0		1	2.3
Total	89,302	97	10.9	22	2.5	34	3.8	38	4.3

Note: 3 children with unknown ages are excluded from the age-specific rates.

a. The original hypothesis that smoking during pregnancy increases the cancer risk in the offspring could still be correct with the increase being confined to the age groups under 2 years.

b. Smoking by mothers during pregnancy may speed the development of cancer in children destined to succumb to the disease anyway because of susceptibility to cancer from other unknown causes, e.g., environmental or genetic. If this were the only effect of smoking, the apparently lower cancer risk at the higher ages for children of smoking mothers would be a real deficiency and could be verified if the study were repeated with larger numbers.

c. The above two interpretations could each explain part of the observed differences.

d. The results came about by chance only and smoking during pregnancy has no real effect on childhood cancer.

Before ending the presentation of the results on the relation between maternal smoking habits in pregnancy and childhood cancer, the possibility has to be considered that such a relation may be affected by a third factor. The effect of such factors can be calculated by indirect standardization. Tables 6 to 9 show the distribution of sex of child, birth weight, birth order and maternal age (which have been implicated in childhood cancer in other studies) by maternal smoking habits. In all cases the standardizing factor is near one, demonstrating that the variables considered have negligible effects on the comparison of childhood cancer rates for the groups with different smoking habits. For further detail on the method used to calculate the standardizing factor, see Appendix B.

TABLE 6

Smoking Habits by Sex of Child

Ont. PMS 1960, 1961, Brit. PMS

Sex	N	%	Standardizing Factor
(i) Nonsmokers			
Male	19,982	51.9%	
Female	18,504	48.1%	
Total	38,486	100.0%	1.00
(ii) Smokers			
Male	13,101	51.0%	
Female	12,565	49.0%	
Total	25,666	100.0%	1.01
(iii) Unknown smoking habits			
Male	1,215	52.7%	
Female	1,089	47.3%	
Total	2,304	100.0%	1.00

Note: The standard population is the Ont. PMS 1959, 1960, 1961, Brit. PMS base population.

TABLE 7

Smoking Habits by Birth Weight

Ont. PMS, 1960, 1961, Brit. PMS

Birth Weight	N	%	Standardizing Factor
(i) Nonsmokers			
Premature	1,401	3.6%	
Mature	37,085	96.4%	
Total	38,486	100.0%	1.01
(ii) Smokers			
Premature	1,803	7.0%	
Mature	23,863	93.0%	
Total	25,666	100.0%	1.01
(iii) Unknown smoking habits			
Premature	149	6.5%	
Mature	2,155	93.5%	
Total	2,304	100.0%	1.00

Note: The standard population is the Ont. PMS 1959, 1960, 1961, Brit. PMS base population.

TABLE 8

Smoking Habits by Birth Order

Ont. PMS, 1960, 1961, Brit. PMS

Birth Order	N	%	Standardizing Factor
(i) Nonsmokers			
First	13,552	35.2%	
Second	11,309	29.4%	
Third & over & unknown	13,625	35.4%	
Total	38,486	100.0%	1.00
(ii) Smokers			
First	8,271	32.2%	
Second	6,919	27.0%	
Third & over & unknown	10,476	40.8%	
Total	25,666	100.0%	1.05
(iii) Unknown smoking habits			
First	842	36.5%	
Second	617	26.8%	
Third & over & unknown	845	36.7	
Total	2,304	100.0%	1.00

Note: Total births with unknown birth order are 1,041.

The standard population is the Ont. PMS 1959, 1960, 1961, Brit. PMS base population.

TABLE 9

Smoking Habits by Maternal Age

Ont. PMS, 1960, 1961, Brit. PMS

Maternal Age Groups	N	%	Standardizing Factor
(i) Nonsmokers			
Under 25	13,398	34.8%	
25-29	11,802	30.7%	
30-34	8,009	20.8%	
35 +	5,271	13.7%	
Total	38,480	100.0%	1.00
(ii) Smokers			
Under 25	9,988	38.9%	
25-29	7,618	29.7%	
30-34	5,099	19.9%	
35 +	2,958	11.5%	
Total	25,663	100.0%	1.01
(iii) Unknown smoking habits			
Under 25	967	42.0%	
25-29	645	28.0%	
30-34	420	18.3%	
35 +	268	11.7%	
Total	2,300	100.0%	1.05

Note: Unknown maternal age is excluded

The standard population is the Ont. PMS 1959, 1960, 1961, Brit. PMS base population.

IV. Maternal, Paternal Age and Birth Order

In the remainder of this section the association of childhood cancer with a variety of maternal variables will be discussed. Some of these have been tested in other studies while others have not been considered earlier. If tests of statistical significance were routinely performed for all rates given, one out of twenty may be expected to show statistical significance at the 5% level even when no real difference exists. On the other hand, if the level of acceptance of the null hypothesis were raised to 99% then the danger increases of accepting a null hypothesis of no difference while a real difference exists. For these reasons,the rates will be discussed without reference to statistical significance in spite of the occasional mention of statistical significance, especially where other studies have considered the same variable.

Table 10 shows the childhood cancer rates by maternal age at the birth of the child. The rates rise with increasing maternal age although the trend stops with the oldest age group where the rate is unexpectedly low. A χ^2 for trend (Cochran, 1951) was calculated and found not to be significant.

The low rate for the highest maternal age group is rather surprising although the deficiency is not statistically significant. Most other studies considering maternal age at birth in relation to childhood cancer found either that mothers of cancer patients were slightly older than controls, or found no difference at all. Stewart et al (1958) found that mothers of leukemia patients were on the average a half year

TABLE 10

Cancer Rates by Maternal Age

1. Ont. PMS 1959, 1960, 1961 and Brit. PMS

Maternal Age	Base Population	All		Leukemia		C.N.S.		Other Cancer	
		No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
Under 20	7,229	7	9.7	2	2.8	2	2.8	3	4.1
20-24	25,359	23	9.1	11	4.3	5	2.0	7	2.8
25-29	27,151	31	11.4	6	2.2	10	3.7	15	5.5
30-34	18,332	27	14.7	5	2.7	7	3.8	15	8.2
35+	11,332	9	7.9	5	4.4	1	0.9	3	2.6
Unknown	46								
Total	89,449	97	10.8	29	3.2	25	2.8	43	4.8

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
Under 20	7,229	7	9.7	3	4.1	3	4.1	6	8.2
20-24	25,359	23	9.1	11	4.3	12	4.7	23	9.1
25-29	27,151	31	11.4	13	4.8	10	3.7	23	8.5
30-34	18,332	27	14.7	14	7.6	8	4.4	22	12.0
35+	11,332	9	7.9	5	4.4	1	0.9	6	5.3
Unknown	46								
Total	89,449	97	10.8	46	5.1	34	3.8	80	8.9

*Rates are per 10,000

older than controls but that this difference was due mainly to an excess of a small group of women over forty on the leukemia side even after mothers of mongols were excluded. When in the present study the average age is calculated for the base population and for the mothers of the cancer cases by using the midpoint of the age interval as an average age for all the women in the age group, it is found that the women in the base population have an average age of 27.7 years, the mothers of all cancer cases 28.1 years, and the mothers of leukemia cases 27.6 years. Thus no substantial difference can be seen in the average age.

MacMahon and Newill (1962) found a trend of increasing rates of childhood leukemia with increasing maternal age. In the prospective study by MacMahon (1962) no difference was found in maternal age distribution either for all cancer cases together, or for leukemia cases and cases with cancer of the central nervous system separately. In the present study no trend in maternal age distribution is evident for the diagnostic subdivisions.

The second part of Table 10 shows childhood cancer rates by maternal age and age group of the children. Only the children under four show a trend similar to that of the overall rates. Using the midpoints of the age intervals, the average age of their mothers is 28.3. This can perhaps be compared to the results of Ager *et al* (1965) who studied children under four years, although only those with leukemia. In their study the mothers of the patients were on the average 2-1/4 years older than of controls which is a greater increase than found in most other

studies with older children.

Table 11 shows the childhood cancer rates by the father's age at the birth of the child. The paternal age is divided into two categories, those fathers less than 30 years old and those 30 years and over. This particular age division was chosen mainly because it divided the fathers into two approximately equal groups. The ratio of rates of the two paternal age groups is 1.44 with 95% confidence limits of 0.91 to 2.3 and thus the higher cancer rates for the older fathers is not statistically significant at the 5% level in this study. The children with leukemia and with "other cancers" also show the higher cancer rates for the older fathers as do the children under four years old. Table 12 shows the childhood cancer rates for paternal age further subdivided into maternal age groups. In this table, the differences between the paternal age groups appear to override the differences between the maternal age groups. Other studies did not pay much attention to paternal age with respect to childhood cancer but the present results show that further investigation of this might be profitable.

The childhood cancer rates for various birth order divisions are given in Table 13. In this study birth order is defined as the number of all previous term pregnancies plus premature births. The overall rates show a slightly lower cancer rate for first-born than for other birth orders. None of the other sections of this table show any outstanding differences in rates. Most other studies are quite consistent in showing an excess of first-born among the cancer cases. Even a somewhat different definition of birth order, e.g., inclusion of abortions, or exclusion of previous stillbirths does not change the base

TABLE 11

Cancer Rates by Paternal Age

1. Ont. PMS. 1959, 1960, 1961

Paternal Age	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	C.N.S. No.	C.N.S. Rate*	Other Cancer No.	Other Cancer Rate*
Less than 30 yrs.	33,685	30	8.9	8	2.4	12	3.6	10	3.0
30 yrs. & over	34,364	44	12.8	15	4.4	10	2.9	19	5.5
Unknown	4,903	10	20.4	1	2.0	3	6.1	6	12.2
Total	72,952	84	11.5	24	3.3	25	3.4	35	4.8

2.

				Age 0-48 mos.		49-84 mos.		0-84 mos.	
Less than 30 yrs.	33,685	30	8.9	15	4.5	13	3.9	28	8.4
30 yrs. & over	34,364	44	12.8	22	6.4	9	2.6	31	9.0
Unknown	4,903	10	20.4	3	6.1	4	8.2	7	14.3
Total	72,952	84	11.5	40	5.5	26	3.6	66	9.1

*Rates are per 10,000

TABLE 12

Cancer Rates for Paternal Age by Maternal Age

Ont. PMS 1959, 1960, 1961

Paternal Age	Maternal Age	Base Population	Cancer Cases	Cancer Rate per 10,000
Less than 30 years	Less than 25 years	21,285	18	8.5
	25 and over	12,397	12	9.7
30 and over	Less than 25 years	3,013	4	13.3
	25 and over	31,339	40	12.8

Note: Unknown maternal age and paternal age omitted.

TABLE 13

Cancer Rates by Birth Order

1. Ont. PMS, 1959, 1960, 1961 and Brit. PMS

Birth Order	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	C.N.S. No.	C.N.S. Rate	Other Cancer No.	Other Cancer Rate*
First	30,657	29	9.5	9	2.9	5	1.6	15	4.9
Second	25,143	31	12.3	11	4.4	10	4.0	10	4.0
Third & over	32,364	37	11.4	9	2.8	10	3.1	18	5.6
Unknown	1,285								
Total	89,449	97	10.8	29	3.2	25	2.8	43	4.8

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
First	30,657	29	9.5	14	4.6	12	3.9	26	8.5
Second	25,143	31	12.3	12	4.8	13	5.2	25	10.0
Third & over	32,364	37	11.4	20	6.2	9	2.8	29	9.0
Unknown	1,285								
Total	89,449	97	10.8	46	5.1	34	3.8	80	8.9

*Rates are per 10,000

population to such an extent that it could explain different results in the present study.

Table 14 shows childhood cancer rates for birth order by maternal age. However, no trend can be noted that could not be seen in the separate tables for maternal age and birth order.

V. Birth Weight and Gestation

Table 15 shows childhood cancer rates divided into two birth weight groups: premature (less than 5 lbs. 9 oz. at birth) and mature (5 lbs. 9 oz. and more). No consistent difference in cancer risk can be seen when comparing the premature infants with those of mature birth weight. MacMahon and Newill (1962) found a slightly higher birth weight for their cancer cases than their controls but explained this by saying that the only criterion for the controls was that the infant had to be born alive and thus a certain percentage probably died of causes precipitated by prematurity while the cancer patients had to survive until old enough to develop cancer. To qualify for inclusion in the present study, the infant had to survive seven days and thus many infants who died on account of prematurity have been removed. Because of the small number of premature infants, no further subdivisions are given in Table 15.

In Table 16 childhood cancer rates are given by length of gestation. The overall rates are somewhat higher for infants with a gestational period of less than 40 weeks than for those of forty weeks and higher.

TABLE 14

Cancer Rates for Maternal Age by Birth Order

Ont. PMS 1959, 1960, 1961, Brit. PMS

Maternal Age	First Birth Order			Second Birth Order & over			Total		
	Base Population	Cancer Cases	Rate*	Base Population	Cancer Cases	Rate*	Base Population	Cancer Cases	Rate*
Less than 25 years	17,049	15	8.8	15,488	15	9.7	32,537	30	9.2
25 and over	11,342	14	12.3	45,382	53	11.7	56,724	67	11.9
Total	28,391	29	10.2	60,870	68	11.2	89,261	97	10.9

Note: Births with unknown birth weight and unknown maternal age are excluded.

*Rates are per 10,000

TABLE 15

Cancer Rates by Birth Weight

1. Ont. PMS, 1959, 1960, 1961, Brit. PMS

	Base Population	All Cancer Cases No.	Rate
Premature	4,477	5	11.2
Mature	84,930	92	10.8
Total	89,407	97	10.8

Note: Births with unknown birth weights are excluded.

*Rates are per 10,000

TABLE 16

Cancer Rates by Gestation

1. Ont. PMS, 1960, 1961, Brit. PMS

	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	C.N.S. No.	C.N.S. Rate*	Other Cancers No.	Other Cancers Rate*
Under 38 weeks	4,108	5	12.2	1	2.4	3	7.3	1	2.4
38-39	13,274	17	12.8	8	6.0	2	1.5	7	5.3
40-41	36,657	32	8.7	16	4.4	4	1.1	12	3.3
42 and over	9,876	8	8.1	5	5.1	1	1.0	2	2.0
Unknowns	2,541	3	11.8	1	3.9	0		2	7.8
Total	66,456	65	9.8	31	4.7	10	1.5	24	3.6

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
Under 38 weeks	4,108	5	12.2	3	7.3	1	2.4	4	9.7
38-39	13,274	17	12.8	6	4.5	8	6.0	14	10.5
40-41	36,657	32	8.7	18	4.9	11	3.0	29	7.9
42 and over	9,876	8	8.1	4	4.1	2	2.0	6	6.1
Unknowns	2,541	3	11.8	2	7.8	1	3.9	3	11.7
Total	66,456	65	9.8	33	5.0	23	3.5	55	8.5

*Rates are per 10,000

VI. Sex

Table 17 shows cancer rates by sex of child. From the table it is obvious that the males have a substantially higher cancer risk than females, the difference being statistically significant. At all ages combined the highest relative risk for males is for cancer of the central nervous system while for all sites combined it is for ages under four years. Most other studies found approximately 60% males in their cancer populations for various diagnostic groups, such as leukemia, brain tumours. On comparing the rates of the present study with those of all Ontario, the discrepancy between males and females in this study is much larger. The main difference between this study and all Ontario would be the almost completely urban nature of the base population as opposed to the rural areas included in the all Ontario rates. It is possible that males are more susceptible to whatever factors produce a higher urban rate of childhood cancer.

A somewhat higher proportion of males among urban cancer patients can be shown elsewhere. For instance, in the period 1962-1967, 175 children under ten years died of malignant neoplasms in the city of Toronto (Ontario Vital Statistics). Of these 101 (57.7%) were males and 74 (42.3%) were females. In the rest of Ontario for the same time period, 570 children under ten died of cancer, of which 312 (54.7%) were males and 258 (45.3%) were females. Thus Toronto which is more urban than the rest of Ontario had a higher percentage of males dying of cancer, while having no larger percentage of males (50.9%) in its population than the rest of Ontario (51.2%). In the present study 410

TABLE 17

Cancer Rates by Sex

1. Ont. PMS, 1959, 1960, 1961, Brit. PMS

	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	CNS No.	CNS Rate*	Other Cancer No.	Other Cancer Rate*
Male	46,206	61	13.2	14	3.0	20	4.3	27	5.8
Female	43,243	36	8.3	15	3.5	5	1.2	16	3.7
Total	89,449	97	10.8	29	3.2	25	2.8	43	4.8

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
Male	46,206	61	13.2	32	6.9	17	3.7	49	10.6
Female	43,243	36	8.3	14	3.2	17	3.9	31	7.1
Total	89,449	97	10.8	46	5.1	34	3.8	80	8.9

*Rates are per 10,000

cancer cases, born in 1959, 1960, 1961, were collected prior to 1968, before selecting those born in the relevant hospitals. Of these 300 were from towns and cities larger than 5,000 and 110 from those smaller. Of the 300, 164 (54.7%) were males and 136 (45.3%) were female. Of the 110 from more rural areas exactly 50% were male and 50% female.

The two situations mentioned above have lower proportions of males than the 62.9% males in the present study of the children born in the relevant hospitals. However, the above does suggest a somewhat higher proportion of males among childhood cancer patients in the urban areas than in the rural areas.

VII. X-rays during, or prior to the Relevant Pregnancy

Table 18 shows the childhood cancer rates according to maternal x-ray exposure during the relevant pregnancy. The cancer rates for women who received abdominal x-rays at any time during pregnancy are 45% higher than the rates for women who had no x-ray during this time. This increase is very similar to the 40% increase found by MacMahon (1962). In his prospective study the results are statistically significant while in the present study, because of smaller numbers, the difference is not statistically significant. Similar results were found in several other studies as has been described above in the literature survey. In MacMahon's study the excess mortality was found mainly in the five to seven age group but no such conclusion can be drawn from this study. Among site-specific rates the increased rate for abdominal x-ray is most pronouncedin the other cancer category.

The rates in seven and under age group do not show precisely

TABLE 18

Cancer Rates by X-Ray during Relevant Pregnancy

1. Ont.PMS, 1959, 1960, 1961 and Brit. PMS

	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	CNS No.	CNS Rate*	Other Cancers No.	Other Cancers Rate*
No X-ray	55,992	61	10.9	16	2.9	19	3.4	26	4.6
Chest & other	25,060	23	9.2	10	4.0	3	1.2	10	4.0
Abdominal	7,603	12	15.8	3	3.9	3	3.9	6	7.9
Unknown	675	1	14.8	0		0		1	14.8
Total	89,330	97	10.8	29	3.2	25	2.8	43	4.8

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
No X-ray	55,992	61	10.9	33	5.9	20	3.6	53	9.5
Chest & other	25,060	23	9.2	8	3.2	10	4.0	18	7.2
Abdominal	7,603	12	15.8	5	6.6	3	3.9	8	10.5
Unknown	675	1	14.8	0		1	14.8	1	14.8
Total	89,330	97	10.8	46	5.1	34	3.8	80	8.9

*Rates are per 10,000

the same trend as the over-all rates. In the under seven age group, the mothers who had abdominal x-rays during pregnancy show less increase in cancer risk for their children than in the overall cancer rates. In order to eliminate the possibility that this may be due to the different years of exposure, the rates were calculated in terms of person-years. The mothers with no x-ray exposure during pregnancy had a cancer rate of 13.3 for their children, the mothers with chest x-rays 13.0 and the mothers with abdominal x-rays 19.2 per 100,000 person-years. The relative risk for women with abdominal x-ray as compared to women with no x-ray based on rates per person-years (1.44) is very similar to that based on rates per 10,000 births (1.45) and thus is not dependent on years of exposure.

Table 19 shows the cancer rates by pre-conception irradiation of the mother. This information was available for the 1960 and 1961 Ontario data only. The women who had an abdominal x-ray prior to conception show a 40% increase in cancer rate for their offspring over women having had only a chest x-ray or an "other" x-ray which refers mainly to extremities and teeth. Since the information in this table depends mainly on the women's memory, its reliability may be questioned but there is no reason to believe that a bias exists with respect to childhood cancer. The results are in agreement with the few other studies which took preconception x-rays into consideration, although in the present study the difference is not statistically significant.

VIII. Maternal Environmental Factors

Table 20 shows the socioeconomic class of the parents at birth

TABLE 19

Cancer Rates by X-ray Prior to Relevant Pregnancy

1. Ont. PMS, 1960, 1961

Type of X-ray	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	CNS No.	CNS Rate*	Other Cancers No.	Other Cancers Rate*
None	847	1	11.8	1	11.8	0		0	
Chest & other only	40,000	38	9.5	12	3.0	13	3.3	13	3.3
Any abdominal	8,163	11	13.4	3	3.7	3	3.7	5	6.1
Unknown	1,124	2	17.8	1	8.9	1	8.9	0	
Total	50,134	52	10.4	17	3.4	17	3.4	18	3.6

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
None	847	1	11.8	1	11.8	0		1	11.8
Chest & other only	40,000	38	9.5	18	4.5	16	4.0	34	8.5
Any abdominal	8,163	11	13.4	5	6.3	3	3.7	8	10.0
Unknown	1,124	2	17.8	2	17.8	0		2	17.8
Total	50,134	52	10.4	26	5.2	19	3.8	45	9.0

*Rates are per 10,000

TABLE 20

Cancer Rates by Socioeconomic Class

1. Ont. PMS, 1959, 1960, 1961, Brit. PMS

Socioeconomic Class	Base Population	All		Leukemia		CNS		Other Cancers	
		No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
Upper	22,450	19	8.5	5	2.2	8	3.6	6	2.7
Middle	33,109	36	10.9	9	2.7	8	2.4	19	5.7
Lower	33,890	42	12.4	15	4.4	9	2.7	18	5.3
Total	89,449	97	10.8	29	3.2	25	2.8	43	4.8

2.

				Ages 0 - 48 mos.		49-84 mos.		0-84 mos.	
Upper	22,450	19	8.5	11	4.9	7	3.1	18	8.0
Middle	33,109	36	10.9	18	5.4	10	3.0	28	8.4
Lower	33,890	42	12.4	17	5.0	17	5.0	34	10.0
Total	89,449	97	10.8	46	5.1	34	3.8	80	8.9

*Rates are per 10,000

of the child, which is based entirely on the occupation of the father. The upper socioeconomic level consists of those with professional and managerial occupations, the middle class contains the clerical, sales and skilled persons while the lower class has the semi-skilled, unskilled and unknown. In the British population the farmers were included in the upper socioeconomic class while in the Ontario population in the lower socioeconomic class. However, so few farmers are included in the Ontario study that this could not have any appreciable effect. In Table 20 a trend towards increasing cancer rate can be seen from the upper towards the lower socioeconomic class but this trend is not statistically different. Two other studies (Stewart et al, 1958, Graham et al, 1960) which related socioeconomic class, based on occupation of the father, to childhood cancer rates found no correlation at all. Others who did find a relation between socioeconomic class and childhood cancer rate based the measurement of the socioeconomic class on census tracts and hospital pay status. In those studies a trend was found, opposite to that of the present study, with the highest rate for the highest class. MacMahon (1962) found lower rates for children born under clinic pay status than for private patients. In the present study, Table 21 shows little difference in cancer risk for births with private or public hospital status. In the subsections of Tables 20 and 21, neither age-specific nor site-specific results show any other trends.

Table 22 shows cancer rates by marital status of the mother at the birth of the child. The childhood cancer rates are quite similar

TABLE 21

Cancer Rates by Hospital Status

1. Ont. PMS, 1959, 1960, 1961

Hospital Status	Base Population	All		Leukemia		CNS		Other Cancers	
		No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
Private	57,003	66	11.6	18	3.2	20	3.5	28	4.9
Public	15,893	18	11.3	6	3.8	3	1.9	9	5.7
Unknown	203								
Total	73,099	84	11.5	24	3.3	23	3.1	37	5.1

2.

				Ages					
				0-48 mos.		49-84 mos.		0-84 mos.	
Private	57,003	66	11.6	31	5.4	22	3.9	53	9.3
Public	15,893	18	11.3	9	5.7	7	4.4	16	10.1
Unknown	203								
Total	73,099	84	11.5	40	5.5	29	4.0	69	9.5

*Rates are per 10,000

TABLE 22

Cancer Rates by Marital Status

Ont. PMS, 1959, 1960, 1961

Marital Status	Base Population	Cancer Cases	Rate*
Married	68,496	80	11.7
Single, divorced widowed, separated	4,463	4	9.0
Unknown	140	0	
Total	73,099		11.5

*Rates are per 10,000

for the two categories. However the "single, divorced, widowed and separated" mothers is a small category; the childhood cancer rate is not very reliable. This is also the reason why the age-specific and site-specific rates are not given for this table.

Table 23 shows childhood cancer rates by country of birth of mother. The cancer rates for children of mothers born in Canada are very similar to those of mothers born outside of Canada. Among site-specific rates some differences in rates are seen for children with leukemia and children with cancer of the nervous system. The women in the unknown category show an unusually high cancer rate among their offspring. This will be mentioned again in the Discussion.

Table 24 suggests that being employed outside the home during pregnancy does not greatly affect the cancer rate of the offspring. Of course, the various types of employment possible would expose the women to quite different environments and this would dilute the effect if only a certain employment provided exposure to a carcinogen which could cause cancer in the offspring. No trends are obvious from the subsections of the table.

IX. Drugs during Pregnancy

Tables 25, 26, and 27 show childhood cancer rates according to the use of hypotensives, diuretics or hormones, respectively, during pregnancy. No differences in cancer rates are noted that cannot be explained by chance. Because of the small numbers in these and some of the following tables, age-specific and site-specific rates are not given.

TABLE 23

Cancer Rates by Birth Place of Mother

1. Ont. PMS, 1959, 1960, 1961

	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	CNS No.	CNS Rate*	Other Cancers No.	Other Cancers Rate*
Born in Canada	50,660	53	10.5	12	2.4	18	3.6	23	4.5
Born elsewhere	19,950	22	11.0	9	4.5	3	1.5	10	5.0
Unknown	2,371	9	38.0	3	12.7	2	8.4	4	16.9
Total	72,981	84	11.5	24	3.3	23	3.2	39	5.3

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
Born in Canada	50,660	53	10.5	26	5.1	20	3.9	46	9.0
Born elsewhere	19,950	22	11.0	9	4.5	6	3.0	15	7.5
Unknown	2,371	9	38.0	5	21.1	3	12.7	8	33.8
Total	72,981	84	11.5	40	5.5	29	4.0	69	9.5

*Rates are per 10,000

TABLE 24

Cancer Rates by Employment During Pregnancy

1. Ont. PMS 1959, 1960, 1961

Employment	Base Population	All		Leukemia		CNS		Other Cancers	
		No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
None	47,231	57	12.1	16	3.4	16	3.4	25	5.3
Any	22,118	22	9.9	8	3.6	7	3.2	7	3.2
Unknown	3,750	5	13.3	0		0		5	13.3
Total	73,099	84	11.5	24	3.3	23	3.1	37	5.1

2.

				Ages 0-48 mos.		49-84 mos.		0-84 mos.	
None	47,231	57	12.1	28	5.9	22	4.7	50	10.6
Any	22,118	22	9.9	8	3.6	7	3.2	15	6.8
Unknown	3,750	5	13.3	4	10.7	0		4	10.7
Total	73,099	84	11.5	40	5.5	29	4.0	69	8.0

*Rates are per 10,000

TABLE 25

Cancer Rates by Hypotensives during Pregnancy

Ont. PMS 1959, 1960, 1961

Hypotensives	Base Population	Cancer Cases	Rates*
None and unknown	72,023	83	11.5
Hypotensives taken	1,076	1	9.3
Total	73,099	84	11.5

*Rates are per 10,000

TABLE 2 6

Cancer Rates by Diuretics during Pregnancy

Ont. PMS 1959, 1960, 1961

Diuretics	Base Population	Cancer Cases	Rate*
None and unknown	62,343	75	12.0
Diuretics taken	10,756	9	8.4
Total	73,099	84	11.5

*Rates are per 10,000

TABLE 27

Cancer rates by Hormones during Pregnancy

Ont. PMS 1959, 1960, 1961

Hormones	Base Population	Cancer Cases	Rate*
None and unknown	71,242	82	11.5
Hormones	1,857	2	10.8
Total	73,099	84	11.5

*Rates are per 10,000

Table 28 consists of two parts. The first part contains the data from the 1959 Ontario study in which each woman was asked if she was depressed, anxious, or worried during pregnancy. Of the 6024 women who answered yes, only 261 were depressed and the remainder mentioned anxiety or worry. The two categories were added together because of the small number of the former and the probable lack of distinction between the two. In the 1959 Ontario study no question regarding the taking of tranquilizers was asked. In the 1960, 1961 perinatal study, no question was asked concerning the mental state of the woman but only whether tranquilizers were taken during pregnancy. These results are shown in the second part of Table 28. In both sections of the table the "none" category shows a substantially lower childhood cancer rate. In Table 28(i) the ratio of childhood cancer rates of women with anxiety to that of women with no anxiety is 2.25, giving 95% confidence limits of 0.99 to 5.11 and thus nearly significant at the 5% level. In part (ii), the ratio of women taking tranquilizers to those taking none or unknown is 1.71 which is not statistically significant. This latter ratio might have been somewhat higher if the unknowns could have been separated as in Section (i). The unknown categories sometimes show rather high childhood cancer rates for no apparent reason (see, e.g., Table 28(i)).

It seems unlikely that sections (i) and (ii) of Table 28 are measuring the same property. In the 1960, 1961 study 5.8% of the total women had taken tranquilizers. Even if all the 5.8% would be in the anxious group in the 1959 Ontario data, no more than 22% of women who were anxious and worried, are likely to have taken tranquilizers during

TABLE 28

Cancer Rates by Anxiety or Tranquilizers during Pregnancy

	Base Population	Cancer Cases	Rate*
(i) Ont. PMS 1959			
Anxiety			
None	11,356	10	8.8
Depression, anxiety and worry	6,024	12	19.9
Unknown	5,465	10	18.3
Total	22,845	32	13.9
(ii) Ont. PMS 1960, 1961			
Tranquilizers			
None and unknown	47,215	47	10.0
Any tranquilizer	2,919	5	17.1
Total	50,134	52	10.4

*Rates are per 10,000

pregnancy and thus the tranquilizers as such cannot be blamed completely for the increase in childhood cancer rate. The increase must be at least partially due to some property of the anxiety or depression itself.

Table 29 shows childhood cancer rates by maternal sedation during labour. The women who did receive sedation have a slightly higher cancer rate in their offspring. The more surprising results are shown in Table 30 where the women who had no anaesthesia at birth have a considerably higher childhood cancer rate for their offspring. This is especially prominent in the "other cancer" category. Of course, women who do not receive anaesthesia at delivery are not representative of the whole population of deliveries and have, for instance, a much higher rate of perinatal mortality. In the Ontario Perinatal Mortality Study these women showed a perinatal mortality rate of 66.0/1000 live births as opposed to an overall rate of 26.3/1000 (Ontario Perinatal Mortality Study Committee, 1967).

Table 31 shows childhood cancer rates by the presence or absence of both sedation and anaesthesia. This table shows that the women who did not receive anaesthesia have a higher rate of cancer in their offspring regardless of sedation.

X. Previous Fetal Wastage and Congenital Malformation

Previous studies have shown that a history of abortions and stillbirths appears to be associated with an increase in the risk of childhood cancer in later offspring. This was particularly prominent when a history of fetal wastage in the mother was combined with irradiation both during and before pregnancy (Gibson et al, 1968). In the

TABLE 29

Cancer Rates by Sedation

1. Ont. PMS 1959, 1960, 1961

	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	C.N.S. No.	C.N.S. Rate*	Other Cancers No.	Other Cancers Rate*
No sedation	18,210	18	9.9	4	2.2	4	2.2	10	5.5
Any sedation	54,889	66	12.0	20	3.6	19	3.5	27	4.9
Total	73,099	84	11.5	24	3.3	23	3.1	37	5.1
				Age					
				0-48 mos.		49-84 mos.		0-84 mos.	
No sedation	18,210	18	9.9	9	4.9	4	2.2	13	7.1
Any sedation	54,889	66	12.0	31	5.6	25	4.6	56	10.2
Total	73,099	84	11.5	40	5.5	29	4.0	69	9.4

*Rates are per 10,000

TABLE 30

Cancer Rates by Anaesthesia

1. Ont. PMS, 1959, 1960, 1961

	Base Population	All No.	All Rate *	Leukemia No.	Leukemia Rate*	C.N.S. No.	C.N.S. Rate*	Other Cancers No.	Other Cancers Rate*
No anaesthesia	6,953	16	23.0	3	4.3	3	4.3	10	14.4
Any anaesthesia	66,146	68	10.3	21	3.2	19	2.9	27	4.1
Total	73,099	84	11.5	24	3.3	23	3.1	37	5.1
				Age 0-48 mos.		49-84 mos.		0-84 mos.	
No anaesthesia	6,953	17	24.4	8	11.5	4	5.8	12	17.3
Any anaesthesia	66,146	67	10.1	32	4.8	25	3.8	57	8.6
Total	73,099	84	11.7	40	5.5	29	4.0	69	9.4

*Rates are per 10,000

TABLE 31

Cancer Rates by Sedation and Anaesthesia at Birth

Ont. P.M.S. 1959, 1960, 1961

Anaesthesia	None Base Population	None Cancer Cases	None Rate*	Any Sedation Base Population	Any Sedation Cancer Cases	Any Sedation Rate*	Total Base Population	Total Cancer Cases	Total Rate*
None	2,563	7	27.3	4,389	9	20.5	6,952	16	23.0
General	10,603	4	3.8	29,108	38	13.1	39,711	42	10.6
Regional	3,528	6	17.0	16,552	14	8.5	20,080	20	10.0
Both	1,161	1	8.6	4,099	5	12.2	5,260	6	11.4
Total	17,855	18	10.1	54,148	66	12.2	72,003	84	16.7

Note: Births with unknown sedation and anaesthesia are excluded.

* Rates are per 10,000.

present study a history of stillbirths was associated with a doubling of childhood cancer rate in later offspring (Table 32) which was not statistically significant. A history of abortions (Table 33) appeared to have little influence upon the risk of cancer. A combination of a history of fetal wastage with x-ray during the relevant pregnancy could only be determined for the 1960, 1961 Ontario population and consequently the numbers were too small (less than 1000 births) to provide reliable rates.

Table 34 shows childhood cancer rates for infants who were born with congenital malformations of any type. The children with congenital malformations have double the cancer rate of normal children although the difference is not statistically significant. Other studies have not been very definite about an association of birth defects with subsequent childhood cancer with the exception of reporting a substantial increase in the incidence of leukemia for children with Down's syndrome (see literature survey). This could not be verified in the present study since it was not possible to be precise about the number of children with Down's syndrome.

XI. Complications of Pregnancy and Delivery

Table 35 shows childhood cancer rates by the occurrence of hemorrhage during the relevant pregnancy. According to this table the presence of a hemorrhage at any time during pregnancy has little effect on the cancer rate of the offspring.

Table 36 shows childhood cancer rates for various methods of delivery. Delivery by caesarean section shows a higher cancer rate while the rates for cephalic and breech births are very similar.

TABLE 32

Cancer Rates by History of Stillbirths

Ont. PMS, 1959, 1960, 1961

Stillbirths	Base Population	Cancer Cases	Rate*
No previous stillbirths	71,066	80	11.3
Any previous stillbirths	1,821	4	22.0
Unknown history	114		
Total	73,001	84	11.5

*Rates are per 10,000

TABLE 33

Cancer Rates by History of Abortions

Abortions	Base Population	Cancer Cases	Rate*
No previous abortions	58,472	64	11.0
Any previous abortions	14,781	20	13.5
Unknown history	168		
Total	73,421	84	11.5

*Rates are per 10,000

TABLE 34

Cancer Rates by Congenital Malformations

Malformations	Base Population	Cancer Cases	Rates*
None	71,256	80	11.2
Any malformation	1,813	4	22.1
Unknown	30		
Total	73,099	84	11.5

*Rates are per 10,000

TABLE 35

Cancer Rates by Hemorrhage during Relevant Pregnancy

Hemorrhage	Base Population	Cancer Cases	Rate*
None or unknown	64,823	76	11.7
Any hemorrhage	8,276	8	9.7
Total	73,099	84	11.5

*Rates are per 10,000

TABLE 36

Cancer Rates by Method of Delivery

Method of Delivery	Base Population	Cancer Cases	Rate*
Cephalic, forceps	67,221	75	11.2
Breech	1,990	2	10.1
Caesarean	3,776	7	18.5
Other and unknown	112		
Total	73,099	84	11.5

*Rates are per 10,000

XII. Blood Groups

Childhood cancer rates for each of the maternal ABO blood groups are shown in Table 37. An interesting feature is the higher childhood cancer rates for the maternal blood groups B and AB than for blood group O and A. The differences are not sufficiently large to show statistical significance. Among diagnostic groups the same trend is very prominent for leukemia while the other two diagnostic groups show no such trend. When age-specific rates are examined the under-four group shows higher cancer rates for B and AB mothers.

Table 38 shows the childhood cancer rates by maternal Rh factor. The mothers with Rh negative blood have the higher cancer rate in their offspring but the difference is not significant at the 5% level. This trend is again most pronounced among children with leukemia and in the under four age groups. The high cancer rate for children of mothers with unknown Rh factor is difficult to explain.

Table 39 shows that the increase in childhood cancer rate is least for the Rh negative mother known to be nonsensitized and greatest for women known to be sensitized and for those with sensitization unknown. Why this last group should present an unusually high childhood cancer rate is difficult to understand unless one makes the rather unlikely assumption that this group includes a high proportion of sensitized women not recorded as such.

Table 40 shows the childhood cancer rates by both maternal ABO blood group and by maternal Rh factor. For blood group O, the cancer rates are very similar for both Rh positive and Rh negative mothers

TABLE 37

Cancer Rates by Maternal ABO Blood Groups

1. Ont. PMS, 1959, 1960, 1961, Brit. PMS

Blood Groups	Base Population	All		Leukemia		C.N.S.		Other Cancers	
		No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
O	24,899	26	10.4	5	2.0	11	4.4	10	4.0
A	20,587	21	10.2	7	3.4	2	1.0	12	5.8
B	5,434	9	16.6	4	7.4	2	3.7	3	5.5
AB	1,927	3	15.6	2	10.4	0		1	5.2
Unknown ABO	36,680	38	10.4	10	2.7	10	2.7	18	4.9
Total	89,527	97	10.8	28	3.1	25	2.8	44	4.9

2.

				0-48 mos.		49-84 mos.		0-84 mos.	
O	24,899	26	10.4	12	4.8	7	2.8	19	7.6
A	20,587	21	10.2	13	6.3	6	2.9	19	9.3
B	5,434	9	16.6	4	7.4	2	3.7	6	11.1
AB	1,927	3	15.6	2	10.4	1	5.2	3	15.6
Unknown ABO	36,680	38	10.4	15	4.1	16	4.4	31	8.5
Total	89,527	97	10.8	46	5.1	34	3.8	90	8.9

*Rates are per 10,000

TABLE 38

Cancer Rates by Maternal Rh Factor

1. Ont. PMS, 1959, 1960, 1961, Brit. PMS

	Base Population	All No.	All Rate*	Leukemia No.	Leukemia Rate*	C.N.S. No.	C.N.S. Rate*	Other Cancers No.	Other Cancers Rate*
Rh positive	69,724	67	9.6	16	2.3	21	3.0	30	4.3
Rh negative	13,505	19	14.1	7	5.2	3	2.2	9	6.7
Unknown	6,300	11	17.5	6	9.5	1	1.6	4	6.4
Total	89,529	97	10.8	29	3.2	25	2.8	43	4.8

2.

				Age 0-48 mos.		49-84 mos.		0-84 mos.	
Rh positive	69,724	67	9.6	32	4.6	24	3.4	56	8.0
Rh negative	13,505	19	14.1	11	8.1	3	2.2	14	10.3
Unknown	6,300	11	17.5	3	4.8	7	11.1	10	15.9
Total	89,529	97	10.8	46	5.1	34	3.8	80	8.9

*Rates are per 10,000

TABLE 39

Cancer Rates for Rh Sensitized and Rh Nonsensitized

Ont. PMS 1959, 1960, 1961

	Base Population	Cancer Cases	Rate*
Rh positive	57,007	56	9.8
Rh negative - all	10,845	18	16.6
- nonsensitized	7,736	9	11.6
- sensitized	357	1	28.0
- sensitization unknown	2,752	8	29.1
Unknown Rh	5,256	10	19.0
Total	73,108	84	11.5

*Rates are per 10,000

TABLE 40

Cancer Rates by Maternal ABO
Blood Group and Rh Factor

Ont. PMS 1959, 1960, 1961, Brit. PMS

ABO Blood Group	Rh Positive			Rh Negative		
	Base Population	Cancer Cases	Rate*	Base Population	Cancer Cases	Rate*
O	20,546	21	10.2	4,294	4	9.3
A	16,614	14	8.4	3,955	7	23.7
B	4,455	6	13.5	968	3	30.9
AB	1,555	2	12.9	373	1	26.8
Total	43,170	43	10.0	9,590	15	15.6
Cases for which either ABO blood group or Rh factor or both are unknown:				36,767	39	10.6
			Total	89,527	97	10.8

*Rates are per 10,000

while for the other blood groups the Rh negative mothers have a very much higher cancer rate among their offspring.

The pattern in Table 40 is reminiscent of the pattern of hemolytic disease of the newborn caused by Rh incompatibility. It has been shown in a number of studies (as reviewed by Marcus, 1969, and Muschel, 1967) that ABO incompatibility between mother and fetus reduces the frequency of isoimmunization to the Rh factor. Almost all ABO incompatibility reactions occur in infants of mothers with O blood group whose anti-A and anti-B antibodies are of the IgG class, which of the major immunoglobulin classes is the only one able to cross the placenta (Marcus, 1969). Therefore for blood group O the incidence of erythroblastosis due to the Rh factor is reduced because of the protection afforded by ABO incompatibility. No such protection occurs in blood groups A, B and AB.

This similarity in pattern suggests (but does not prove) a similarity in mechanism between Rh isoimmunization and the association of maternal blood groups and childhood cancer. The Rh incompatibility, even when erythroblastosis is not clinically evident, could in some manner start a train of events which results in a greater susceptibility of the child to cancer. This possibility is especially suspected for leukemia, since both in Tables 37 and 38 the leukemia rates show the most pronounced association with maternal Rh blood group.

If the maternal-fetal Rh incompatibility influences childhood cancer, the cancer rate among children of Rh negative mothers may be expected to increase with birth order because the likelihood of sensitization of the mother increases with each successive birth. Table 41

TABLE 41

Cancer Rates by Maternal Blood Group and Birth Order of Child

Ont. PMS 1960, 1961

Birth Order	Rh Factor of Mother					
	Rh Positive			Rh Negative		
	Base Population	Cancer Cases	Rate	Base Population	Cancer Cases	Rate
First	13,298	9	6.8	2,497	1	4.0
Second	10,863	11	10.1	2,134	5	23.4
Third and over	15,452	17	11.0	2,913	4	13.7
Total	39,613	37	9.3	7,544	10	13.3

Notes: Births with unknown birth order or unknown Rh factors are not included.

shows the childhood cancer rates by maternal Rh factor and birth order of the child. The fact that the cancer rate for the first-born children of Rh negative mothers is based on only one case, detracts greatly from the value of the table. Tables showing childhood cancer rates for maternal blood groups by infant blood groups would be very interesting but cannot be provided here since infant blood group was recorded for only one quarter of the infants.

For Tables 37 and 38, cancer rates were also calculated based on person-years in order to determine whether the difference in years of exposure of the various subdivisions of the base population affects the trends in the relationship between childhood cancer and maternal blood groups. For maternal blood group O the childhood cancer rate is 14.0, for blood group A it is 12.7, for blood group B it is 20.4 and for blood group AB it is 19.2 per 100,000 person-years. The trend shown when rates are given per 100,000 person-years is very similar to that when the rates are given per 10,000 births. Similarly, for the maternal Rh positive blood group, the childhood cancer rate is 11.7 while for mothers with Rh negative blood the childhood cancer rate is 17.2 per 100,000 person-years. The ratio of rates is 1.47 whether the rates are calculated for 10,000 births or per 100,000 person-years. Thus both for the maternal ABO blood groups and presence or absence of Rh factor, the relative risks of childhood cancer are not affected by years exposure of the children to cancer risk.

Another factor to be considered is the variation of both blood groups and cancer incidence with a third factor, ethnic origin, as described in the literature survey. The presence of an excess of persons

of Jewish ethnic origin in certain blood groups as well as in the cancer population has been found previously (MacMahon & Folusiak, 1958) but is unlikely to affect results of the present study. The percentage of the total population of Jewish origin in Kingston, London, Ottawa and Toronto is less than 1.5% (Canada, Census 1961). Thus among the 84 cancer cases from these places one or two may be expected to be of Jewish origin. However, even a doubling or tripling of this number, because of the greater susceptibility of persons of Jewish origin to leukemia, is very unlikely to account for the differences in the cancer rates for certain ABO and Rh blood groups. This could not be checked more precisely in this study, since the ethnic origin was not recorded on the perinatal record.

A need for further investigation of the relation between maternal and fetal blood groups, on the one hand, and development of childhood cancer, on the other, is strongly indicated by the present results. Such further research may shed some light on the mechanism and causation of cancer in children.

DISCUSSION

I. Smoking during Pregnancy

In the present study, the women who smoked any amount during pregnancy showed a cancer rate in their offspring 33% higher than that among the children of nonsmokers. This excess cannot be shown to be statistically significant (the 95% confidence limits of the ratio 1.33 are 0.81 to 2.2). In addition, a dose-response relation is lacking since the children of heavy smokers show a cancer rate numerically similar to that of nonsmokers. A dose-response relation could be expected here since an increased amount of smoking has been found to be associated with an increased risk of lung cancer. However, the heavy smokers in this study are the smallest group and thus present the least reliable rates. In this context the investigation by Welch et al (1969) may be mentioned, in which the placentas of smokers and of nonsmokers were examined for the presence of 3,4-benzpyrenehydroxylase. This enzyme was present in the placentas of smokers but not in those of nonsmokers, although no dose-response relation could be shown. They explained this by the varying amounts of this carcinogen present in the different brands of cigarettes and were able to show a dose-response relation when they subjected rats to known amounts of carcinogen. The same reasoning might apply in a dose-response relation between the association of smoking in pregnancy and subsequent cancer in the offspring. Of course, this latter relationship may involve other or additional carcinogens of those present in tobacco smoke.

MacMahon (1962) found a 40% increase in childhood cancer risk for children of women who were irradiated during pregnancy. An increase of this magnitude due to smoking in pregnancy is possible and can neither by proved nor disproved by the present results. Studies like those of MacMahon (1962) and Stewart et al (1958) were instrumental in reducing X-ray exposure during pregnancy to the necessary minimum. Judicious use of prenatal X-rays is still needed to reduce complications by anticipating obstetrical difficulties, or diagnosing maternal problems, e.g. kidney disorders. In considering smoking during pregnancy, the practical situation is quite different. An increase in childhood cancer due to smoking during pregnancy is not necessary as an argument to stop women smoking during pregnancy, since a more powerful argument lies in the relation between smoking and prematurity. In the 1960, 1961 Ontario study, 659 perinatal deaths occurred among infants of nonsmoking mothers (23.2 per 1000 births) and 645 among smokers (29.4 per 1000 births), the increased rate for the latter being mainly due to the higher prematurity rate for smokers (Ontario Perinatal Mortality Study Committee, 1967). If the smokers had experienced the same perinatal mortality rate as nonsmokers, only 508 infants would have died in this group, a saving of 137 infants' lives. In the same 1960, 1961 population of births, 52 children were found to have cancer before the end of 1968. Thus any possible increase in number of cancer cases due to smoking is small when compared to the increase in prematurity and hence and increase in number of perinatal deaths.

The main importance of the examination of an association between smoking during pregnancy and the childhood cancer rate is in terms of the etiology of cancer. Any further knowledge of the causation of cancer is

gain. In this perspective the results of this study can be summarized by saying that in increase of childhood cancer due to smoking is still possible but that a tripling in rates, or even a 2.5-fold increase, is extremely unlikely. This becomes particularly meaningful when one considers that smoking multiplies the risk of lung cancer as much as ten times for men smoking less than one pack per day, and five times for women with the most exposure (Public Health Service Publication. No. 1696, p. 34).

II. Blood Groups

A number of other variables other than smoking during pregnancy were considered in relation to the development of cancer in the offspring. Some of these variables have been investigated in other studies, while others have not. Of the latter, the most interesting results were obtained by examining the relation between blood groups and childhood cancer. Although many of the associations between maternal blood groups and childhood cancer were not statistically significant, what encourages further investigation is the congruence of the results with other knowledge and the consistency of these results with each other.

The congruence with other knowledge becomes clear in comparing the present results with the association between maternal blood group and hemolytic disease of the newborn due to Rh incompatibility. The highest childhood cancer rates are shown for the offspring of mother with B and AB blood groups, and for mothers with Rh negative blood (Tables 37 and 38). When cancer rates are shown subdivided for both ABO and Rh blood groups (Table 40), the Rh negative mothers consistently have the highest rate re-

gardless of ABO blood group, excepting those of blood group O. This is consistent with the trend expected for hemolytic disease of the newborn due to Rh incompatibility.

The other analyses are also consistent with this trend. Thus the cancer rate is lower for mothers known to be Rh negative unsensitized than for the other Rh negative women. For the site-specific rates it is seen that for both maternal ABO blood and maternal Rh factor the trend appears to be mainly due to leukemia, while for the age-specific rates to the under four age-group. Further investigation is needed here to confirm these observations, and if confirmed, to make further analyses, e.g., childhood cancer rates by both maternal and infant blood groups. At that time speculation regarding the possible immunological mechanism becomes feasible.

The question can be raised as to why none of the children in the base population with erythroblastosis developed cancer. In the 1960, 1961 Ontario data, 359 infants were coded as having Rh erythroblastosis and surviving at least seven days. At a rate of 21.5 per 10,000 (the rate for Rh negative mothers) 0.8 cancer cases would be expected in the 359 cases with erythroblastosis. According to a table of individual terms of the Poisson distribution (Table 39, Pearson and Hartley, 1966) the probability of zero cases in this situation is 0.45. Similarly at a rate of 30 per 10,000, 1.1 cases may be expected and the probability of no cases is 0.33. At a rate of 40 per 10,000 the probability of no cases is 0.25; and at rate of 50 per 10,000 it is still 0.17. Therefore even at a very high cancer rate, the likelihood is substantial that no cases might have occurred in the 359 children with

erythroblastosis.

III. The Unknown Categories

Several of the tables show unusually high childhood cancer rates among the offspring of women whose status with respect to the pertinent variable was unknown. This is particularly true for unknown paternal age (Table 11) with a rate of 20.4 per 10,000, unknown birthplace of mother (Table 23) with a rate of 38.0 per 10,000, unknown anxiety in the mother during pregnancy (Table 28) with a rate of 18.3 per 10,000 and unknown Rh (Table 38) with a rate of 17.5 per 10,000. These rates are based on 9 to 11 cancer cases. In many other tables the unknown category is too small to give a reliable rate.

There are some reasons why the unknowns may be different from the rest of the table in which they occur. For example, the unknown paternal age category includes the single women. However, Table 22 shows that the single, divorced and separated women do not show a higher rate for childhood cancer. Also the perinatal forms may not have been completed as carefully for public patients as for private patients. However, the cancer rate for public patients was no higher than that for the private hospital patients (Table 21).

What is the difference between the unknown category and the other women for any variable? It is unlikely to be a random process where each woman in the study has an equal chance of being in the unknown category. Whatever factors cause a mother to be in the unknown category could possibly be associated with the risk of childhood cancer. Further investigation of the unknown category would entail a separate

examination of the data for this purpose, perhaps by interviewing a sample of unknowns. This is beyond the scope of the present study.

IV. Other Variables Needing Further Examination

The present study was begun on the basis of a hypothesis concerning the relation of smoking in pregnancy to cancer in the offspring. Since a great deal of other information was available on the course of the pregnancy, other variables could be investigated as well in relation to childhood cancer. Because these relations are being considered without a priori hypotheses, conclusions should be drawn with great care. However, one important aspect of studying such a series of relations is that it may lead to further research.

Table 42 lists the variables for which a 50% in childhood cancer risk was found for one of the categories. Of these, sex of child, history of stillbirths and congenital malformations of the child have been mentioned in other studies, but certainly have not been studied exhaustively. The higher cancer rates for the offspring of women showing depression, anxiety and worry, or taking tranquilizers (Table 28) are fascinating, and further work here would be of great interest. The differences in rates associated with the presence or absence of anaesthesia are very puzzling since it is the category without anaesthesia that has the high rate. The presence of a higher rate for the caesarean births than for the vaginal deliveries is opposed to that expected from the anaesthesia results since a larger proportion of caesarean births received anaesthesia.

Since few of the sets of rates mentioned in Table 42 have

TABLE 42

Variables Showing a 50% or Higher Increase in Cancer Risk

	Low Childhood Cancer Rate	High Childhood Cancer Rate	% increase in Cancer Rate
Sex	Female	Male	59%
Anxiety	None	Any	126%
Tranquilizers	None	Any	71%
Previous Stillbirths	None	Any	95%
Anaesthesia	Any	None	121%
Congenital Malformation	None	Any	97%
Method of Delivery	Cephalic	Caesarian	65%
ABO Blood Group	O,A	B, AB	58%

ratios statistically significantly different from one, it is quite probable that many of the differences have arisen by chance. Nevertheless, further investigation is necessary and may be very informative in the study of the epidemiology of childhood cancer.

SUMMARY AND CONCLUSIONS

This study is a prospective investigation of a possible relationship between smoking during pregnancy and the development of cancer in the offspring. A number of other prenatal factors were also examined for possible influence on childhood cancer risk.

Extensive records were available on events during the pregnancy and delivery for the 73,099 births, surviving at least seven days, of the Ontario Perinatal Mortality Study conducted in 1959, 1960 and 1961, in ten university teaching hospitals in Ontario. Lists of childhood cancer deaths were received from the Cancer Statistics Section of the Ontario Department of Health. All cancer clinics in the province were visited, as well as the Hospital for Sick Children and the Princess Margaret Hospital in Toronto, for data on any children of the right ages, who were being treated for cancer. The names and further information were then sent to the Deputy Registrar of Ontario in order to complete the data necessary for linkage with the Ontario Perinatal Study records. By this method 54 deaths and 30 survivors were collected until the cut-off point in December 1968.

The data from the British Perinatal Mortality Survey, consisting of 16,350 survivors could be added as well. These were followed from birth to between seven and eight years and provided 13 cancer cases -- 11 deaths and 2 survivors.

All smokers combined showed a 33% increase in cancer rate for

their offspring when compared to the children of nonsmokers. However, this difference was not statistically significant. A tripling of cancer risk for the children of smokers could be excluded, which is important in view of the greater increase in lung cancer risk for smokers. A dose-response relation between amount smoked during pregnancy and childhood cancer rate was not evident, casting further doubt upon the hypothesis. No site-specific trends could be shown. The age-specific rates showed a substantial increase in cancer rates for the children, under two, of mothers who were heavy smokers during pregnancy, for children, between two and four years old of light smokers, and an apparent deficiency in cancer risk for children, in the age group five and over, of all smokers.

Many other factors were also examined in relation to childhood cancer risk: age of parent, birth order of child, sex of child, birth weight, gestation period, environmental factors during pregnancy, preconception and in utero irradiation, the history of fetal wastage of the mother, the presence of congenital malformations in the child, drugs taken by the mother during pregnancy, the method of delivery, the presence of hemorrhage during pregnancy, and maternal blood groups.

Of the variables mentioned above, the maternal blood groups provided the most interesting results. Among the ABO blood groups, B and AB showed the highest childhood cancer rates and in the comparison of Rh groups, the children of Rh negative mothers showed the highest cancer risk in children. Both of these trends were especially prominent for leukemia. When cancer rates were made specific for both ABO and Rh blood groups, the Rh negative mothers consistently had the higher rate

regardless of ABO blood group, with the exception of blood group O. This is consistent with the trend expected for hemolytic disease of the newborn due to Rh isoimmunization.

A number of suggestions for further research were made on the basis of the other variables investigated.

BIBLIOGRAPHY

Ager, E.A., Schuman, L.M., Wallace, H.M., Rosenfield, A.B. & Gullen, W.H. (1965). An epidemiological study of childhood leukemia. J. Chronic. Dis. 18: 113-132.

Berenblum, I. & Schoental, R.C. (1943). The metabolism of 3, 4-benzpyrene in mice and rats. I. The isolation of a hydroxy and a quinone derivative, and consideration of their biological significance. Cancer Res. 3: 145-150.

Buck, C., Gregg, R. Stavraky, K., Subrahmaniam, K. & Brown, J. (1969). The effect of single prenatal and natal complications upon the development of children of mature birth weight. Pediatrics 43: 942-955.

Butler, N.R. & Alberman, E.D. ed. (1969). Perinatal problems. The second report of the 1958 British Perinatal Mortality Survey. Edinburgh and London: E. & S. Livingstone Ltd.

Butler, N.R. & Bonham, D.G. ed. (1963). Perinatal Mortality. The First Report of the 1958 British Perinatal Mortality Survey. Edinburgh and London: E. & S. Livingstone Ltd.

Campbell, A.C., Gaisford, W., Patterson E. & Steward, J.K. (1961). Tumours in children. A survey carried out in the Manchester region. Brit. Med. J. 1: 448-452.

Canada, Dominion Bureau of Statistics (1960=1968). Vital Statistics. Ottawa: Queen's Printer.

Canada, Dominion Bureau of Statistics (1961). Reports of the Census of Canada, vol. 1 (part 1). Ottawa: Queen's Printer.

Cochran, W.G. (1954). Some methods for strengthening the common X^2 tests. Biometrics 10: 417-451.

Comstock, G.W. & Lundin, F.E. Jr. (1967). Parental smoking and perinatal mortality. Amer. J. Obstet. Gynec. 98: 708-718.

Cordone, G. & Tavella, F. (1963). Blood groups and leukemia during childhood. Minverva Pediat. 15: 631-633.

Court Brown, W.M., Doll, R. & Hill, A.B. (1960). The incidence of leukemia after exposure to diagnostic radiation in utero. Brit. Med. J. 2: 1539-1545.

Doll, R. & Hill, A.B. (1956). Lung cancer and other causes of death in relation to smoking; second report on mortality of British doctors. Brit. M.J. 2: 1071-1081.

Ederer, F., Miller, R.W., & Scotto, J. (1965). U.S. childhood cancer mortality patterns, 1950-1959, J.A.M.A. 192: 593-596.

Ederer, F., Myers, M.H. & Mantel, N. (1964). A statistical problem in space and time: do leukemia cases come in clusters? Biometrics 20: 626-636.

Elliot, E., Githens, J.H. & Saunders, L.H. (1961). The influence of socioeconomic factors on the incidence of childhood leukemia. Am. J. Dis. Child. 102: 483-484.

Ford, D.D., Paterson, J.C.S. & Treuting, W.L. (1959). Fetal exposure to diagnostic x-rays, and leukemia and other malignant diseases in childhood. J. Nat. Cancer Inst. 22: 1093-1104.

Fraumeni, J.F. Jr. (1968). Cigarette smoking and cancer of the urinary tract: geographic variation in the United States. J. Nat. Cancer Inst. 41: 1205.

Fraumeni, J.F. Jr. & Miller, R.W. (1969). Cancer deaths in the newborn. Amer. J. Dis. Child. 117: 186-189.

Gibson, R.W., Bross, I.D., Graham, S., Lilienfeld, A.M., Schuman, L.M., Levin, M.L. & Dowd, J.E. (1968). Leukemia in children exposed to multiple risk factors. New Eng. J. Med. 279: 906-909.

Graham, S., Levin, M.L., Lilienfeld, A.M., Dowd, J.E., Schuman, L.M., Gibson, R., Hempelman, L.H. & Gerhardt, P. (1963). Methodological problems and design of the tristate leukemia survey. Ann. N.Y. Acad. Sci. 107: 557-569.

Graham, S., Levin, M.L., Lilienfeld, A.M., Schuman, L.M., Gibson, R., Dowd, J.E. & Hempelmann, L. (1966). Preconception, intrauterine, and postnatal irradiation as related to leukemia. Nat. Cancer Inst., Monogr. 19: 347-371.

Hammond, E.C. & Horn, D.J. (1958). Smoking and death-rates. Report on forty-four months of follow up of 187,783 men. I. Total mortality, p. 1159. II. Death rates by cause, p. 1294. J.A.M.A. 166: 1159, 1294.

Heath, C.W. & Hasterlik, R.J. (1963). Leukemia among children in a suburban community. Amer. J. Med. 34: 796-812.

Hernandez, K. & Tokuhata, G. (1966). Epidemiologic study of childhood leukemia in Memphis and Shelby County, 1939-62. Public Health Rep. 81: 598-606.

Iversen, T. (1965). Leukemia in children. Acta Paediat. Scan. Suppl. 159: 161-162.

Jarvinnen, P.A. & Osterlund, K. (1963). Effect of smoking during pregnancy of the fetus, placenta and delivery. Ann. Paediat. Fenn. 9: 18-26.

Kerr, W.K., Barkin, M., Levers, P.E., Woo, S.K-C. & Menczyk, Z. (1965). The effect of cigarette smoking on bladder carcinogens in man. Canad. Med. Ass. J. 93: 1-7.

Kjelsberg, H. (1957). Relationship between leukemia and x-rays. T. Norsk. Laegeforen 77: 1052.

Klauber, M.R. (1968). A study of clustering childhood leukemia by hospital of birth. Cancer Res. 28: 1790-1792.

Knox, G. (1964). Epidemiology of childhood leukemia in Northumberland and Durham. Brit. J. Prev. Soc. Med. 18: 17-24.

Lewis, T.L.T. (1960). Leukemia in childhood after antenatal exposure to x-rays. Brit. Med. J. 2: 1551-1552.

Lilienfeld, A.M. (1964). The relationship of bladder cancer to smoking. Amer. J. Public Health 54: 1864-1875.

Lowe, C.R. (1959). Effects of mother's smoking habits on birth weight of their children. Brit. Med. J. 2: 673-676.

MacMahon, B. (1962). Prenatal x-ray exposure and childhood cancer. J. Nat. Cancer Inst. vol. 28: 1173-1191.

MacMahon, B., Alpert, M. & Salber, E.J. (1965). Infant weight and parental smoking habits. Amer. J. Epidem. 82: 247-261.

MacMahon, B. & Folusiak, J.C. (1958). Leukemia and ABO blood group. Amer. J. Hum. Genet. 10: 287-293.

MacMahon, B. & Hutchison, G.B. (1964). Prenatal x-ray and childhood cancer: a review. Acta Un. Int. Cancr. 20: 1172-1174.

MacMahon, B. & Newill, V.A. (1962). Birth characteristics of children dying of malignant neoplasms. J. Nat. Cancer Inst. 28: 231-244.

Manning, M.D. & Carroll, B.E. (1957). Some epidemiological aspects of leukemia in children. J. Nat. Cancer Inst. 19: 1087-1094.

Marcus, D.M. (1969). The ABO and Lewis blood group system. Immunochemistry, genetics and relation to human disease. New Eng. J. Med. 280: 994-1006.

Meadors, G.F. (1956). Epidemiology of leukemia. Public Health Rep. 71: 103-108.

Meighan, S.S. & Knox, G. (1965). Leukemia in childhood. Epidemiology in Oregon. Cancer 18: 811-814.

Miller, R.W., Fraumeni, J.F. Jr., & Hill, J.A. (1968). Neuroblastoma: epidemiologic approach to its origin. Amer. J. Dis. Child. 115: 253-261.

Miller, R.W., Fraumeni, J.F. Jr. & Manning, M.D. (1964). Association of Wilms's tumor with anicridia, hemihypertrophy and other congenital malformations. New Eng. J. Med. 270: 922-927.

Murray, R., Heckel, P. & Hempelmann, L.H. (1959). Leukemia in children exposed to ionizing radiation. New Eng. J. Med. 261: 585-589.

Muschel, L.H. (1966). Blood groups, disease, and selection. Bact. Rev. 30: 427-441.

O'Lane, J.M. (1963). Some fetal effects of maternal cigaret smoking. Obstet. Gynec. 22: 181-184.

Ontario, Department of Health, Research and Planning Branch (1967). Special Report #41. The 32nd annual statistical report on cancer.

Ontario, Registrar General (1962-1967). Vital Statistics. Toronto: Queen's Printer.

Ontario Perinatal Mortality Study Committee (1961). Report of the perinatal mortality study, 1959, in ten university teaching hospitals, Ontario, Canada.

Ontario Perinatal Mortality Study Committee (1967). Second report of the perinatal mortality study in ten university teaching hospitals, Ontario, Canada.

Pearson, E.S. & Hartley, H.O. (1966). Biometrika tables for statisticians. Vol. 1, 3rd ed. Cambridge: University Press.

Pinkel, D. & Nefzger, D. (1959). Some epidemiological features of childhood leukemia in the Buffalo, N.Y., area. Cancer 12: 351-358.

Pinkel, D., Dowd, J.E. & Bross, I.D. (1963). Some epidemiological features of malignant solid tumors of children in the Buffalo, N.Y. area. Cancer 16: 28-33.

Ravenholt, R.T., Levinski, M.J., Nellist, D.J., & Takenaga, M. (1966). Effects of smoking upon reproduction. Amer. J. Obstet. Gynec. 96: 267-281.

Savel, L.E. & Roth, E. (1962). Effects of smoking in pregnancy: A continuing retrospective study. Obstet. Gynec. 20: 313-316.

Sessions, R.T., McSwain, B. & Stephenson, S.E. Jr. (1964). Malignancy occurring during the first two decades of life: An analysis of 35 years experience. Acta Un. Int. Cancr. 20: 774-778.

Stark, C.R. & Mantel, N. (1966). Effects of maternal age and birth order on the risk of mongolism and leukemia. J. Nat. Cancer Inst. 37: 687-698.

Stark, C.R. & Oleinich, A. (1966). Urban or rural residence and histologic type distribution in 21,000 childhood leukemia deaths in the United States, 1950-1959. J. Nat. Cancer Inst. 37: 369-379.

Stavraky, K.M. (1963). A study of the development and behaviour of the young child in relation to the pre-natal and natal history. Unpublished thesis. London: University of Western Ontario.

Stewart, A., Webb, J. & Hewitt, D. (1958). A survey of childhood malignancies. Brit. Med. J. 1, 1495-1508.

U.S. Department of Health, Education, and Welfare (1964). Smoking and health. Report of the advisory committee to the Surgeon-general of the Public Health Service. Washington: Public Health Service Publication No.1103.

U.S. Department of Health, Education and Welfare (1967). The health consequences of smoking. Washington: Public Health Service Publication No. 1696.

Welch, R.M., Harrison, Y.E. & Conney, A.H. (1968). Cigarette smoking: stimulatory effect on metabolism of 3, 4-benzpyrene by enzymes in in human placenta. Science 160: 541-542.

Welch, R.M., Harrison, Y.E., Gommi, B.W., Poppers, P.J., Finster, M. & Conney, A.H. (1969). Stimulatory effect of cigarette smoking on the hydroxylation of 3, 4-benzpyrene and the N-demethylation of 3-methyl-4-monomethylaminoazobenzene by enzymes in human placenta. Clin. Pharmacol. Ther. 10: 100-109.

Wells, J. and Steer, C.M. (1961). Relationship of leukemia in children to abdominal irradiation of mothers during pregnancy. Amer. J. Obstet. Gynec. 81: 1059-1063.

Wiener, A.S. (1965). Advances in blood grouping, vol. II. New York: Grune and Stratton.

Woolf, B. (1954). On estimating the relation between blood group and disease. Ann. Hum. Genet. 19: 251-253.

Wynder, E.L. ed. (1955). The biologic effects of tobacco. Boston: Little, Brown.

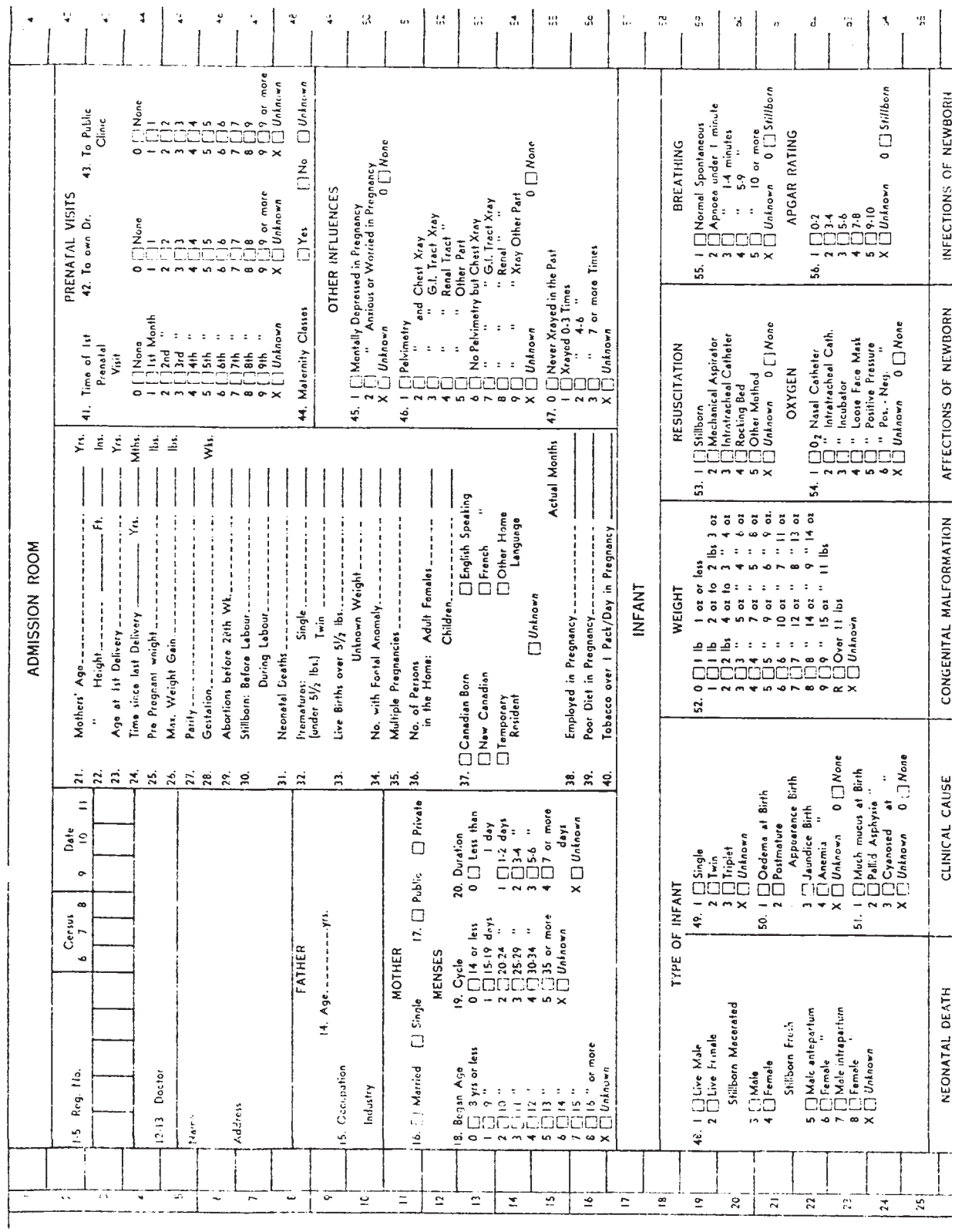
Wynder, E.L. & Hoffmann, D. (1967). Tobacco and tobacco smoke. New York: Academic Press.

Yerushalmy, J. (1964). Mother's cigarette smoking and survival of infant. Amer. J. Obstet. Gynec. 88: 505-518.

Zabriskie, J.R. (1963). Effect of cigaret smoking during pregnancy. Obstet. Gynec. 21: 405-414.

APPENDIX A

1959 Perinatal Record, Side 1



13 [ ] [ ]
14 [ ] [ ]
15 [ ] [ ]
16 [ ] [ ]
17 [ ] [ ]
18 [ ] [ ]
19 [ ] [ ]
20 [ ] [ ]
21 [ ] [ ]
22 [ ] [ ]
23 [ ] [ ]
24 [ ] [ ]
25 [ ] [ ]
26 [ ] [ ]
27 [ ] [ ]
28 [ ] [ ]
29 [ ] [ ]
30 [ ] [ ]
31 [ ] [ ]
32 [ ] [ ]
33 [ ] [ ]
34 [ ] [ ]
35 [ ] [ ]
36 [ ] [ ]
37 [ ] [ ]
38 [ ] [ ]
39 [ ] [ ]
39 [ ] [ ]
40 [ ] [ ]

3 [ ] 11 "
4 [ ] 12 "
5 [ ] 13 "
6 [ ] 14 "
7 [ ] 15 "
8 [ ] 16 " or more
X [ ] *Unknown*

3 [ ] 25-29 "
4 [ ] 30-34 "
5 [ ] 35 or more
X [ ] *Unknown*

4 [ ] 7 or more days
X [ ] *Unknown*

[ ] *Temporary Resident*

[ ] *Other Home Language*

[ ] *Unknown*

Actual Months

38. Employed in Pregnancy _____
39. Poor Diet in Pregnancy _____
40. Tobacco over 1 Pack/Day in Pregnancy _____

9 [ ] " " " Xray Other Part
X [ ] *Unknown* 0 [ ] *None*

47. 0 [ ] Never Xrayed in the Past
1 [ ] Xrayed 0-3 Times
2 [ ] " 4-6 "
3 [ ] " 7 or more Times
X [ ] *Unknown*

54 [ ] [ ]
55 [ ] [ ]
56 [ ] [ ]
57 [ ] [ ]
58 [ ] [ ]
59 [ ] [ ]
60 [ ] [ ]
61 [ ] [ ]
62 [ ] [ ]
63 [ ] [ ]
64 [ ] [ ]
65 [ ] [ ]
66 [ ] [ ]
67 [ ] [ ]
68 [ ] [ ]
69 [ ] [ ]
70 [ ] [ ]
71 [ ] [ ]
72 [ ] [ ]
73 [ ] [ ]
74 [ ] [ ]
75 [ ] [ ]
76 [ ] [ ]
77 [ ] [ ]
78 [ ] [ ]
79 [ ] [ ]
80 [ ] [ ]

INFANT

TYPE OF INFANT

48. 1 [ ] Live Male
2 [ ] Live Female

Stillborn Macerated

3 [ ] Male
4 [ ] Female

Stillborn Fresh

5 [ ] Male antepartum
6 [ ] Female "
7 [ ] Male intrapartum
8 [ ] Female "
X [ ] *Unknown*

49. 1 [ ] Single
2 [ ] Twin
3 [ ] Triplet
X [ ] *Unknown*

50. 1 [ ] Oedema at Birth
2 [ ] Postmature
Appearance Birth
3 [ ] Jaundice Birth
4 [ ] Anemia "
X [ ] *Unknown* 0 [ ] *None*

51. 1 [ ] Much mucus at Birth
2 [ ] Pallid Asphyxia "
3 [ ] Cyanosed at "
X [ ] *Unknown* 0 [ ] *None*

WEIGHT

52. 0 [ ] 1 lb 1 oz or less
1 [ ] 1 lb 2 oz to 2 lbs 3 oz
2 [ ] 2 lbs 4 oz to 3 " 4 oz
3 [ ] 3 " 5 oz " 4 " 6 oz
4 [ ] 4 " 7 oz " 5 " 8 oz
5 [ ] 5 " 9 oz " 6 " 9 oz.
6 [ ] 6 " 10 oz " 7 " 11 oz
7 [ ] 7 " 12 oz " 8 " 13 oz
8 [ ] 8 " 14 oz " 9 " 14 oz
9 [ ] 9 " 15 oz " 11 lbs
R [ ] Over 11 lbs
X [ ] *Unknown*

RESUSCITATION

53. 1 [ ] Stillborn
2 [ ] Mechanical Aspirator
3 [ ] Intratracheal Catheter
4 [ ] Rocking Bed
5 [ ] Other Method
X [ ] *Unknown* 0 [ ] *None*

OXYGEN

54. 1 [ ] O_2 Nasal Catheter
2 [ ] " Intratracheal Cath.
3 [ ] " Incubator
4 [ ] " Loose Face Mask
5 [ ] " Positive Pressure
6 [ ] " Pos. - Neg. "
X [ ] *Unknown* 0 [ ] *None*

BREATHING

55. 1 [ ] Normal Spontaneous
2 [ ] Apnoea under 1 minute
3 [ ] " 1-4 minutes
4 [ ] " 5-9 "
5 [ ] " 10 or more
X [ ] *Unknown* 0 [ ] *Stillborn*

APGAR RATING

56. 1 [ ] 0-2
2 [ ] 3-4
3 [ ] 5-6
4 [ ] 7-8
5 [ ] 9-10
X [ ] *Unknown* 0 [ ] *Stillborn*

NEONATAL DEATH

57. 1 [ ] Within 1 hr. of delivery
2 [ ] 1- 5 hrs " "
3 [ ] 6-11 " " "
4 [ ] 12-23 " " "
5 [ ] 24-47 " " "
6 [ ] 2- 7 days " "
7 [ ] 8-28 " " "
X [ ] *Unknown* 0 [ ] *None*

AUTOPSY

58 1 [ ] Live infant
2 [ ] Stillborn Autopsy
3 [ ] Neonate Autopsy
X [ ] *Unknown* 0 [ ] *None*

PATHOLOGY COLS. 70-79

CLINICAL CAUSE

59. 0 [ ] No Neonatal Death
1 [ ] Anoxia
2 [ ] Abnormal Pulm. Vent.
3 [ ] Birth Injury
4 [ ] Intestinal Infection
5 [ ] Respiratory "
6 [ ] Other "
7 [ ] Cong. Malformation
8 [ ] Erythroblastosis
9 [ ] Prematurity Alone
R [ ] Other Condition
X [ ] *Unknown*

CONGENITAL MALFORMATION

60. 1 [ ] Anencephaly
2 [ ] Other Skull & Spine
3 [ ] Skin, Muscle , Subcut.
4 [ ] Harelip , Cleft Palate
5 [ ] G.U. System
6 [ ] G.I. "
7 [ ] Cardiovascular
8 [ ] Bones & Joints
9 [ ] Multiple Malformations
R [ ] Other "
X [ ] *Unknown* 0 [ ] *None*

AFFECTIONS OF NEWBORN

61. 1 [ ] Stillborn
2 [ ] Erythroblastosis RH
3 [ ] " ABO
X [ ] *Unknown* 0 [ ] *None*

62. 1 [ ] Stillborn
2 [ ] Rh Transfused
3 [ ] Other Anemia
4 [ ] Other Jaundice
X [ ] *Unknown* 0 [ ] *None*

63. 1 [ ] Stillborn
2 [ ] Abnormal Pulm. Vent
3 [ ] Cardiac Failure
4 [ ] Cerebral Dysfunction
5 [ ] Other Birth Injury
6 [ ] Hmgic Disease of NB.
7 [ ] Other Condition
X [ ] *Unknown* 0 [ ] *None*

INFECTIONS OF NEWBORN

64. 1 [ ] Stillborn
2 [ ] Conjunctivitis
3 [ ] Omphalitis
4 [ ] Diarrhea
X [ ] *Unknown* 0 [ ] *None*

65. 1 [ ] Stillborn
2 [ ] Thrush
3 [ ] Pneumonia
4 [ ] Pyoderma
5 [ ] Other Dermatitis
6 [ ] Meningitis
7 [ ] Other Infection
X [ ] *Unknown* 0 [ ] *None*

BACTERIOLOGY

66. 1 [ ] Staph. Aureus
2 [ ] Other Staph.
3 [ ] Strep.
4 [ ] Specific Coli.
5 [ ] Other Organism
X [ ] *Unknown* 0 [ ] *None*

OXYGEN IN NURSERY

67 1 [ ] Stillborn
2 [ ] Under 24 hrs.
3 [ ] 24-47 hrs.
4 [ ] 3 or more days
X [ ] *Unknown* 0 [ ] *None*

WEIGHT LOSS

68. 1 [ ] Stillborn
2 [ ] 1- 3 oz
3 [ ] 4- 6 oz
4 [ ] 7-10 oz
5 [ ] 11-16 oz
6 [ ] Over 16 oz
X [ ] *Unknown* 0 [ ] *None*

INFANT FEEDING

69 1 [ ] Stillborn
2 [ ] Breast Only
3 [ ] " & Supplement
4 [ ] Bottle Hand Fed
5 [ ] Bottle Prepped
X [ ] *Unknown* 0 [ ] *None*

COMMENT

80. 1 [ ] Yes
2 [ ] No

1-5 REG. NO.

OBSTETRICIAN

DRUGS TAKEN IN PREGNANCY	NAME	MONTHS TAKEN
6	HORMONE	
7	HYPOTENSIVE	
8	DIURETIC	
9	CALCIUM	

	NAME	MONTHS TAKEN
10	VITAMIN A	
11	" D	
12	" E	
13	IRON	

PAST OBS. HISTORY

14. 1 [ ] Infection
2 [ ] Other Med. Complication
X [ ] *Unknown* 0 [ ] *None*

15. 1 [ ] Toxaemia
X [ ] *Unknown* 0 [ ] *None*

16. 1 [ ] Antepartum Hge
2 [ ] Post " "
3 [ ] Other Labour Difficulty
X [ ] *Unknown* 0 [ ] *None*

17. 1 [ ] Surgical Complication
X [ ] *Unknown* 0 [ ] *None*

18. 1 [ ] Caesarian Section
X [ ] *Unknown* 0 [ ] *None*

19. 1 [ ] Isoimmunization
X [ ] *Unknown* 0 [ ] *None*

BLOOD GROUP

20. 1 [ ] Blood Group O
2 [ ] " " A
3 [ ] " " B
4 [ ] " " AB
X [ ] " " Unknown

21. 1 [ ] Rh Positive
2 [ ] Rh Negative
X [ ] Rh Not Tested

22. 1 [ ] Rh Rising Titre
X [ ] " Titre Unknown

23. 1 [ ] Past Blood Transfusion
X [ ] *Post Unknown* 0 [ ] None

COMPLICATIONS OF PREGNANCY

24. 1 [ ] Diabetes
2 [ ] Heart Disease
3 [ ] Tuberculosis
4 [ ] Other Chronic Disease
X [ ] *Unknown* 0 [ ] *None*

25. 1 [ ] Pyelitis
2 [ ] Rubella
3 [ ] Other Infectious Dis.
4 [ ] " Acute Disease
X [ ] *Unknown* 0 [ ] *None*

26. 1 [ ] Physical Injury
2 [ ] Surgical Operation
X [ ] *Unknown* 0 [ ] *None*

27. 1 [ ] Anemia under 8 gms.
2 [ ] " 8-11 gms.
3 [ ] " over 11 gms.
X [ ] *Unknown* 0 [ ] *None*

28. 1 [ ] Hyperemesis
X [ ] *Unknown* 0 [ ] *None*

29. 1 [ ] Glycosuria
X [ ] *Unknown* 0 [ ] *None*

30. 1 [ ] Albuminuria
X [ ] *Unknown* 0 [ ] *None*

31. 1 [ ] Spotting in early Preg.
2 [ ] Threatened Abortion
3 [ ] Vaginal Hge after 28 wks
X [ ] *Unknown* 0 [ ] *None*

32. 1 [ ] B.P. 120-140/80
2 [ ] " over 140/80
X [ ] *Unknown* 0 [ ] *None*

33. 1 [ ] Cervical Lesion
2 [ ] " Infection
X [ ] *Unknown* 0 [ ] *None*

34. 1 [ ] Abnormal Uterus
X [ ] *Unknown* 0 [ ] *None*

35. 1 [ ] Hydramnios
2 [ ] " Aspirated
X [ ] *Unknown* 0 [ ] *None*

36. 1 [ ] Foetal Movements Stopped
X [ ] *Unknown* 0 [ ] *None*

37. 1 [ ] Preeclampsia
2 [ ] Eclampsia
3 [ ] Essential Hypertension
4 [ ] Other "
X [ ] *Unknown* 0 [ ] *None*

ADMISSION

38. 1 [ ] In Labour
2 [ ] Unconnected with Preg.
3 [ ] Delivered Elsewhere
4 [ ] Failed Delivery "
5 [ ] For Toxaemia
6 [ ] " Abruptio Placenta
7 [ ] " Induction
8 [ ] " Caesarian
9 [ ] " Other Obst. Cause
X [ ] *Unknown*

LABOUR ONSET

39. 1 [ ] Spontaneous Onset
2 [ ] Accidental "
3 [ ] Medical Induction
4 [ ] Surgical "
5 [ ] Combined "
X [ ] *Unknown* 0 [ ] *None*

40. 1 [ ] 24-47 hrs after induction
2 [ ] Over 48 hrs " "
X [ ] *Unknown* 0 [ ] *None*

VERSION

41. 1 [ ] Prenatal
2 [ ] Intranatal
3 [ ] 2nd Twin
X [ ] *Unknown* 0 [ ] *None*

LABOUR METHOD

42. 1 [ ] Normal
2 [ ] Natural Childbirth
3 [ ] Persistent Occiput Post.
4 [ ] " " Lateral
X [ ] *Unknown* 0 [ ] *None*

43. 1 [ ] Manual Rotation
2 [ ] Forceps "
3 [ ] Conversion Face or Brow to Vertex
X [ ] *Unknown* 0 [ ] *None*

44. 1 [ ] Reposition of Cord
2 [ ] " Presenting Part
X [ ] *Unknown* 0 [ ] *None*

45. 1 [ ] Abnormal Final Presentation
2 [ ] Other Procedure
X [ ] *Unknown* 0 [ ] *None*

DELIVERY

46. 0 [ ] Spontaneous Cephalic
1 [ ] Cephalic After Manipulation
2 [ ] Forceps Low or Outlet
3 [ ] " Mid
4 [ ] " Difficult
5 [ ] " Failed
6 [ ] Breech Assisted
7 [ ] " Extracted
8 [ ] Forceps After Coming Head
9 [ ] Caesarian Section
R [ ] Destructive Operation
X [ ] *Unknown*

MEMBRANES RUPTURE TO BIRTH

Antibiotic Given

47. 1 [ ] Under 24 hrs 4 [ ]
2 [ ] 24-48 hrs 5 [ ]
3 [ ] Over 48 hrs 6 [ ]
X [ ] *Unknown*

AMNIOTIC FLUID

48. 1 [ ] Meconium Stained
2 [ ] Blood "
3 [ ] Infected
X [ ] *Unknown* 0 [ ] *None*

FOETAL HEART

49. 1 [ ] Abnormal
2 [ ] Absent on Admission
3 [ ] " 1st Stage
4 [ ] " 2nd Stage
X [ ] *Unknown* 0 [ ] *Normal*

COMPLICATIONS OF LABOUR & DELIVERY

50. 1 [ ] Abnormal Pelvis
2 [ ] " Uterine Action
3 [ ] Major Placenta Previa
X [ ] *Unknown* 0 [ ] *None*

51. 1 [ ] Shoulder Disproportion
2 [ ] Fetopelvic
[ ] *Unknown* 0 [ ] *None*

52. 1 [ ] Rupture of Uterus
2 [ ] Cord Complication
X [ ] *Unknown* 0 [ ] *None*

53. 1 [ ] Intrapartum Infection
2 [ ] Rapid 2nd Stage
X [ ] *Unknown* 0 [ ] *None*

54. 1 [ ] Intrapartum Shock
2 [ ] Post " "
X [ ] *Unknown* 0 [ ] *None*

55. 1 [ ] PP H'ge from Laceration
2 [ ] " " " Uterus
X [ ] *Unknown* 0 [ ] *None*

56. 1 [ ] Laceration Vaginal
2 [ ] " Cervical
3 [ ] " 3rd or 4th Degree
X [ ] *Unknown* 0 [ ] *None*

57. 1 [ ] Other Complication
2 [ ] Maternal Death
X [ ] *Unknown* 0 [ ] *None*

DURATION OF LABOUR

58. Total	59. 2nd Stage
0 [ ] Caesarian	0 [ ] Caesarian
1 [ ] Under 1 hr.	1 [ ] 0- 9 Mins
2 [ ] 1- 3 hrs.	2 [ ] 10-19 "
3 [ ] 4- 5 "	3 [ ] 20-29 "
4 [ ] 6-11 "	4 [ ] 30-39 "
5 [ ] 12-17 "	5 [ ] 40-49 "
6 [ ] 18-23 "	6 [ ] 50-59 "
7 [ ] 24-35 "	7 [ ] 1-1/2 Hrs.
8 [ ] 36-47 "	8 [ ] 1½-2 "
9 [ ] 48-71 "	9 [ ] 2 - 3 "
R [ ] Over 3 days	R [ ] Over 3 "
X [ ] *Unknown*	X [ ] *Unknown*

PLACENTA

60. 1 [ ] Diffuse Atrophy
2 [ ] Significant Infarct
3 [ ] Subchorionic Hematoma
4 [ ] Adherent Clot to ¼ or more
5 [ ] Oedematous
X [ ] *Unknown* 0 [ ] *None*

61. 1 [ ] Vasa Previa
2 [ ] Villamentous Insert.
3 [ ] Rupture of Cord Vessel
X [ ] *Unknown* 0 [ ] *None*

62. 1 [ ] Manual Removal
X [ ] *Unknown* 0 [ ] *None*

OBSTETRICIAN ESTIMATE CAUSE OF FOETAL LOSS

63. 1 [ ] Live Child
2 [ ] Maternal Disease
3 [ ] Abnormal Pelvic Tissues or Disproportion
4 [ ] Abruptio Placenta
5 [ ] Cord Complication
6 [ ] Other Obstet. Cause
X [ ] *Unknown* 0 [ ] *None*

64. 2 [ ] Foetal Malformation
3 [ ] " Injury
4 [ ] " Anoxia
5 [ ] " Other Cause
X [ ] *Unknown* 0 [ ] *None*

1959 Perinatal Record, Side 2

196

7 [ ] " Induction
8 [ ] " Caesarian
9 [ ] " Other Obst. Cause
X [ ] *Unknown*

40. 1 [ ] 24-47 hrs after induction
2 [ ] Over 48 hrs " "
X [ ] *Unknown* 0 [ ] *None*

VERSION

41. 1 [ ] Prenatal
2 [ ] Intranatal
3 [ ] 2nd Twin
X [ ] *Unknown* 0 [ ] *None*

43. 1 [ ] Manual Rotation
2 [ ] Forceps "
3 [ ] Conversion Face or Brow to Vertex
X [ ] *Unknown* 0 [ ] *None*

44. 1 [ ] Reposition of Cord
2 [ ] " Presenting Part
X [ ] *Unknown* 0 [ ] *None*

45. 1 [ ] Abnormal Final Presentation
2 [ ] Other Procedure
X [ ] *Unknown* 0 [ ] *None*

5 [ ] " Failed
6 [ ] Breech Assisted
7 [ ] " Extracted
8 [ ] Forceps After Coming Head
9 [ ] Caesarian Section
R [ ] Destructive Operation
X [ ] *Unknown*

AMNIOTIC FLUID

48. 1 [ ] Meconium Stained
2 [ ] Blood "
3 [ ] Infected
X [ ] *Unknown* 0 [ ] *None*

FOETAL HEART

49. 1 [ ] Abnormal
2 [ ] Absent on Admission
3 [ ] " 1st Stage
4 [ ] " 2nd Stage
X [ ] *Unknown* 0 [ ] *Normal*

COMPLICATIONS OF LABOUR & DELIVERY

50. 1 [ ] Abnormal Pelvis
2 [ ] " Uterine Action
3 [ ] Major Placenta Previa
X [ ] *Unknown* 0 [ ] *None*

51. 1 [ ] Shoulder Disproportion
2 [ ] Fetopelvic
[ ] *Unknown* 0 [ ] *None*

52. 1 [ ] Rupture of Uterus
2 [ ] Cord Complication
X [ ] *Unknown* 0 [ ] *None*

53. 1 [ ] Intrapartum Infection
2 [ ] Rapid 2nd Stage
X [ ] *Unknown* 0 [ ] *None*

54. 1 [ ] Intrapartum Shock
2 [ ] Post " "
X [ ] *Unknown* 0 [ ] *None*

55. 1 [ ] PP H'ge from Laceration
2 [ ] " " " Uterus
X [ ] *Unknown* 0 [ ] *None*

56. 1 [ ] Laceration Vaginal
2 [ ] " Cervical
3 [ ] " 3rd or 4th Degree
X [ ] *Unknown* 0 [ ] *None*

57. 1 [ ] Other Complication
2 [ ] Maternal Death
X [ ] *Unknown* 0 [ ] *None*

DURATION OF LABOUR

58. Total
0 [ ] Caesarian
1 [ ] Under 1 hr.
2 [ ] 1- 3 hrs.
3 [ ] 4- 5 "
4 [ ] 6-11 "
5 [ ] 12-17 "
6 [ ] 18-23 "
7 [ ] 24-35 "
8 [ ] 36-47 "
9 [ ] 48-71 "
R [ ] Over 3 days
X [ ] *Unknown*

59. 2nd Stage
0 [ ] Caesarian
1 [ ] 0- 9 Mins
2 [ ] 10-19 "
3 [ ] 20-29 "
4 [ ] 30-39 "
5 [ ] 40-49 "
6 [ ] 50-59 "
7 [ ] 1-1½ Hrs.
8 [ ] 1½-2 "
9 [ ] 2 - 3 "
R [ ] Over 3 "
X [ ] *Unknown*

PLACENTA

60. 1 [ ] Diffuse Atrophy
2 [ ] Significant Infarct
3 [ ] Subchorionic Hematoma
4 [ ] Adherent Clot to ¼ or more
5 [ ] Oedematous
X [ ] *Unknown* 0 [ ] *None*

61. 1 [ ] Vasa Previa
2 [ ] Villamentous Insert.
3 [ ] Rupture of Cord Vessel
X [ ] *Unknown* 0 [ ] *None*

62. 1 [ ] Manual Removal
X [ ] *Unknown* 0 [ ] *None*

OBSTETRICIAN ESTIMATE CAUSE OF FOETAL LOSS

63. 1 [ ] Live Child
2 [ ] Maternal Disease
3 [ ] Abnormal Pelvic Tissues or Disproportion
4 [ ] Abruptio Placenta
5 [ ] Cord Complication
6 [ ] Other Obstet. Cause
X [ ] *Unknown* 0 [ ] *None*

64. 2 [ ] Foetal Malformation
3 [ ] " Injury
4 [ ] " Anoxia
5 [ ] " Other Cause
X [ ] *Unknown* 0 [ ] *None*

65. 2 [ ] Preventable Loss
3 [ ] Non " "
X [ ] *Unknown* 0 [ ] *None*

ANAESTHESIA

ANALGESIA

66. 1 [ ] Demerol Under 200 mg.
2 [ ] " Over " "
3 [ ] Morphine
4 [ ] Other Drug
X [ ] *Unknown* 0 [ ] *None*

AMNESIA

67. 1 [ ] Seconal
2 [ ] Nembutal
3 [ ] Amytal
4 [ ] Other Barbiturate
5 [ ] Hyoscine/Scopolamine
6 [ ] Tranquilizer
7 [ ] Other Drug
X [ ] *Unknown* 0 [ ] *None*

TIME

68. 1 [ ] None within 2 hrs. of Birth
2 [ ] Analgesic but no Amnesic within 2 hrs
3 [ ] Amnesic but no Analgesic within 2 hrs
4 [ ] Both within 2 hrs
X [ ] *Unknown* 0 [ ] *None at all*

ANESTHETIC AGENT

69. 1 [ ] Ether
2 [ ] " & Nitrous Oxide
3 [ ] " & Trilene
4 [ ] Nitrous Oxide
5 [ ] " & Trilene
6 [ ] Trilene
7 [ ] Cyclopropane
8 [ ] Other Agent
X [ ] *Unknown* 0 [ ] *None*

ANESTHETIC METHOD

70. 1 [ ] Open
2 [ ] Semi open
3 [ ] Closed
4 [ ] Intermittent
5 [ ] Continuous
X [ ] *Unknown* 0 [ ] *None*

71. 1 [ ] Oxygen given in Labour
X [ ] *Unknown* 0 [ ] *None*

ANESTHETIC DURATION ONSET TO BIRTH

72. 1 [ ] Under 15 Mins.
2 [ ] 15-29 Mins.
3 [ ] 30-44 "
4 [ ] 45-59 "
5 [ ] 1-1½ Hrs.
6 [ ] Over 1½ Hrs.
X [ ] *Unknown* 0 [ ] *None*

REGIONAL TYPE

73. 1 [ ] Local
2 [ ] Spinal
3 [ ] Epidural
4 [ ] Other
X [ ] *Unknown* 0 [ ] *None*

REGIONAL AGENT

74. 1 [ ] Procaine
2 [ ] Metycaine
3 [ ] Pontocaine
4 [ ] Nupercaine
5 [ ] Xylocaine
6 [ ] Other Agent
X [ ] *Unknown* 0 [ ] *None*

REGIONAL DOSE

75. 1 [ ] Under 10 Mgms
2 [ ] 10-19 Mgms
3 [ ] 20-49 "
4 [ ] 50-99 "
5 [ ] 100 Mgms or More
X [ ] *Unknown* 0 [ ] *None*

REGIONAL HEIGHT

76. 1 [ ] Local Infiltration
2 [ ] Pudendal Block
3 [ ] Perineal
4 [ ] Umbilical
5 [ ] Intercostal
6 [ ] Above Intercostals
X [ ] *Unknown* 0 [ ] *None*

OTHER DRUGS

77. 1 [ ] Relaxant
2 [ ] Atropine
3 [ ] I.V. Anesthesia
4 [ ] Rectal "
X [ ] *Unknown* 0 [ ] *None*

COMPLICATIONS

78. 1 [ ] Cyanosis
2 [ ] Vomiting
3 [ ] Cyanosis & Vomiting
4 [ ] Hypotension
5 [ ] " & Cyanosis
6 [ ] Anesthetic Death
7 [ ] Other
X [ ] *Unknown* 0 [ ] *None*

PERSON GIVING ANESTHETIC

79. 1 [ ] Certified Anesthetist
2 [ ] Non " "
3 [ ] Interne
4 [ ] Nurse
5 [ ] More than one above
X [ ] *Unknown* 0 [ ] *None*

COMMENT

80. 1 [ ] Yes
2 [ ] No

2

1961

PERINATAL STUDY

PATIENT'S NAME _____ DELIVERY DATE _____

ADDRESS _____ HOSPITAL No. _____

1-5 Registration No.	6-7 Date Month	Year	8-9 Doctor's Code No.

10. FATHER'S OCCUPATION

0 Professional, technical and kindred worker
1 Farmer and farm manager
2 Manager, official and proprietor (except farm)
3 Clerical and kindred worker
4 Sales worker
5 Craftsman, foreman and kindred worker
6 Operative and kindred worker
7 Private household and service worker
8 Farm labourer and foreman
9 Labourer, except farm
Y Unemployed
X Occupation not reported

11 FATHER'S AGE	12 MOTHER'S AGE This Delivery	13 MOTHER'S AGE At Marriage	14 MOTHER'S AGE At First Pregnancy

AGE CODE

0 Under 15 years
1 15-19 years
2 20-24 "
3 25-29 "
4 30-34 "
5 35-39 "
6 40-44 "
7 45-49 "
8 50-59 "
9 60 years or more
Y Not applicable
X Unknown

HISTORY OF PREVIOUS PREGNANCIES

15 TOTAL PREVIOUS PREGNANCIES

0 None
1 1
2 2
3 3
4 4
5 5
6 6
7 7
8 8
9 9
Y 10 or more
X Unknown

16 SF TERM (more than 5 lb. 8 oz.)

0 None
1 1
2 2
3 3
4 4
5 5 or more
6 Unknown

NEONATAL DEATHS (within 28 days)

7 None
8 1
9 2
Y 3 or more
X Unknown

17 SF PREMATURE (5 lb. 8 oz. or less)

0 None
1 1
2 2
3 3
4 4 or more
5 Unknown

PREMATURE MULTIPLE BIRTHS

6 None
7 1
8 2
9 3
Y 4 or more
X Unknown

18 SF ABORTIONS (under 20 wks. gestation)

0 None
1 1
2 2
3 3
4 4 or more
5 Unknown

MALFORMED INFANTS

6 None
7 1
8 2
9 3
Y 4 or more
X Unknown

19 FOETAL DEATHS (20 wks. gestation or over) SF

ANTEPARTUM PMP
0 None
1 1
2 2
3 3
4 4 or more

INTRAPARTUM
5 None
6 1
7 2
8 3
9 4 or more
Y Previous foetal losses, time unknown.
X Previous losses, time unknown.

20. STATUS SF

0 Married Private
1 " Public
2 Single Private
3 " Public
4 Div., Wid., or Sep. Private
5 " " " Public
6 Marital Status Unknown

CONSANGUINITY
7 None
8 1st Cousins
9 2nd "
Y Other Blood Relations
X Unknown

21. BIRTHPLACE & RESIDENCE SF

BIRTHPLACE
0 Canada (French)
1 " (English)
2 Great Britain
3 Italy
4 Other European
5 Orient
6 Other
7 Birthplace Unknown

RESIDENCE
8 Canada 5 yrs. or more
9 " under 5 years
Y Canadian Indian
X Duration in Canada Unknown

PRENATAL CARE

22. TIME OF FIRST PRENATAL VISIT

0 None
1 1st month
2 2nd "
3 3rd "
4 4th "
5 5th "
6 6th "
7 7th "
8 8th "
9 9th "
X Unknown

23. MEDICAL CARE SF PMP

0 None

OWN DOCTOR
1 1-3 visits
2 4-7 "
3 More than 7 visits

PUBLIC CLINIC
4 1-3 visits
5 4-7 "
6 More than 7 visits

X Unknown

24. MATERNITY CLASSES SF

0 No Maternity Classes
1 Classes Only in this Pregnancy
2 Classes and Exercises in this Pregnancy
3 Exercises Only in this Pregnancy
4 Unknown

TOBACCO HABIT
5 Non-smoker
6 Less than 1 pack a day
7 1 pack or more a day
X Unknown

25. MENARCHE and MENSTRUAL CYCLE SF

MENARCHE
0 Unknown
1 Under 11 years
2 11-14 years
3 15 years or more

CYCLE
4 Under 25 days
5 25-34 days
6 35 days or more (regular)
7 Irregular
X Cycle unknown

26. GESTATION

0 under 20 weeks
1 20-27 weeks
2 28-31 "
3 32-33 "
4 34-35 "
5 36-37 "
6 38-39 "
7 40-41 "
8 42-43 "
9 44-45 "
Y 46 weeks or more
X Unknown

27. HEIGHT OF MOTHER

0 60 ins. or under
1 61 "
2 62 "
3 63 "
4 64 "
5 65 "
6 66 "
7 67 "
8 68 "
9 69 "
Y 70 " or over
X Unknown

28. PRE-PREGNANT WEIGHT

Y Under 100 lbs.
0 100-109 lbs.
1 110-119 "
2 120-129 "
3 130-139 "
4 140-149 "
5 150-159 "
6 160-169 "
7 170-179 "
8 180-199 "
9 200 lbs. or over
X Unknown

29. WEIGHT GAIN PMP OR LOSS IN PREGNANCY

0 Loss of weight
1 0-4 lbs.
2 5-9 "
3 10-14 lbs.
4 15-19 "
5 20-24 "
6 25-29 "
7 30-34 "
8 35-39 "
9 40 lbs. and over
X Unknown

30. EMPLOYMENT PMP

0 None
1 1st trimester only
2 2nd " "
3 3rd " "
4 1st & 2nd trimesters only
5 2nd & 3rd " "
6 1st & 3rd " "
7 Entire Pregnancy
8 Sedentary Employment only

(Any employment outside of home)

9 Not employed outside of home —kept domestic help
Y Exposure to noxious chemical agents in this Pregnancy
X Unknown

COMPLICATIONS OF PREGNANCY

1960, 1961 Perinatal Record, Side 1

137

2 11-14 years
3 15 years or more

CYCLE
4 Under 25 days
5 25-34 days
6 35 days or more (regular)
7 Irregular
X Cycle unknown

4 34-35 "
5 36-37 "
6 38-39 "
7 40-41 "
8 42-43 "
9 44-45 "
Y 46 weeks or more
X Unknown

3 63 "
4 64 "
5 65 "
6 66 "
7 67 "
8 68 "
9 69 "
Y 70 " or over
X Unknown

2 120-129 "
3 130-139 "
4 140-149 "
5 150-159 "
6 160-169 "
7 170-179 "
8 180-199 "
9 200 lbs. or over
X Unknown

2 5-9 "
3 10-14 lbs.
4 15-19 "
5 20-24 "
6 25-29 "
7 30-34 "
8 35-39 "
9 40 lbs. and over
X Unknown

4 1st & 2nd trimesters only
5 2nd & 3rd " "
6 1st & 3rd " "
7 Entire Pregnancy
8 Sedentary Employment only
} employment outside of home
9 Not employed outside of home —kept domestic help
Y Exposure to noxious chemical agents in this Pregnancy
X Unknown

COMPLICATIONS OF PREGNANCY

31. PMP
0 None
1 Rheumatic Heart Disease
2 Congenital Heart "
3 Heart Failure
4 Diabetes Mellitus
5 Tuberculosis
6 Rubella
7 Hepatitis
8 Other Virus Infection
9 Under Psychiatric Care
Y Shock or Fright
X Unknown

32. PMP
0 None
1 Syphilis
2 Hyperemesis
3 Chronic Renal Disease
4 Acute Pyelonephritis
5 Other Chronic Illness
6 " Acute Illness
7 Surgical Operation this Pregnancy (abdominal or pelvic)
8 Surgical Operation this Pregnancy (other than 7)
9 Physical Injury this Pregnancy
Y Cervical Incompetence and/or Suture
X Unknown

33. PMP
0 None
1 Vaginal bleeding Only under 20 weeks
2 Vaginal bleeding and Cramps under 20 weeks
3 Vaginal bleeding after 20 weeks
4 Carcinoma Cervix
5 Other Cervical Lesion
6 Myomata Uteri
7 Uterine Anomaly
8 Vaginal Infection —Specify:
9 Other—Specify:
X Unknown

IRRADIATION

34. PREVIOUS EXPOSURE SF PMP

35. PRESENT PREGNANCY SF PMP

0 None
1 Chest
2 Foetus
3 Placentography
4 Other abdomen
5 Pelvimetry
6 Other Pelvis or Hip
7 Other

TIMES X-RAYED
8 0-5 times
9 6-15 "
Y 16 or more times
X Unknown

I N F A N T

36. TYPE OF BIRTH SF PMP
0 Sex undetermined

MALE—
1 Single birth
2 Twin birth (1)
3 " " (2)
4 Other multiple birth

FEMALE—
5 Single birth
6 Twin birth (1)
7 " " (2)
8 Other multiple birth
Y Single plus blighted foetus
X Unknown

37. BIRTH WEIGHT
0 Under 400 gms. (14 oz.)
1 400— 749 gms. (14 oz.—1 lb. 10 oz.)
2 750— 999 " (1 lb. 11 oz.— 2 lb. 3 oz.)
3 1000—1499 " (2 " 4 " — 3 " 4 ")
4 1500—1999 " (3 " 5 " — 4 " 6 ")
5 2000—2499 " (4 " 7 " — 5 " 8 ")
6 2500—2999 " (5 " 9 " — 6 " 9 ")
7 3000—3499 " (6 " 10 " — 7 " 11 ")
8 3500—3999 " (7 " 12 " — 8 " 13 ")
9 4000—4999 " (8 " 14 " —11 ")
Y 5000 gms. or over (Over 11 lb.)
X Unknown

38. BLOOD SF PMP
0 Unknown
1 O
2 A
3 B
4 AB

5 Rh Positive (Anti D)
6 Rh Group Unknown

7 Direct Coomb's Positive
8 " " Negative
9 Other Antibodies Positive
X Antibody Tests not known

Y Bilirubin 15 mgm. and over

39. AFFECTIONS PMP
0 None Listed
1 Erythroblastosis Rh
2 " ABO
3 " Other
4 Haemorrhage (incl. cord or circumcision)
5 Other Anaemias
6 Cardiac Failure
7 Any Respiratory Difficulty
8 Cerebral Dysfunction
9 Other Birth Injury
Y " Conditions
X Unknown

40. INFECTIONS PMP
0 None
1 Thrush
2 Diarrhoea
3 Conjunctivitis
4 Pyoderma
5 Other Dermatitis
6 Pneumonia
7 Omphalitis
8 Meningitis
9 Other Infection
Y Organism Cultured —Specify:
X Unknown

41. MALFORMATIONS PMP
0 None Listed
1 Anencephaly
2 Other Brain and Cord
3 Pelvic and/or G.U.
4 Oral Cavity
5 Thoracic
6 Heart and Circulatory
7 Abdominal and/or G.I.
8 Bone and Joint
9 Other
Y Multiple Malformations
X Unknown

42. INFANT THERAPY PMP
0 None
1 Oxygen under 24 hours
2 " for 24 or more hours
3 " Concentration not measured
4 Vitamin K
5 Digitalis
6 Transfusion—Exchange
7 " —Other
8 Antibiotic to Infant—Systemic
9 Other Therapy
X Unknown

43. INFANT CARE SF PMP
0 Paediatrician Spec.
1 Obstetrician Spec.
2 General Practitioner
3 Resident Staff
4 Unknown

FEEDING
5 Bottle
6 Breast
7 Gavage
8 No Feeding
X Unknown

44. INFANT LOSS PMP
0 No Infant Loss
1 Antepartum death
2 Intrapartum "
3 Stillbirth—time of death unknown
4 Heartbeat—no respiration
5 Neonatal—less than one hour
6 " —1 hour to 11 hours
7 " —12 hours to 23 hours
8 " —24 " to 47 "
9 " —2 days to 7 days
Y Autopsy
X No Autopsy

45. CLINICAL CAUSE OF DEATH PMP
0 No Infant Loss
1 Anoxia—Intrapartum
2 Respiratory Difficulty
3 Birth Injury
4 Respiratory Infection
5 Other Infection
6 Malformation
7 Prematurity Alone
8 Haemolytic Disease
9 Other Condition
Y Death due to Maternal Cause
X Unknown

COMMENTS:

REG. No. | | | | | | |

OBSTETRICIAN

46. DRUGS PMP
- 0 None
- 1 Multiple Vitamins
- 2 Tranquillizers
- 3 Hypotensives
- 4 Diuretics
- 5 Oestrogens
- 6 Progestins
- 7 Thyroid
- 8 Insulin
- 9 Adrenal Steroids
- Y Other Drugs and List:
- X Unknown

PAST OBSTETRIC HISTORY

47. PMP
- 0 None
- 1 Pre-eclampsia
- 2 Eclampsia
- 3 Other Hypertension
- 4 Postpartum Infection
- 5 Phlebitis
- 6 Other Medical Complication
- 7 Antepartum Haemorrhage
- 8 Postpartum Haemorrhage
- 9 Involuntary Infertility (more than one year)
- Y 3 or More Consecutive Abortions
- X Unknown

48. PMP
- 0 None
- 1 Caesarean
- 2 Ectopic Pregnancy
- 3 Myomectomy
- 4 Curettage
- 5 Tubal Insufflation
- 6 Other Gynaec. Surgery
- 7 Dystocia
- 8 Other Labour Difficulty
- 9 Previous Multiple Births
- Y Other Relevant Surgery
- X Unknown

49. ADMISSION STATUS PMP
- 0 False Labour
- 1 True Labour
- 2 Delivered Elsewhere
- 3 Failed Delivery
- 4 For Toxaemia
- 5 " Abruptio
- 6 " Elective Caesarean
- 7 " Induction
- 8 " Ruptured Membranes Only
- 9 Other Obstetric Reason
- Y " Non-Obstetric Cause
- X Unknown

50. TOXAEMIAS—PRESENT PREG. PMP
- 0 None
- 1 Eclampsia—Antepartum
- 2 " —Intrapartum
- 3 " —Postpartum
- 4 " —More than 1, 2, or 3 alone
- 5 Pre-Eclampsia—140/90*
- 6 Essential Hypertension 140/90
- 7 Other Hypertension 140/90
- 8 Other Hypertension 120-139/80-89
- X Unknown

* OR: Rise of systolic of 30 and/or diastolic of 15

51. PRESENTATION and POSITION
- 1 OA
- 2 OL or OT
- 3 OP
- 4 Breech—frank
- 5 " —other
- 6 Brow
- 7 Face
- 8 Transverse
- 9 Compound
- Y Cephalic Position Unknown
- X Unknown

52. LABOUR ONSET SF PMP
- 0 None
- 1 Spontaneous
- 2 Accidental
- 3 Medical Induction
- 4 Pitocin Induction
- 5 Stretch and Sweep
- 6 Amniotomy Induction
- 7 Method of Onset Unknown

TIME FROM INDUCTION TO ONSET OF LABOUR (OR CAESAREAN)
- 8 Under 24 hours
- 9 24-48 hours
- Y More than 48 hours
- X Time Lapse Unknown

53. FOETAL HEART RATE PMP
- 0 Not Recorded on Admission
- 1 Regular, 100-160 on Admission
- 2 (?) Absent on Admission
- 3 Absent on Admission
- 4 " 1st Stage
- 5 " 2nd "
- 6 Under 80
- 7 80-100
- 8 Over 160
- 9 Both Under 100 and Over 160
- Y Other Abnormality
- X Unknown

54. DELIVERY SF PMP
- 0 Spontaneous or None Listed
- 1 Manual Rotation—Vertex
- 2 Forceps Rotation— "
- 3 Assisted Breech
- 4 Extracted "
- 5 Caesarean Section—Classical
- 6 " " —Low Segment
- 7 Destructive Operation
- 8 Hysterectomy
- 9 Pitocin Stimulation in Labour—1st Stage
- Y Pitocin Stimulation in Labour—2nd Stage
- X Unknown

55. DELIVERY METHOD PMP
- 0 None Listed
- 1 Forceps—Low
- 2 " —Mid
- 3 " —Aftercoming Head
- 4 " Difficult
- 5 " Trial or Failed
- 6 Natural Childbirth
- 7 Laparotomy Delivery for Ruptured Uterus
- 8 Laparotomy Delivery for Abdominal Pregnancy
- 9 Therapeutic Interruption
- Y Other Delivery Procedure
- X Unknown

56. VERSION SF
- 0 No version

EXTERNAL
- 1 Antepartum under 36 weeks
- 2 " 36 weeks or more
- 3 Intrapartum

INTERNAL
- 4 Intrapartum—Single
- 5 " —2nd Twin or Other Multiple
- 6 Version Unknown

PERINEUM
- 7 No Episiotomy
- 8 Median "
- 9 Mediolateral Episiotomy
- Y 3° or 4° Laceration
- X Episiotomy—Type Unknown

57. AMNIOTIC FLUID SF PMP
- 0 Normal Amount
- 1 Polyhydramnios
- 2 Oligohydramnios

MECONIUM STAINING
- 3 Lightly —Before Labour
- 4 Heavily— " "
- 5 Lightly —First Stage
- 6 Heavily— " "
- 7 Lightly —Second Stage
- 8 Heavily— " "
- 9 Aspiration of Amniotic Fluid
- Y Other abnormality
- X Unknown

58. TIME FROM MEMBRANE RUPTURE TO DELIVERY SF
- 0 Unknown
- 1 In caul
- 2 Under 24 hours
- 3 24-48 hours
- 4 Over 48 hours

ANTIBIOTICS OR SULPHA COMMENCEMENT TO DELIVERY
- 5 Under 12 hours
- 6 12-24 "
- 7 Over 24 "
- 8 None
- X Unknown

59. COMPLICATIONS—LABOUR/DELIVERY PMP
- 0 None
- 1 Placenta Praevia—Central
- 2 " " —Other
- 3 Abruptio Placentae
- 4 Other Intrapartum Haemorrhage
- 5 Abnormal Uterine Action
- 6 Foetopelvic Disproportion
- 7 Tumultuous Labour
- 8 Shoulder Dystocia
- 9 Postpartum Haemorrhage—Fundus
- Y " " — Laceration Cervix or Vagina
- X Unknown

60. MATERNAL DISTRESS PMP
- 0 None
- 1 Maternal Death
- 2 Uterine Rupture
- 3 Amniotic Fluid Embolism
- 4 Hypofibrinogenaemia
- 5 Heart Failure
- 6 Diabetic Acidosis
- 7 Inversion of Uterus
- 8 Non-obstetric Trauma
- 9 Intrapartum Fever—100.4°F. or more
- Y Other Complications (Maternal)
- X Unknown

MOTHER'S BLOOD

61. TYPE SF
- 0 Unknown
- 1 O
- 2 A
- 3 B
- 4 AB

HAEMOGLOBIN

62. SF PMP
- 0 Rh Positive
- 1 Rh Negative—Fixed Titre
- 2 " " —Rising Titre
- 3 " " —Unsensitized
- 4 " " —Sensitization Unknown
- 5 Other Antibodies Detected
- 6 Rh Unknown

63. CORD COMPLICATIONS SF PMP
- 0 None
- 1 True Knot
- 2 Prolapsed Cord
- 3 Tight Cord Around Neck
- 4 Rupture of Cord Vessel
- 5 Other Cord Complication
- 6 Unknown

CORD MANAGEMENT

64. PLACENTA DESCRIPTION PMP
- 0 No Abnormality
- 1 Atrophy
- 2 Significant Infarct
- 3 Subchorionic Haematoma
- 4 Clot over ¼ or more
- 5 Oedema
- 6 Velamentous
- 7 Incised at Caesarean

65. SPECIAL STUDY

1960, 1961 Perinatal Record, Side 2

138

3 B
4 AB

HAEMOGLOBIN
5 Over 11.0 grams
6 Under 8.0 grams
7 8.0-11.0 grams
X Hb Unknown

3 " " —Unsensitized
4 " " —Sensitization Unknown
5 Other Antibodies Detected
6 Rh Unknown
7 Isoimmunization—Previous Pregnancies

TRANSFUSION
8 Past Transfusion—None
9 " " —Before This Pregnancy
Y " " —This Pregnancy
X " " —Unknown

5 Other Cord Complication
6 Unknown

CORD MANAGEMENT
7 Clamped Before 1st Breath
8 " After " "
9 Allowed to Drain—Gravity
Y Manually Stripped
X Unknown

3 Subchorionic Haematoma
4 Clot over ¼ or more
5 Oedema
6 Velamentous
7 Incised at Caesarean
8 Binovular
9 Marginal Sinus Rupture
Y Other—Specify:
X Nature of Placenta Unknown

DURATION OF LABOUR

66. FIRST STAGE
0 None
1 0- 3 hours
2 4- 9 "
3 10-17 "
4 18-23 "
5 24-29 "
6 30-35 "
7 36 or more hours
X Unknown

67. SECOND STAGE
0 None
1 0- 9 minutes
2 10-19 "
3 20-29 "
4 30-59 "
5 60-89 "
6 90-119 "
7 2-3 hours
8 More than 3 hours
X Unknown

68. PLACENTA WEIGHT
0 Less than 100 gms.
1 100-199 gms.
2 200-299 "
3 300-399 "
4 400-499 "
5 500-599 "
6 600-699 "
7 700-799 "
8 800-999 "
9 1000-1499 gms.
Y 1500 gms. or more
X Unknown

COMMENTS

A N A E S T H E S I A

69. ANALGESIA PMP
(Within 6 hours Before Birth)
0 None
1 Demerol—100 mgm. or less
2 " —more than 100 mgm.
3 Morphine
4 Other Narcotics
5 Trilene self-administered
6 Other Drugs
7 Continuous Regional
Y Any of above within 2 hours Before Birth
X Unknown

70. AMNESIA PMP
(Within 6 Hours Before Birth)
0 None
1 Barbiturate—Short Acting
2 " —Mid or Long Acting
3 Hyoscine/Scopolamine
4 Promethazine (e.g. Phenergan)
5 Promazine (e.g. Sparine)
6 Other Tranquillizer
7 Other Drugs
Y Any of above within 2 hours Before Birth
X Unknown

71. OTHER DRUGS TO MOTHER PMP
(Within 4 hours Before Delivery)
0 None
1 Relaxant
2 Narcotic Antagonist I.M.
3 " " I.V.
4 Hypotensive
5 Oxygen—2nd Stage of Labour
6 Oxygen—1st Stage or during Caesarean Section
7 Vitamin K
8 Magnesium Sulphate
9 Dilantin
Y Other Drugs
X Unknown

72. ANAESTHETIC TECHNIQUE SF PMP
0 None
INHALATION
1 Open Drop
2 Circle Absorber
3 Non-rebreathing
4 Partial Rebreathing
CONDUCTION
5 Local
6 Pudendal Block
7 Subarachnoid
8 Lumbar Epidural
9 Caudal
Y Hypnosis
X Unknown

73. ANAESTHETIST PMP
0 None
1 Certified Anaesthetist
2 Non-certified Anaesthetist
3 House Officer—Obstetric
4 House Officer—Anaesthetic
5 Nurse
6 Medical Student
7 General Practitioner
8 Obstetrician
X Unknown

74. GENERAL ANAESTHESIA SF
0 — None

TIME FROM ANAESTHETIC INDUCTION TO BIRTH
1 — Less than 5 mins.
2 — 5-9 mins.
3 — 10-14 mins.
4 — 15-29 "
5 — 30 or more mins.
6 — Unknown

STAGE AT TIME OF DELIVERY
7 — 1st Stage
8 — 2nd "
9 — 3rd "
X — Unknown

ANAESTHETIC AGENT PMP

75. INDUCTION	76. BETWEEN	77. CROWNING

0 None
1 Nitrous Oxide
2 Trilene
3 Ether
4 " and Trilene
5 Chloroform
6 Cyclopropane
7 Halothane (Fluothane)
8 Vinethene
9 Other Agent
Y Intravenous Barbiturate
X Unknown

78. ANAESTHETIC COMPLICATION SF PMP
0 None

BEFORE DELIVERY
1 Cyanosis
2 Hypoventilation
3 Vomiting—Food
4 " —Other
5 Aspiration
6 Hypotension (to less than 100 systolic or fall of 30 systolic or more)
7 Other Complication
8 Postpartum Shock
9 Anaesthetic Death
X Unknown

INFANT RESUSCITATION

79. METHOD PMP
0 None
1 Suction
2 Positive Pressure—Mechanical
3 Positive and Negative Pressure
4 Mouth to Mouth
5 Intratracheal Intubation
6 Rocking Bed
7 Incubator
8 Other
X Unknown

80. THERAPY SF PMP
0 None
1 Narcotic Antagonist I.M.
2 " " Into Cord
3 Respiratory Stimulant
4 Apnoea over 5 minutes
5 Unknown

APGAR
6 0-2
7 3-4
8 5-6
9 7-8
Y 9-10
X Unknown

APPENDIX B

Some Further Detail on Statistical Methods Employed in the Text

1. Confidence Limits

The variance was calculated by the method described by Woolf (1954). The natural logarithm of the confidence limits is $y \pm 1.96 \times S.D.$

where: S.D. is the square root of the variance,
y is the natural logarithm of the ratio of two rates around which the confidence limits are to be constructed.

The antilogarithm of these limits is then found, giving the 95% confidence limits of the ratio of the two rates.

2. Standardizing Factor

The method of indirect standardization for an extraneous variable, used in this study, is that described by A. B. Hill in Principles of Medical Statistics, Oxford University Press, 1967, p. 212. The standardizing factor is the ratio of the overall cancer rate in the standard population to the index rate for each category of smokers. The index rate is calculated as follows, taking sex of child as an extraneous variable. The standard rates specific for male and female are applied to the male and female populations within each category of smokers and thus the number of cases expected with the population at standard rates are obtained. The index rate is then calculated by taking this expected number over the total population within the category of smokers.