The Relationship of Antenatal and Postnatal Factors to Sudden Unexpected Death in Infancy

ROBERT STEELE, M.D., D.P.H.* and JANE T. LANGWORTH, B.N.Sc.,†
Kingston, Ont.

ABSTRACT

In the investigation of sudden unexpected death in infancy (S.U.D.) the antenatal and immediate postnatal history of the child and associated maternal circumstances have been virtually unexplored. These areas were studied using data gathered in a perinatal mortality study carried out in Ontario. By using rigid criteria, 80 cases of S.U.D. were identified and matched with live controls. Subsequent analysis showed that S.U.D. occurred slightly more often in males than females, and that the majority of deaths occurred under 4 months of age. S.U.D. was shown to be significantly related to prematurity; feeding other than at the breast; low maternal age at time of marriage, first pregnancy and the delivery of the infant under study; delayed first prenatal visits; maternal blood group and cigarette smoking. Confirmation of these findings may allow the construction of profiles of infants particularly at risk and permit the institution of preventive measures. Further prospective studies in this field are required.

SOMMAIRE

Dans l'étude des morts subites et inattendues (M.S.I.) du nourrisson, on laisse virtuellement inexplorés l'histoire clinique anténatale et postnatale immédiate du nourrisson et les circonstances connexes relatives à la mère. On a saisi l'occasion d'approfondir ces éléments à partir de données recueillies au cours d'une étude de la mortalité périnatale effectuée en Ontario. Au moyen de critères très stricts, on a relevé 80 cas de M.S.I. qui ont été comparés à des cas témoins d'enfants vivants. Une analyse a révélé que les M.S.I. se produisent subséquente un peu plus souvent chez les sujets de sexe masculin que chez ceux de sexe féminin et que la majorité des décès sont survenus chez des bébés de moins de quatre mois. On a démontré que les M.S.I. ont un lien étroit avec la prématurité, le type d'alimentation différent de l'allaitement maternel, la jeunesse de la mère au moment de son mariage, de sa première grossesse et de cet accouchement, le retard apporté par la mère à consulter la naissance de l'enfant, le groupe sanguin de la mère et le fait que la mére fume la cigarette. La confirmation de ces constations pourrait permettre d'établir des portraits-types d'enfants constituant des risques particuliers et d'adopter des mesures préventives. It faut pour cela procéder à de nouvelles études.

THE major lines of approach in research directed at elucidation of the enigma of sudden death in infancy focus on the period from birth, the second week of life, or the end of the first month, through to the end of the first or second year of life. The studies may be fairly specific in that particular pathological processes, e.g. acute viral infection[1, 2] or hypersensitivity to cows' milk protein,[3, 4] are investigated, or conversely, because of the confusion which tends to obscure the concept of causation, a more general epidemiological approach may be adopted.[5, 6] From an examination of the voluminous literature on sudden unexpected death (S.U.D.) it became clear that a major area remained virtually unexplored and poorly documented, viz. the antenatal and early postnatal history of the child, and associated circumstances in the mother. It seemed desirable to study this period of development of children—if acceptable data were available—to determine whether infants who subsequently die suddenly and unexpectedly can be identified *in utero* or during extrauterine life by characteristics which show them to be particularly at risk, and thereby to institute preventive measures which might circumvent a fatal outcome.

METHOD

On reading preliminary reports of the Perinatal Mortality Study carried out in 10 university teaching hospitals in Ontario during 1959-1962, inclusive, it was felt that although by definition the interests of the study committee did not extend beyond the first week of life, some of the infants extensively documented might subsequently have died suddenly and might meet the criteria formulated for a proposed study of the sudden death syndrome in Eastern Ontario.[5]

*Associate Professor, Department of Preventive Medicine, Director of Research, Child Health Program, Queen's University, Kingston, Ontario.
†Research Assistant, Department of Preventive Medicine, Queen's University.

In the Introduction to the 1959 report of the Perinatal Morality Study[7] it was stated that "a study of all deliveries at the 10 teaching hospitals associated with the four medical schools was desirable for the following reasons:

"(1) The collection and recording of uniform data concerning all deliveries including fetal and early neonatal deaths would present a more complete picture of the overall problem.

"(2) It would stimulate interest on the part of the attending physician regarding the preventable aspects of maternal and infant care.

"(3) It would stimulate improvements in standards of such care."

The scientific attractiveness of the project was enhanced by the uniform collection and recording of data which could be of value in a study of sudden unexpected death. The direction of the original work was carried out by a Perinatal Mortality Committee which included professors of obstetrics and pediatrics from each of the four medical schools in the province, as well as representatives from other specialties including anesthesia, medical statistics and pathology.

Data regarding each hospital delivery were obtained by research assistants, who were appointed by the university concerned. The duties of research assistants were as follows:

(1) To ensure completion of the data form: (a) with information obtained directly from the mother in hospital, (b) with assistance from the obstetrician, anesthetist and the hospital staff, and (c) by obtaining information from the hospital records.

(2) To obtain autopsy records, when available.

(3) To forward data forms and autopsy reports each month to the Ontario Department of Health.

The study conducted in 1959 was regarded as a pilot project and from this much experience in the complex method of data-consistency checks, mechanical sorting and statistical verification was acquired and utilized in planning the studies for the ensuing years.[7]

For the purposes of the study of sudden unexpected death it was decided to restrict the investigation to infants born in the 10 teaching hospitals in 1960 and 1961 and those who subsequently died in Ontario in 1960 and 1961. We realized that some infants born in 1961 who died suddenly and unexpectedly in 1962 would be excluded. However, this seemed a reasonable course to adopt because of the necessity to hand-search the death certificates for over 7000 infants (i.e. 3500 infant deaths under one year of age in Ontario per annum) to select in broad terms those that met certain criteria for identification, viz. cases in which the duration of illness was stated to be one day or less, and in which the diagnosis was "sudden unexpected"; "sudden unexplained"; "sudden death syndrome", "crib death", "accidental mechanical suffocation" (E921-E925), upper respiratory infections, influenza, pneumonia, bronchitis and other diseases of the respiratory system (470-475, 480-483, 490-493, 500-502), and in which the infants were aged between 28 days and one year. In formulating these criteria it seemed reasonable to assume that the deaths would be certified as "unexplained", or included under one of the respiratory causes of death.[8] We realized that the duration of illness recorded on the death certificates of infants who died suddenly or were found dead may be open to question, particularly where there was no antecedent history of illness. The inclusion of infants aged 28 days to one year only in the study was done deliberately to exclude pathological processes peculiar to the neonatal period which might otherwise have confused the subject under investigation.

After this general selection of death certificates was made, a list of infants who died and the names of physicians who completed the certificates was compiled. Coroners', pathologists', general practitioners' and pediatricians' reports were obtained and the list of infants was gradually refined according to the following criteria: the infants were apparently well when last seen alive, gave no indication of a clinical condition which might reasonably be expected to result in death, and death occurred suddenly and unexpectedly.

In addition to these criteria, the decision as to what constituted a "case" was influenced by pathological findings at autopsies in which a specific cause of death was not identified. (Throughout this paper, the term "case" or "cases" refers to infants who died suddenly and unexpectedly. All of these infants came to autopsy.)

The death certificates were matched with the corresponding birth certificates to confirm that infants who died suddenly and unexpectedly had been born in the 10 teaching hospitals, and to obtain birth registration numbers by which the perinatal records could be identified. The perinatal study records for 80 infants were identified in this way. After identification, each of the 80 records was matched with the records of two children who had not died during the first year of life. Matching of cases and controls was done by sex, hospital, parity of mother and age, i.e. one control born within five days before the case and one born within five days after the case. In three instances it was not possible to match cases with two controls because of the limits enforced with regard to dates of birth. However, no case lacked both controls.

The data forms of the Perinatal Study have four major areas: social and antenatal history; information about the infant after birth; the obstetric history; and the anesthetic history.

ANALYSIS

Table I shows the age-sex distribution of the 80 infants who were identified as having died suddenly and unexpectedly. The data suggest that

TABLE I.—SUDDEN DEATH BY AGE AND SEX

Age	Sex		Total
	Male	Female	
Over 28 days	14	9	23
2 months	12	10	22
3 "	7	9	16
4 "	4	5	9
5 "	1	1	2
6 "	1	—	1
7 "	1	—	1
8 "	2	1	3
9 "	1	—	1
10 "	2	—	2
11 "	—	—	—
12 "	—	—	—
Total	45	35	80

the risk of infants dying suddenly and unexpectedly is associated with the early months of life, with major concentration of deaths under 4 months of age. The male:female ratio of deaths was 1.3:1.

TABLE II.—LEVELS OF STATISTICAL SIGNIFICANCE ASSOCIATED WITH CERTAIN VARIABLES

	Levels of statistical significance			
	$P < 0.001$	$P < 0.01$	$P < 0.02$	$P < 0.05$
Variables	Mother's age (first pregnancy)	Mother's age (this delivery)*	Birth weight	Father's age (this delivery)*
	Tobacco habit	Mother's age (at marriage)	Blood group (maternal)	Abortions
	Infant feeding			Time of first prenatal visit
				Gestation

The remaining variables tested were not statistically significant ($P > 0.05$).

*At time of delivery of case or control child.

Statistical tests of significance were applied to all of the data specified on the Perinatal Study Forms, for cases and controls. The results of this analysis are shown in Table II.

The variables that were statistically significant were examined further.

Maternal age.—Examination of maternal age at marriage, at time of first pregnancy, and at time of delivery of case and control infants showed the following:

1. Whereas 51.3% of mothers of S.U.D. cases were married at age 15-19 years, 31.2% of mothers of controls were married at this age; in contrast, 32.5% of mothers of cases and 40.1% of mothers of controls had married between 20 and 24 years of age (Table III).

2. Forty-five per cent of mothers of cases and 22.9% of mothers of controls were aged 15-19 years at time of first pregnancy; in contrast, 31.3% and 42.7% of mothers of cases and controls, respectively, were aged 20-24 years at time of first pregnancy (Table IV).

3. 21.3% and 8.9% of mothers of cases and controls, respectively, were aged 15-19 years at time of delivery of infants included in this study; 35% and 25.5% of mothers of cases and controls were aged 20-24 years (Table V).

Thus it may be shown that mothers of cases were significantly different from mothers of controls in that they were younger at time of marriage, at time of first pregnancy, and at time of delivery of infants under study.

Tobacco habit.—Table VI shows the tobacco smoking patterns of the mothers of cases and mothers of controls.

Whereas 60.5% of mothers of controls were non-smokers, 38.8% of mothers of cases did not smoke during the pregnancies studied. Of the mothers of cases, 36.2% smoked less than one pack of cigarettes per day, and 23.7% smoked one pack or

TABLE III.—MOTHER'S AGE AT MARRIAGE FOR CASES AND CONTROLS

		Mother's age at marriage										
		Under 15 years	15-19	20-24	25-29	30-34	35-39	40-44	45-49	Unknown	Not applicable	Total
Cases	%	—	51.3	32.5	7.5	1.3	—	—	—	1.3	6.1	100
	No.	—	41	26	6	1	—	—	—	1	5	80
Controls	%	0.6	31.2	40.1	15.3	5.7	1.9	—	—	1.9	3.3	100
	No.	1	49	63	24	9	3	—	—	3	5	157

TABLE IV.—MOTHER'S AGE AT FIRST PREGNANCY FOR CASES AND CONTROLS

		Mother's age at first pregnancy										
		Under 15 years	15-19	20-24	25-29	30-34	35-39	40-44	45-49	Unknown	Not applicable	Total
Cases	%	—	45.0	31.3	18.7	2.5	2.5	—	—	—	—	100
	No.	—	36	25	15	2	2	—	—	—	—	80
Controls	%	—	22.9	42.7	21.7	8.9	1.9	1.3	—	0.6		100
	No.	—	36	67	34	14	3	2	—	1	—	157

TABLE V.—MOTHER'S AGE AT TIME OF DELIVERY OF CASES AND CONTROLS

		*Mother's age at this delivery**									
		Under 15 years	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*	*45-49*	*Unknown*	*Not applicable*	*Total*
Cases	%	—	21.3	35.0	21.3	16.3	6.1	—	—	—	—	100
	No.	—	17	28	17	13	5	—	—	—	—	80
Controls	%	—	8.9	25.5	32.5	23.6	7.0	2.5	—	—	—	100
	No.	—	14	40	51	37	11	4	—	—	—	157

*At time of delivery of case or control child.

more per day, during pregnancy; in contrast, 27.4% and 10.2%, respectively, of mothers of controls smoked. (These data on mothers who smoked relate to the maximum number of cigarettes smoked at any stage during pregnancy.)

TABLE VI.—SMOKING HABITS OF MOTHERS OF CASES AND CONTROLS

	Smoking habits of mothers							
	Non-smokers		*Less than one pack/day*		*More than one pack/day*		*Unknown*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Cases	31	38.8	29	36.2	19	23.7	1	1.3
Controls	95	60.5	43	27.4	16	10.2	3	1.9

It was noted that there was a highly significant difference in the smoking habits of the mothers of cases as compared with mothers of controls ($P < 0.001$). In view of the relationship which is known to exist between cigarette smoking and prematurity as demonstrated in retrospective and prospective studies[9] it was decided to examine the birth weights of cases and controls relative to the smoking habits of the respective groups of mothers.

TABLE VII.—SMOKING HABITS OF MOTHERS IN RELATION TO INFANTS WEIGHING UNDER 2500 G.

Smoking habits of mothers	*Infants under 2500 g. birth wt.*		*Ratio*	*S / NS*
	No.	*%*		
Cases				
Smokers (S)	9	11.4	16.5	2.2 : 1
Non-smokers (NS)	4	5.1		
Controls:				
Smokers	6	3.9	6.5	1.5 : 1
Non-smokers	4	2.6		

16.5% (13) of the cases (N = 79) were premature.
6.5% (10) of the controls (N = 154) were premature.

Although the numbers are small, they show that mothers of cases and controls who smoked had more infants under 2500 g. than did mothers who did not smoke. Furthermore, the ratio of smokers to non-smokers for cases and controls was 2.2:1 and 1.5:1, respectively.

Infant feeding.—Table VIII shows the patterns of infant feeding on the day of discharge from hospital or on the seventh day post partum, whichever was earlier.

Although the periods of observation for patterns of feeding are short, it is noted that only 26.3% of cases had been wholly breast fed at the time of leaving hospital, as compared with 47.8% of control infants. The difference is statistically highly significant ($P < 0.001$).

Birth weights.—Of the 80 cases, 16.2% weighed under 2500 g. and 33.7% weighed under 3000 g. at birth. In contrast, of the 157 control infants 6.4% and 21.7% were under 2500 and 3000 g., respectively. The birth weight of 58.8% of the cases and 71.4% of the controls was between 3000 and 4000 g. The birth weight of 7.5% of cases and 7.0% of controls was over 4000 g. (Table IX). In summary, cases tended to be of lower birth weight than controls and this difference was statistically significant ($P < 0.05$).

Maternal blood group.—The records were reviewed to determine the ABO blood group distributions (Table X) for mothers of cases and controls. Among the mothers of cases 47.5% of groups were unknown and among mothers of controls 40.8% were unknown. If the mothers of cases (and the infants themselves) had been specifically at risk with respect to one or other form of illness related to blood groups there probably would have

TABLE VIII.—PATTERN OF INFANT FEEDING OF CASES AND CONTROLS

	Pattern of infant feeding									
	Bottle		*Breast*		*Gavage*		*Mixed*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Cases	49	61.3	21	26.3	6	7.5	4*	4.9	80	100
Control	75	47.8	75	47.8	2	1.3	5**	3.1	157	100

*One case fed bottle and gavage.
Three cases fed bottle and breast.
**One control fed bottle and gavage.
Four controls fed bottle and breast.

TABLE IX.—BIRTH WEIGHTS OF CASES AND CONTROLS

		Birth weights											*Total*
		Under 400 g. (14 oz.)	*400-749 g. (14 oz. - 1 lb. 10 oz.)*	*750-999 g. (1 lb. 11 oz. - 2 lb. 3 oz.)*	*1000-1499 g. (2 lb. 4 oz. - 3 lb. 4 oz.)*	*1500-1999 g. (3 lb. 5 oz. - 4 lb. 6 oz.)*	*2000-2499 g. (4 lb. 7 oz. - 5 lb. 8 oz.)*	*2500-2999 g. (5 lb. 9 oz. - 6 lb. 9 oz.)*	*3000-3499 g. (6 lb. 10 oz. - 7 lb. 11 oz.)*	*3500-3999 g. (7 lb. 12 oz. - 8 lb. 13 oz.)*	*4000-4999 g. (8 lb. 14 oz. - 11 lb.)*	*5000 g. or over (over 11 lb.)*	
Cases	%	—	—	—	2.5	6.2	7.5	17.5	37.5	21.3	7.5	—	100
	No.	—	—	—	2	5	6	14	30	17	6	—	80
Controls	%	—	—	—	0.6	0.7	5.1	15.3	41.4	29.9	7.0	—	100
	No.	—	—	—	1	1	8	24	65	47	11	—	157

been fewer unknown blood groups among these mothers. The distribution of blood groups (excluding unknown) for cases and controls is shown in Table XI.

Statistically there was a significant difference in the distributions ($P < 0.05$).

TABLE X.—ABO BLOOD GROUPS OF MOTHERS OF CASES AND CONTROLS

		ABO blood groups of mothers					
		Unknown	*O*	*A*	*B*	*AB*	*Total*
Cases	%	47.5	22.5	13.8	12.5	3.7	100
	No.	38	18	11	10	3	80
Controls	%	40.8	26.8	25.5	6.3	0.6	100
	No.	64	42	40	10	1	157

TABLE XI.—ABO BLOOD GROUPS OF MOTHERS OF CASES AND CONTROLS (EXCLUDING UNKNOWNS)

		ABO blood groups				
		O	*A*	*B*	*AB*	*Total*
Cases	%	42.9	26.2	23.8	7.1	100
	No.	18	11	10	3	42
Controls	%	45.2	43.1	10.6	1.1	100
	No.	42	40	10	1	93

Abortions.—The maternal experience related to abortions was examined. (Abortions were defined as all miscarriages of infants weighing less than 400 g. (14 oz.) or born dead at less than 20 weeks' gestation; extrauterine pregnancies, including tubal pregnancies, were considered as abortions unless the fetus exceeded 400 g. (14 oz.) in weight.) It was noted that 6.3% of the mothers of cases had had one or more abortions, as contrasted with 15.9% of the mothers of controls (Table XII). The differences were statistically significant ($P < 0.05$).

TABLE XII.—PATTERN OF ABORTIONS ASSOCIATED WITH MOTHERS OF CASES AND CONTROLS

		Number of abortions						
		None	*1*	*2*	*3*	*4 or more*	*Unknown*	*Total*
Cases	%	93.7	3.7	1.3	1.3	—	—	100
	No.	75	3	1	1	—	—	80
Controls	%	84.1	12.7	1.9	1.3	—	—	100
	No.	132	20	3	2	—	—	157

Time of first prenatal visit.—When the pattern of the times of first prenatal visits was examined, it was noted that approximately twice as many mothers of controls visited the physician during the first and second months as did mothers of cases. From the third to the fifth month, inclusive, more mothers of cases than of controls visited for the first time—28.8% and 21.1%, 16.3% and 7.6%, 12.5% and 8.3%, respectively. In summary, mothers of controls tended to make their first prenatal visit before the third month and mothers of cases from the third month to the sixth month, when mothers of cases and controls were the same in terms of percentages making prenatal visits to term (Table XIII). The differences were statistically significant ($P < 0.05$).

Gestation.—Examination of periods of gestation for the mothers of cases and controls revealed that 13.7% of the former and 6.3% of the latter were of less than 37 weeks' duration and that 45.0% and

TABLE XIII.—TIME OF FIRST PRENATAL VISIT MADE BY MOTHERS OF CASES AND CONTROLS

		Time of first prenatal visit										
		None	*1st month*	*2nd month*	*3rd month*	*4th month*	*5th month*	*6th month*	*7th month*	*8th month*	*9th month*	*Unknown*	*Total*
Cases	%	1.2	7.5	18.8	28.8	16.3	12.5	5	3.7	5	1.2		100
	No.	1	6	15	23	13	10	4	3	4	1		80
Controls	%	2.5	15.3	31.2	21.1	7.6	8.3	5.7	4.4	1.3	1.3	1.3	100
	No.	4	24	49	33	12	13	9	7	2	2	2	157

TABLE XIV—PERIODS OF GESTATION ASSOCIATED WITH CASES AND CONTROLS

	Period of gestation (in weeks)											
	Under 20	*20-27*	*28-31*	*32-33*	*34-35*	*36-37*	*38-39*	*40-41*	*42-43*	*44-45*	*Unknown*	*Total*
Cases												
%	—	—	2.5	2.5	1.2	7.5	31.3	41.3	11.3	1.2	1.2	100
No.	—	—	2	2	1	6	25	33	9	1	1	80
Controls												
%	—	—	0.6	—	0.6	5.1	22.3	59.3	8.9	1.3	1.9	100
No.	—	—	1	—	1	8	35	93	14	2	3	157

28.6%, respectively, were of less than 40 weeks' duration. Among infants born at 40-41 weeks, there were 41.3% of cases and 59.3% of controls; and at 42-43 weeks, 11.3% and 8.9%, respectively (Table XIV). These differences were statistically significant ($P < 0.05$).

TABLE XV.—FATHER'S AGE AT TIME OF DELIVERY OF CASES AND CONTROLS

		Father's age											
		Under 15 years	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*	*45-49*	*50-59*	*60 years or more*	*Unknown*	*Total*
Cases.....	%	—	3.8	28.6	27.5	20	10	3.8	1.3	—	—	5	100
	No.	—	3	23	22	16	8	3	1	—	—	4	80
Controls...	%	—	4.5	12.1	33.8	28	11.5	4.5	2.5	0.6	—	2.5	100
	No.	—	7	19	53	44	18	7	4	1	—	1	157

Father's age.—There were 3.8% of fathers of cases and 4.5% of fathers of controls aged 15-19 years; 28.6% of fathers of cases and 12.1% of fathers of controls were aged 20-24 years (Table XV). The differences between the ages of fathers of cases and controls are statistically significant ($P < 0.05$).

DISCUSSION

The age at death in these 80 S.U.D. cases is similar to that observed in many other studies in various parts of the world, in so far as the majority of deaths tend to occur in the very early months of life (i.e. under 4 months), with a rapid falling off in number after that time. Because of the possibility of confusion of diseases peculiar to the neonate with diseases occurring after the first month of life, the former period was deliberately excluded from this study. The clustering of deaths in the early months suggested to one of us (R.S.) that the underlying pathological processes which resulted in death may have had an antenatal or perinatal component which was worthy of investigation. This hypothesis seemed to be supported by the rarity of sudden unexpected death after this initial peak, as if a group of infants existed who were particularly at risk and that either a rapid reduction in their numbers occurred through death, or a rapid increase in resistance developed.

In view of the evidence for and against a possible relationship between prematurity and S.U.D., it is interesting to note that, in this study, prematurity (as defined by low birth weight—under 2500 g., and gestation—under 37 weeks' pregnancy) appeared to be related to sudden infant deaths. The difference in statistical significance was more marked for low birth weight than for length of gestation, when cases were contrasted with controls. Examination of the data collected for 1959 (Perinatal Mortality Study) showed that 6% of all deliveries were premature, compared with 16.2% of cases and 6.4% of controls in the present study. Also, the period of gestation was less than 37 weeks in 13.7% of the cases and 6.3% of controls; in the 1959 Perinatal Mortality Study a gestation period of less than 37 weeks was reported in 6% of all births.

From the present data it would appear that S.U.D. and prematurity are related.

Low maternal age and cigarette smoking have both been shown to be associated with prematurity, defined in terms of low birth weight. Donnelly *et al.*[10] reported that the incidence of prematurity was considerably higher in women under 20 years of age. This finding was confirmed by the Ontario data in which it was found that the mothers of cases were significantly younger than mothers of controls. Mothers of S.U.D. cases had significantly more infants of low birth weight than did mothers of controls.

Examination of birth weights of cases and controls relative to the smoking habits of their mothers revealed that although the numbers were small, mothers of cases and controls who smoked had more infants under 2500 g. than did mothers who did not smoke.

The evidence from the Ontario study appears to establish significant relationships between S.U.D.

and prematurity, maternal age and maternal cigarette smoking.

Although there is a statistically significant difference between mothers of cases and controls with regard to previous abortions—mothers of controls had more abortions than mothers of cases—this difference did not appear to be explained by the smoking patterns of the two groups of mothers; the numbers, however, are too small for detailed analysis.

In considering the history of abortions and time of first prenatal visit, if the mothers of cases made their first prenatal visits for previous pregnancies later than did mothers of controls, abortions may have occurred that were not recorded and may account for the discrepancy in numbers of abortions between mothers of cases and mothers of controls. On the other hand, during the pregnancies under study, mothers of controls may have sought prenatal advice sooner because of a past history of abortion.

The question of the relationship of smoking to infant survival is important in the light of the findings of Yerushalmy[11] who reported an apparent paradox in that although mothers who smoked more frequently gave birth to low-birth-weight infants, these infants had a significantly lower neonatal mortality rate than did infants of similar low birth weight delivered of non-smoking mothers. This evidence, of course, cannot be extrapolated to the postnatal period but warrants further study.

It may be that infants who die suddenly and unexpectedly have some form of congenital defect related to immunity or enzymatic processes that becomes manifest only when these infants are challenged by infection or sustain some other form of injury early in life. In keeping with this concept, Landing[12] suggested that the sudden-death syndrome may represent a genetically determined response of an unusual and individual nature to an environmental toxin, perhaps analogous to the apnea which develops as a result of the abnormally slow splitting of succinyl choline present at pharmacologic levels in the blood of persons with pseudocholinesterase deficiency.

It was interesting to note in our study that significantly fewer S.U.D. cases were breast-fed than were controls, in view of the suggested relationship between S.U.D. and hypersensitivity to cows' milk aspirated into the bronchial tree[4] and the reported absence or rarity of the S.U.D. syndrome in totally breast-fed infants. These findings are in agreement with those of Carpenter and Shaddick,[8] although the percentages in England differ—56% of S.U.D. cases were wholly breast-fed compared with 70% of controls. It cannot be assumed that the difference in the feeding patterns was maintained after discharge from hospital. As has been demonstrated on many occasions, the percentage of infants who are breast-fed falls rapidly with the infant's age and following discharge to the home.

In this study a large number of variables bearing on the antenatal and early postpartum histories were examined. For most of these variables it was shown that there was no statistically significant difference between cases and controls. Statistically significant differences were found in mother's age at first pregnancy, at the delivery of the infant in this study and at marriage; maternal cigarette smoking habit; infant feeding; birth weight; maternal blood group; father's age (at time of the delivery of the infant included in this study); abortions; time of first prenatal visit; and length of gestation. It is noteworthy that certain factors which have been postulated in the past or might possibly have had a significant relationship to sudden and unexpected infant loss, were not shown in fact to have such a relationship; these factors have included father's occupation, consanguinity, history of maternal weight gain or loss during pregnancy, employment of mother, complications of pregnancy, infant infections, infant therapy (e.g. oxygen, vitamin K, digitalis, transfusions, antibiotics, etc.), distress in the newborn, and anesthesia.

Further work is clearly required to establish (1) whether cause-effect relationships exist between the variables which in this study were significantly related to S.U.D., (2) whether a constellation of these variables can be used to identify infants at risk where other factors, e.g. infection, may be directly responsible for "triggering" the fatal outcome.

The authors wish to thank the Ontario Perinatal Mortality Study Committee for permission to use their data in this investigation. Our gratitude is expressed also to Dr. C. M. Hoffman and Miss M. Neilson, R.N., of the Maternal and Child Health Branch, Ontario Department of Health; Mr. E. W. Pike of the Office of the Registrar-General, Toronto; Dr. John Read and our other colleagues in the Department of Preventive Medicine for much helpful advice; and Dr. E. H. Botterell, Dean of the Faculty of Medicine, Queen's University, for encouragement and support.

REFERENCES

1. VALDES-DAPENA, M. A. AND HUMMELER, K.: *J. Pediat.*, **63:** 398, 1963.
2. GOLD, E. *et al.*: *New Eng. J. Med.*, **264:** 53, 1961.
3. COE, J. I. AND PETERSON, R. D. A.: *J. Lab. Clin. Med.*, **62:** 477, 1963.
4. PARISH, W. E. *et al.*: *Lancet*, **2:** 1106, 1960.
5. STEELE, R.: *Canad. Med. Ass. J.*, **92:** 554, 1965.
6. ADELSON, L. AND KINNEY, E. R.: *Pedatrics*, **17:** 663, 1956.
7. Ontario Perinatal Mortality Study Committee: Report of the perinatal mortality study, 1959, in ten university teaching hospitals, Ontario, Canada. Maternal and Child Health Branch, Department of Health, Toronto, 1961.
8. CARPENTER, R. G. AND SHADDICK, C. W.: *Brit. J. Prev. Soc. Med.*, **19:** 1, 1965.
9. GOLDSTEIN, H. *et al.*: *Public Health Rep.*, **79:** 553, 1964.
10. DONNELLY, J. F. *et al.*: *Amer. J. Obstet. Gynec.*, **88:** 918, 1964.
11. YERUSHALMY, J.: *Ibid.*, **88:** 505, 1964.
12. LANDING, B. H.: *In*: Proceedings of the conference on causes of sudden death of infants, Department of Pathology and Pediatrics, University of Washington, Seattle, 1963.