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EPIDEMIOLOGY OF SUDDEN UNEXPECTED DEATH IN INFANTS ('COT DEATH') IN NORTHERN IRELAND

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Sudden unexpected death in infants ('cot death' or 'crib death') is now recognized as a clinical entity and existing knowledge has been recently summarized (Valdés-Dapena, 1967; Froggatt, Lynas, and Marshall, 1968; Bergman, Beckwith and Ray, 1970). The 'final common pathway' of death (assumed to be identical in most cases) is, however, unknown. The consensus view is that throughout life these infants are essentially healthy; they die because while passing through a developmental stage of physiological vulnerability some critical combination of extrinsic and intrinsic factors occurs which proves lethal through either (*a*) a respiratory mechanism—in whose production various processes have been incriminated (e.g., Bergman *et al.*, 1970; Ray, Beckwith, Hebestreit, and Bergman, 1970; Shaw, 1970); (*b*) a lethal cardiac arrhythmia or conduction disturbance—for which an anatomic basis has been demonstrated (James, 1968); or (*c*) a hypersensitivity reaction to antigens at present unidentified but often thought to be cow's milk proteins (e.g., Parish *et al.*, 1960b; Gunther, 1966). Numerous other hypotheses have been postulated but they are either untenable or purely speculative.

One aetiological concept—lethal cardiac arrhythmia—is based on data (Froggatt *et al.*, 1968) and special examination of hearts (James, 1968) from a two-year study in Northern Ireland. This paper describes the epidemiological aspects of this study and examines how the data accord with the main hypotheses of causation. Other aspects of the study are presented elsewhere (Froggatt *et al.*, 1968; Froggatt, 1970a; Froggatt, Lynas, and Marshall, 1971).

Throughout the text the description of a difference as 'significant' means that it or a greater difference was unlikely to occur by chance in more than 5% of repeated trials. χ^2 is everywhere calculated on absolute numbers and, where appropriate, is corrected for continuity.

The literature on this condition is now extensive. Primary sources are only referenced where essential: thorough reviews and extensive bibliographies are given by Valdés-Dapena (1967, 1970) and Froggatt *et al.* (1968, 1971).

Definition and Criteria of Inclusion

There is no standard designation of the entity (or entities) under study: 'sudden and unexpected death in infants' (Rabson, 1949) and 'the sudden infant death syndrome' (Gold, Adelson, and Godek, 1964), and their variants, are most frequently used. The former indicates selection on clinical criteria alone, e.g., 'the death of a child who was thought to be in good health or whose terminal illness appeared to be so mild that the possibility of a fatal outcome was not anticipated' (Adelson and Kinney, 1956); while the latter involves clinical *and* pathological criteria, i.e., 'the sudden death of any infant or young child which is unexpected by history and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death' (Bergman *et al.*, 1970, p. 18). This again is strictly equivalent to 'sudden unexpected unexplained death in infants' (Fitzgibbons *et al.*, 1969) which, in turn, stems from the earlier 'sudden apparently unexplained death during infancy' (Werne and Garrow, 1953). In practice, the above and variant terms are used as synonyms: in this article we use for brevity the acronym SUD.

None of the above is a certifiable cause of death; accordingly, we must state precisely our criteria. We selected cases on necropsy findings, taking as the criterion the absence of demonstrable pathology (on the thorough procedure of Marshall (1970)) conventionally accepted as sufficient to explain death. Subjects with recognizable anomalies, e.g., polycystic disease and venous sinus thrombosis, were excluded even though these lesions may not have 'caused' the death (sudden death is not uncommon in such children and is usually attributed, perhaps erroneously, to the underlying condition), while in some few instances, e.g., asphyxia due to suspected choking, and infanticide, the history contributed to exclusion. We thus avoided bias inherent in selecting on a case history criterion and could include children with varied premortem clinical findings. Our cases were literally 'unexplained at necropsy'; since, however, most were also 'sudden and unexpected' and in the narrow age range which characterizes SUD (see below), our

ultimate group would have been little restricted even if selected on the strictest possible SUD criteria.

Ascertainment

Selection of Index Cases

Ascertainment was through the Northern Ireland Forensic Pathology Service (NIFPS) and covered the two years 1 August 1965 to 31 July 1967. All deaths which are *inter alia* sudden, unexpected, or unexplained are required to be notified to the coroner under law (Coroners Act, 1959), and to maximize ascertainment general practitioners were contacted and the State Pathologist (Dr. T. K. Marshall) asked the (16) coroners to demand a necropsy on children as a routine. As a result 323 children under 5 years of age were referred, and, of these, 297 (92%) were examined to a standard routine by four similarly trained forensic pathologists in the NIFPS, and 26 (8%) by other 'approved' pathologists. Cases for study were selected exclusively from the former group; in fact not more than five of the latter group could reasonably be accepted as SUD.

Exclusions from these 297 were made as follows. In 78, death was unnatural, e.g., injury, drowning, or severe burns; in 29, there was an adequate natural cause for death other than respiratory inflammation as a sole finding, e.g., congenital heart disease, polycystic disease, or hydrocephalus; in 21, respiratory inflammation co-existed with other lesions—most commonly congenital heart disease, meningococcal septicaemia, sinus thrombosis or adrenal haemorrhages—which together were considered adequate to explain death; and in five, the significance of the presenting lesions was equivocal. Only two of the remaining 164 fell outside the age range 2–103 weeks (4 days; 144 weeks) and these were excluded, leaving 162 'unexplained' cases to comprise the group for study. These are subsequently termed 'index cases'.

The families (nearly always the mothers) of 148 (91·4%) were interviewed by one of us (M.A.L.). Eight refused interview, two were itinerants and untraced, three had left the country, and one was *sub judice* at the time. The entire 162 index cases contribute data to the analyses when accurately known; more frequently, however, adequate information is available only on the 148 whose families were interviewed. Cases ascertained in a third year (1 August 1967 to 31 July 1968) are used in one of the space-time clustering tests.

Selection of Control Group

There is no satisfactory control group for SUD: living infants and those dying from 'explained' causes are clearly strictly inappropriate. Nevertheless some control data are essential.

The control group selected comprised the (chronologically) next like-sexed birth (as identified from birth notifications) in the same administrative area as that of each of the 162 index cases. Matching was therefore by sex, county, or county borough (in the case of four counties and two county boroughs) or sub-area division (in the remaining two counties) of normal domicile, and date of birth—this to never more than four days. Only two second-choice controls were necessary: one first-choice control had died perinatally and the mother of a second was a mental hospital in-patient. The family (nearly always the mother) of each of the relevant 148 controls was interviewed (by M.A.L.): none declined.

Bias in the Ascertainment

As argued elsewhere (Froggatt *et al.*, 1971), we estimate the 'completeness' of the ascertainment as some 95% in Belfast and 85% in the rest of Northern Ireland. Important bias would, therefore, only be introduced by the mechanism of ascertainment and the criteria themselves. We discuss in detail elsewhere (Froggatt *et al.*, 1971) why we consider bias to be unimportant except possibly against neonates, though even here missed cases should be few.

Material and Methods

Data were obtained at family interview (checked where possible from records) and at necropsy. The necropsy routine has been documented elsewhere (Marshall, 1970): interview procedure and data are as follows.

The families were contacted through local health authority staff. The interviews were conducted by one of us (M.A.L.) and timed optimally for two or three weeks after the death. Information, recorded on a standard schedule using where appropriate precoded responses, specified (index cases and controls are collectively designated 'subjects'): essential antenatal, birth, and medical data on subjects and their sibs and the last of these also on their parents; legitimacy; father's social and economic status; parental ages, stature, consanguinity, and marriage date; specific history of (for the index case) the week preceding death and (for the control) the week preceding interview; feeding regime and medicine intake since subject's birth; date, day of the week, time, and detailed circumstances of death of index case; 'normal' sleeping and feeding habits of subjects and those preceding death of index case; state of housing, maternal care, and indices of domestic crowding; and electrocardiogram (bipolar limb leads) of parents of index cases. A two-month pilot study preceded the main survey, cases ascertained being later discarded.

The data were examined by single-parameter tests and matched-pair contingency methods, by multifactor analyses, and by space-time interaction tests. Only those results pertinent to the more plausible hypotheses of causation and which are essential to define the epidemiology of SUD are presented: other findings are reported elsewhere (Froggatt *et al.*, 1968; Froggatt, 1970a, b; Marshall, 1970; Froggatt *et al.*, 1971).

Results

General Factors

Incidence The first estimate is 2·5 per 1,000 live births with SUD as 10% of infant mortality and 30% of postneonatal mortality: 'adjusting' (for overall 90% ascertainment) gives respectively 2·8, 11%, and 33%. These figures accord with most North American and European experience, though both lower (Ministry of Health, 1965; Cameron and Asher, 1965; Fitzgibbons *et al.*, 1969; Houstek, 1970) and higher (Canby and Jaffurs, 1963; Stowens, Callahan, and Clay, 1966; Steele, Kraus, and Langworth, 1967; Kerenyi and Fekete, 1969) estimates are reported. No studies have been published from underdeveloped countries. Survey and population differences could produce such disparities, and an incidence of 2·0 to 3·0 per 1,000 live births can be accepted for Europeanized communities in temperate zones.

Regional Variation Some authors have noted an urban excess in SUD (Jacobsen and Voigt, 1956; Brenner, 1962), others a rural excess (Houstek, Benesova, and Holy, 1959; Maresch, 1961; Steele *et al.*, 1967), and others no regional differences (Peterson, 1966; Melton, Fatteh, and Mann, 1968; Marcusson, Oehmisch, and Grandke, 1968; Houstek, 1970). Table I summarizes our results which are confined to postneonatal (4–51 weeks) deaths to allow population comparisons and to minimize regional ascertainment bias against the very young (Froggatt *et al.*, 1971). In fact this restriction excludes only nine cases.

Table I

INCIDENCE OF SUD PER 1,000 LIVE BIRTHS: POSTNEONATAL (4–51 WEEKS) CASES, 1 AUGUST 1965 TO 31 JULY 1967*

Administrative Area	Incidence per 1,000 Live Births (and No. of Cases)		
	Males	Females	Total
County Borough:			
Belfast	5·4 (47)	2·8 (23)	4·2 (70)
Londonderry	3·1 (5)	1·9 (3)	2·5 (8)
County:			
Antrim	1·8 (14)	2·0 (14)	1·9 (28)
Armagh	1·3 (4)	2·1 (6)	1·7 (10)
Down	2·3 (14)	1·6 (9)	2·0 (23)
Fermanagh	0·0 (0)	1·0 (1)	0·5 (1)
Londonderry	1·3 (4)	1·7 (5)	1·5 (9)
Tyrone	1·2 (4)	1·6 (5)	1·4 (9)

*158 cases from NIFPS (153) and 'approved' pathologists (5).

Inspection shows a clear excess of cases in Belfast, particularly of males. Londonderry C.B. and the two counties with large commuter dormitory populations (Down and Antrim) show higher case rates than do the mainly rural counties, but small numbers of cases and the possibility of any bias in ascertainment favouring Belfast and district (Froggatt *et al.*, 1971) precludes firm conclusions being drawn as regards true regional variation. We examine these, and other facts of regional variation, in detail elsewhere (Froggatt *et al.*, 1971) and conclude (1) that the overall and male Belfast excess of cases is real, and (2) that, on the county material, there is no difference between the case rates in rural districts and in combined urban districts and metropolitan boroughs.

Sex Males predominate in only four series. In three of these (Garsche, 1949; Cooke and Welch, 1964; Ministry of Health, 1965) the sexes are about equal, and in the other (Cameron and Asher, 1965) there is a marked female preponderance (M/F = 80/92).

In the present study, 95 (58·6%) index cases were males and 67 (41·4%) females. Corresponding rates are 2·73 per 1,000 male live births and 2·07 per 1,000 female live births, a male excess which, though non-significant ($\chi^2 = 2{\cdot}82$, D.F. = 1, $0{\cdot}10 > P > 0{\cdot}05$), can be attributed mainly to the atypical Belfast experience (Table I). This male excess is not significantly different from that of infant mortality from all other causes (males 54·8%, females 45·2%; $\chi^2 = 0{\cdot}94$, D.F. = 1, $0{\cdot}50 > P > 0{\cdot}30$), nor is the postneonatal male excess of SUD (males 58·8%, females 41·2%) significantly different from that of postneonatal mortality from (1) all other causes (males 53·2%, females 46·8%; $\chi^2 = 1{\cdot}20$, D.F. = 1, $0{\cdot}30 > P > 0{\cdot}20$) or (2) 'respiratory' causes, i.e., *ICD* (*Seventh Revision*) (World Health Organization, 1957) categories 480–483, 490–493, 500–502, 525, and E921, after SUD cases have been removed (males 46·4%, females 53·6%; $\chi^2 = 3{\cdot}21$, D.F. = 1, $0{\cdot}10 > P > 0{\cdot}05$), even though the sex ratio is reversed. The excess male decrement in SUD therefore patterns that for deaths of infants generally.

Age This study confirms the unique age distribution, not dissimilar between sexes, which characterizes SUD (Table II): the precise ages of the 148 cases whose families were interviewed give a mean of 18·1 weeks (males 15·7, females 21·4) and a median of 13·8 weeks (males 13·1, females 14·4). Of note is the relative immunity in the first three weeks of life, contrasting with other causes of infant mortality. This cannot be quantified and may be partly an

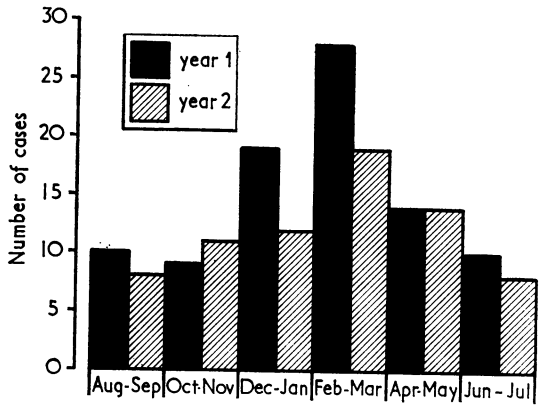
TABLE II
DISTRIBUTION OF INDEX CASES BY SEX AND AGE AT DEATH

Age at Death (weeks)	Index Cases			Cumulative Percentage Frequency
	Males	Females	Total	
2–	1	–	8	4·9
3–	4	3		
4–	16	14	30	23·5
8–	19	12	31	42·6
12–	19	10	29	60·5
16–	12	5	17	71·0
20–	9	3	12	78·4
24–	6	3	9	84·0
28–	6	8	14	92·6
42–	3	9	12*	100·0
Total	95	67	162	—

$\chi^2 = 10{\cdot}65$, D.F. = 8, $0{\cdot}30 > P > 0{\cdot}20$
*Only one child (a girl aged 59 weeks) had attained 1 year.

artifact (Froggatt *et al.*, 1971); but simple extrapolation from the frequency curve at ages 2+ weeks (Table II) suggests a genuinely low prevalence in the first fortnight of life in accord with our ascertainment experience (one 4-day-old boy). On the other hand, the rapid decline after age 3 months is unequivocal.

SEASONAL VARIATION Table III presents relevant data. SUD is commonest in the colder, rarest in the warmer, months and this is not due to the (unimportant) monthly fluctuation in live births. There is no difference in the monthly frequencies by sex ($\chi^2 = 3{\cdot}04$, D.F. = 11, $P > 0{\cdot}99$). This winter excess confirms most survey findings; only the East German (Marcusson *et al.*, 1968) and Minnesota (Fitzgibbons *et al.*, 1969) series give equivocal results. This temporal distribution is different from that of postneonatal deaths from (1) all other causes ($\chi^2 = 27{\cdot}14$, D.F. = 11, $0{\cdot}01 > P > 0{\cdot}001$)—there is no winter peak in the latter (Table III row *b*), and (2) in *ICD* (*Seventh Revision*) categories 480–483, 490–493, 500–502, 525, and E921 after omitting known SUD cases (on calendar quarterly frequencies, $\chi^2 = 10{\cdot}48$, D.F. = 3, $0{\cdot}02 > P > 0{\cdot}01$), though the April–June quarter looks atypical (Table III). The winter peak of SUD was more marked in the first year of the study (Figure), coinciding with an epidemic of



FIGURE—Distribution of 162 index cases by month and survey year (year 1 = 1 August 1965 to 31 July 1966; year 2 = 1 August 1966 to 31 July 1967).

type B influenza in January and February 1966 and type A2 in February and March 1966. A similar pattern (against the null hypothesis of equal monthly frequencies, $\chi^2 = 26{\cdot}38$, D.F. = 11, $0{\cdot}01 > P > 0{\cdot}001$) obtains for the 60 (of the 148) cases alleged at family interview to have been completely symptom-free during the week before death, including the day when last seen alive.

Examining now the form of this temporal distribution, we note that if cases were randomly allocated over time then the frequency distribution of time intervals between successive cases would be negative exponential. Removing the gross seasonal effect (as mandatory on the assumptions), yet preserving adequate numbers, we identified the two 'winter' periods November to April 1965–6 and 1966–7 ('summer' cases during May to October 1966 were

TABLE III
MONTHLY FREQUENCIES (AND PERCENTAGES) OF POSTNEONATAL (4–51 WEEKS) SUD CASES, OTHER CATEGORIES OF INFANT DEATH, AND LIVE BIRTHS (1 AUGUST 1965 TO 31 JULY 1967)

Category (and No. of Subjects)	Month of Occurrence (Category (*a*)) or Registration (Categories (b) to (d))												χ^2 (and D.F.) on Null Hypothesis of Equal Frequencies
	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	
(*a*) Postneonatal SUD (153)	13 (8·5)	23 (15·0)	23 (15·0)	19 (12·4)	8 (5·2)	8 (5·2)	8 (5·2)	6 (3·9)	11 (7·2)	7 (4·6)	12 (7·8)	15 (9·8)	31·71 (11) $P < 0{\cdot}001$
(*b*) Postneonatal deaths minus (*a*) (382)	29 (7·6)	28 (7·3)	37 (9·7)	33 (8·6)	49 (12·8)	34 (8·9)	20 (5·2)	35 (9·2)	36 (9·4)	31 (8·1)	22 (5·8)	28 (7·3)	19·71 (11) $0{\cdot}05 > P > 0{\cdot}02$
(*c*) Postneonatal deaths in respiratory categories* minus (*a*) (96)		26 (27·1)			40 (41·7)			15 (15·6)			15 (15·6)		17·58 (3) $P < 0{\cdot}001$
(*d*) Live births (66,945)	5,724 (8·6)	5,039 (7·5)	5,747 (8·6)	5,605 (8·4)	5,989 (8·9)	6,122 (9·1)	5,600 (8·4)	5,640 (8·4)	5,793 (8·7)	5,471 (8·2)	5,222 (7·8)	4,993 (7·5)	214·42 (11) $P < 0{\cdot}001$

**ICD* (*Seventh Revision*) Nos. 480–483, 490–493, 500–502, 525, E921

TABLE IV

OBSERVED FREQUENCIES OF TIME INTERVALS BETWEEN SUCCESSIVE SUD CASES AND THOSE EXPECTED ON THE NEGATIVE EXPONENTIAL DISTRIBUTION, NORTHERN IRELAND DATA

Time Interval between Successive Cases (days)	November 1965 –April 1966		November 1966 –April 1967		August 1965 July 1967	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
0–	30	22·01	15	12·27	55	36·63
1–	9	14·66	6	9·07	21	28·55
2–	5	9·22	5	6·67	12	22·28
3–	7	6·21	5	4·94	19	17·16
4–	4	4·10	6	3·67	12	13·37
5–	–		3		6	10·23
6–	5		3		10	8·42
7–	1		–		8	6·27
8–	1	9 7·86	1	10 10·38	5	4·95
9–	1		1		2	
10+	1		2		15	17 17·14
Total	64	64·06	47	47·00	165	165·00
χ^2 (D.F.) P	7·30 (4) 0·10–0·20		3·55 (4) 0·30–0·50		18·81 (8) 0·01–0·02	
Parameter (λ)	0·4211		0·3023		0·2513	

too few—25—for meaningful analysis) and for both (ignoring terminal 'open' intervals) there is reasonable concordance of the data with expectation, and the null hypothesis of temporal randomness cannot therefore (by this test) be rejected (Table IV). This is not so for the combined data, possibly because the seasonal fluctuation invalidates the test. We conclude that there is no good evidence for temporal clustering within either 'winter' period, contrary to the findings of Kraus, Steele, and Langworth (1967) on their complete data.

DAY OF WEEK AND TIME OF DAY Most investigators (Emery, 1959; Peterson, 1966; Valdés-Dapena, 1967), though not all (Cameron and Asher, 1965), have found equal frequencies of SUD by day of the week; and SUD cases, unlike other infant deaths, are commonest during normal household sleeping hours (Hildebrand, 1966; Valdés-Dapena, 1967; Steele *et al.*, 1967; Melton *et al.*, 1968; Fitzgibbons *et al.*, 1969; Bergman, 1970; Houstek, 1970). In the present study the exact time of death is perforce known only for those 37 index cases (23%) who were allegedly seen to die or were discovered *in extremis* (a gross overestimate since many of these infants were probably dead when found though the parents would not acknowledge this), and all but seven of these (allegedly) died between 8.00 a.m. and midnight, i.e., when babies are under most frequent surveillance. The time of death for the remaining 125 was taken as the midpoint between the times last seen alive and found dead.

The percentage distribution by day of the week (Sunday to Saturday) of the 162 index cases is 17·9, 15·4, 11·7, 14·2, 13·6, 13·0, and 14·2 (tested against equal frequencies, $\chi^2 = 2{\cdot}63$, D.F. = 6, $0{\cdot}90 > P > 0{\cdot}80$). The percentage distribution by, in order, the three consecutive eight-hour periods from midnight (which should be largely unbiased by normal household regimen) is 50·0, 36·4, and 13·6 (tested against equal frequencies, $\chi^2 = 32{\cdot}93$, D.F. = 2, $P < 0{\cdot}001$) and similar to that (51·7, 33·3, and 15·0) for the subgroup of 60 cases who were allegedly symptom-free throughout the week before death. The presumptive death or 'collapse' during sleep in the great majority of cases was a striking finding.

SOCIAL AND ECONOMIC STATUS Since Templeman's (1892) classic report most authors have noted that SUD is commonest in underprivileged children. In the present study cases were compared with certain relevant groups for social class and economic activity of the father, illegitimacy, and family room-occupancy rate. Belfast, and the rest of Northern Ireland, are treated separately for social class because the incidence of SUD (Table I) and the social class distribution (farmers—S.C.II.—bias the rural figures) are different and, moreover, more control data are available for the former.

Table V gives information on social class: there is no appropriate control group for families ascertained through an SUD child but those chosen seem the most acceptable. In the first column groups (*a*), (*b*), (*f*), and (*g*) relate to the 135 singleton cases (of the 148 interviewed families) and the 147 singletons in the control group; group (*c*) is all singleton live births in 1966 in Belfast to Belfast-resident mothers; groups (*d*) and (*h*) are males aged 20–44 years (the fathers of 93% of our SUD cases are in this age group) from the 1961 census returns (General Register Office, 1963); and group (*e*) is singleton births in Belfast to Belfast-resident mothers over the five years 1962–6 and who died in Belfast aged 7–28 days. (These postperinatal deaths are our choice for non-surviving controls because they contain very few (< 5%) SUD cases yet they do not include the very special group of perinatal deaths.) Inspection indicates that, compared to their controls, both SUD groups ((*a*) and (*f*)) are deficient in classes I and II and over-represented in class V, this difference becoming more marked if the 'unknown' column (mostly illegitimate children) is aggregated with social class V, as seems reasonable.

Other measures of socio-economic disadvantage show that, where classifiable, the fathers of 29 of 139 SUD cases compared to the fathers of 12 of the 148 controls ($\chi^2 = 8{\cdot}51$, D.F. = 1, $P < 0{\cdot}01$) were 'economically inactive', i.e., unemployed or off work through sickness for over six months; 11 (7·4%) of the 148 SUD cases compared to none of the 148

controls were illegitimate ($\chi^2 = 9{\cdot}44$, D.F. = 1, $P < 0{\cdot}01$) (over the same period illegitimate SUD cases were some 21% of illegitimate infant (< 1 year) deaths compared to 10% for the corresponding rate for legitimate infants); while room occupancy ('crowding') was generally higher for the families of SUD cases than for those of the controls, in classes I and II significantly so (Table VI).

Maternal Factors

Pregnancy During the pregnancies producing respectively the SUD cases and controls, health, rhesus factors, prenatal exposure to pelvic or abdominal *x*-rays, and obstetric history were not significantly different and, in general, were unremarkable (Froggatt *et al.*, 1971).

Age and Birth Order Some authors have noted comparatively younger mothers (Peterson, 1966, Valdés-Dapena, 1967; von Sydow, 1969) and higher birth orders (Cameron and Asher, 1965; Peterson, 1966; Houstek, 1970) in SUD: of those few with adequate data, only Bergman (1970) found maternal age and parity unremarkable. In the present study these two confounded factors are examined as follows.

Table VII sets out the distributions, by maternal age and parity, of the control group and the 148 index cases whose families were interviewed, Due to the nature of the condition each case and control was the youngest in the sibship. To provide adequate numbers three age groups (⩽24, 25–29, and 30+) and five parity classes (1, 2 . . . 5+) were distinguished. Within each of these three age groups the distributions by parity of cases and controls were compared and the null hypothesis—that the proportion of cases to controls in the five parity groups does not differ significantly from the proportion of total cases to controls within that age group—could be rejected in two of the three comparisons. (For the three age groups in succession and pooling the 4 and 5+ parity classes in the first and third,

TABLE V

SOCIAL CLASS DISTRIBUTION OF SINGLETON SUD CASES AND GROUPS OF CONTROLS*

Group (and No. of Subjects)	Percentage Distribution (and No. of Subjects)				
	I + II	III	IV	V	Unknown
Belfast					
(*a*) SUD singletons (58)	— (*0*)	53·4 (*31*)	13·8 (*8*)	29·3 (*17*)	3·4 (*2*)
(*b*) Control group singletons (63)	9·5 (*6*)	39·7 (*25*)	19·0 (*12*)	31·7 (*20*)	— (*0*)
(*c*) Singleton live-births 1966 (7,966)	8·5 (*678*)	51·0 (*4,061*)	13·1 (*1,040*)	23·2 (*1,847*)	4·3 (*340*)
(*d*) Males 20–44 years 1961 (59,237)	12·4 (*7,362*)	51·0 (*30,202*)	19·7 (*11,675*)	16·9 (*9,998*)	Negligible
(*e*) Postperinatal deaths of singletons 1962–6 (106)	7·5 (*8*)	51·9 (*56*)	13·2 (*14*)	18·9 (*20*)	7·5 (*8*)
Rest of Northern Ireland					
(*f*) SUD singletons (77)	19·5 (*15*)	36·4 (*28*)	16·9 (*13*)	20·8 (*16*)	6·5 (*5*)
(*g*) Control group singletons (84)	27·4 (*23*)	39·3 (*33*)	14·3 (*12*)	19·0 (*16*)	— (*0*)
(*h*) Males 20–44 years 1961 (145,237)	26·8 (*38,858*)	41·3 (*60,027*)	19·7 (*28,625*)	12·2 (*17,727*)	Negligible

*For details see text.

TABLE VI

ROOM OCCUPANCY BY SOCIAL CLASS

Group (and No. of Subjects)	Persons per Room*											
	I + II		III			IV			V			
	⩽1·20	1·20+	⩽1·20	1·20–1·99	2·00+	⩽1·20	1·20–1·99	2·00+	⩽1·20	1·20–1·99	2·00+
SUD cases (138)†	5	10	20	28	17	10	9	5	4	15	15
Matched controls (148)	22	7	26	21	11	10	8	6	11	15	11
χ^2 (and D.F.)	5·85 (1)		2·68 (2)			0·15 (2)			3·76 (2)		
P	0·01–0·02		0·20–0·30			0·90–0·95			0·10–0·20		

*Persons are those who usually sleep in the house (tents, institutions, etc. are omitted)
Rooms are those normally used as living rooms or bedrooms and with a floor area ⩾ 50 sq. ft.
†Excludes 10 cases where the father's occupation is unknown or unclassifiable.

$\chi^2 = 14{\cdot}68$, D.F. = 3, $P < 0{\cdot}01$; $\chi^2 = 13{\cdot}06$, D.F. = 4, $P < 0{\cdot}01$; and $\chi^2 = 3{\cdot}32$, D.F. = 3, $0{\cdot}50 > P > 0{\cdot}25$). Inspection indicates a tendency for the proportion of cases to controls to increase with increasing parity in the younger two combined age groups, and testing, by a partitioning of χ^2 (Table VIII), shows a significant linear trend in those two age groups but not in the 30+ combined age group.

This association may not be a primary one; the trend may, for example, reflect differences in social class distribution within age and parity groups. Though Table V shows no important difference in the overall social class distribution for cases and the matched control group, this may conceal important interactions. Our data are, however, too sparse to allow meaningful testing of appropriate hierarchical arrangements; larger surveys on unbiased series, difficult to mount because of ascertainment problems in countries which, unlike Northern Ireland, have no national forensic pathology service, would be necessary. In order to carry this line of enquiry further, and to examine the effect of other possible confounding factors, either our study would have to be substantially extended or we must resort to some multivariate technique of analysis such as we have attempted elsewhere (Froggatt, 1970a).

MULTIPLE BIRTHS SUD is frequent among twins, equally so for males and females and in like and unlike pairs. When both partners have been SUD cases their deaths have usually been contemporaneous (Wöckel and Raue, 1961; Cooke and Welch, 1964; Geertinger, 1968).

In the present study 11 index cases were one of twins, and two others were members of one like-sexed (female) but dizygous (by blood grouping) twin-set who died on the same day aged 10 weeks. Nine sets were like-sexed (4MM; 5FF) and the SUD twin was the heavier at birth in six (of the 11) sets. This frequency of twins (8·0%)—which compares with 3·5% for twins of live-born twin-sets who die aged 2–103 weeks from other causes and 14% for all twins who died under 2 weeks—may be a consequence of their low birthweight (mean 5·1 lb (2·3 kg)) since binary multiple regression shows birthweight to be a reasonably powerful independent determinant of infant deaths in Belfast (Elwood, 1969).

TABLE VII

DISTRIBUTION OF SUD CASES AND MATCHED CONTROLS BY MATERNAL AGE AND PARITY

Age of Mother (years)		Birth Order of Child*										Total
		1	2	3	4	5	6	7	8	9	10+	
⩽20	cases	3	7	1								11
	controls	8	1	—								9
20–	cases	11	16	12	11	3	—	1				54
	controls	15	10	6	1	1	—	—				33
25–	cases	2	5	8	8	6	7	3	1	1	2	43
	controls	10	8	9	12	4	3	—	—	—	—	46
30–	cases	3	6	3	5	3	2	2	1	—	1	26
	controls	4	3	8	6	7	3	4	2	1	1	39
35–	cases	—	1	—	2	4	—	1	1	1	1	11
	controls	1	—	3	3	1	1	2	1	2	—	14
40–44	cases	—	—	—	—	—	—	—	—	1	1	2
	controls	1	—	—	1	—	3	—	—	2	—	7
Total	cases	19	35	24	26	16	9	7	3	3	5	147†
	controls	39	22	26	23	13	10	6	3	5	1	148

*(No. of previous livebirths, stillbirths, and miscarriages) +1
†Birth order of one child unknown

TABLE VIII

TEST FOR LINEAR TREND IN THE PROPORTION OF SUD CASES, OVER PARITY, FOR POOLED AGE GROUPS FROM TABLE VII

Source of Variation	Age (years)								
	⩽24			25–			30+		
	χ^2	D.F.	P	χ^2	D.F.	P	χ^2	D.F.	P
Linear trend	11·86	1	<0·005	10·81	1	<0·005	0·12	1	0·50–0·75
Deviations	2·82	2	0·10–0·25	2·25	3	0·50–0·75	3·20	2	0·10–0·25
Total	14·68	3	<0·005	13·06	4	0·01–0·02	3·32	3	0·25–0·50
Regression coefficient ± standard error	+0·140 (0·041)			+0·122 (0·038)			−0·012 (0·036)		

INFANT FACTORS

BIRTHWEIGHT AND GESTATION PERIOD Most authors have noted a higher incidence of prematurity in SUD than among surviving live births but not generally than among infants who died under 1 year (Cameron and Asher, 1965; Marcusson *et al.*, 1968; Houstek, 1970). In the present study there is no evidence of a 'small for dates' effect (and the correlation coefficient between birth weight (lb) and age at death (to nearest week) is nonsignificant ($r = -0{\cdot}128 \pm 0{\cdot}086$)); thus birthweight was chosen as the measure and its influence was examined in two ways: (1) multiple regression analysis of birthweight on other appropriate recorded variables (sex, social class, parity, 'social parity',* father's age, mother's age) in order to compare unconfounded mean birthweights of singleton index cases and surviving singletons from a random sample of births (for details of this sample, restricted to Belfast births to obtain appropriate data, see Froggatt (1970a) and Froggatt *et al.* (1971)); and (2) comparison of mean birthweights, in a suitable hierarchical table, using the Northern Ireland SUD cases and the matched controls.

(1) The multiple regression approach yielded two hyperplanes with heterogeneous residual variances (quotient of residual mean squares = 2·22; 1% critical value for 51 and 943 D.F. = 1·68) which precluded their further testing in the original units. Arbitrarily applying different transformations to the birthweight measures we found that the trigonometric (sine) transformation produced two regression hyperplanes with residual variances acceptable as homogeneous (quotient of residual mean squares = 1·21): accordingly, this transformation was subsequently used.

Testing first these two hyperplanes for 'parallelism', we found that the residual sum of squares ascribable to the differences in their positions ($E_2 = 460{\cdot}06$) approximated the sum of squares for each of the two regressions separately ($E_0 = 457{\cdot}42$) which, with F (= 0·96) below the 1% critical value (2·82 for 6 and 994 D.F.), indicated non-rejection of the null hypothesis. Proceeding then validly to test for confluence of these two hyperplanes, we found that the residual sum of squares for the overall pooled regression ($E_1 = 461{\cdot}68$) also approximated E_0, and, with F = 1·32 again well below the 1% critical value (2·66 for 7 and 994 D.F.), we could consider the hyperplanes also confluent. Thus there is no significant difference between mean birthweight or its relation to the accounted factors in the two groups.

(2) Using data from all Northern Ireland, we tested differences in mean birthweights, within 'social parity' and sex hierarchies (these being the most significant factors in the multiple regressions above), between 135 singleton cases and their matched controls. Results (Table IX) show higher mean birthweights for controls in all six comparisons, two significantly so, and in general smaller differences for females than males. We conclude from these, and discriminant tests (Froggatt, 1970a), that birthweight may be a correlate with, but is not *per se* an important determinant of, SUD.

WEIGHT INCREMENT This is a simple, retrospectively obtainable scalar measure of thriving. Drillien's (1964) work shows parallel population weight increment curves over the first year of life for each sex and all birthweights: thus Table X validly compares weight increment of pooled SUD singletons with standard population series (Tanner, 1958; Watson and Lowrey, 1967). (The necropsy weight of each case is 'corrected' to an estimate at exactly 1, 2, . . . months, whichever is nearest, on the basis of Stuart and Meredith's tables (Watson and Lowrey, 1967) and intra-month linear assumption). The weight increment curve for SUD lies always between the 10th and 50th population percentiles and, allowing for small-number instability, at a probably constant relationship to both (Table X, col. 6).

*Social parity is here used as a convenient term to describe a measure of claims on family resources. It is: number of previous surviving live births + 1.

TABLE IX

MEAN BIRTHWEIGHT OF SINGLETONS BY SEX AND 'SOCIAL PARITY', NORTHERN IRELAND SUD CASES AND THEIR MATCHED CONTROLS

Group (and No. of Singletons)	Mean Birthweight (lb) ± (S.E.)					
	Social Parity 1 and 2		Social Parity 3 and 4		Social Parity 5+	
	M	F	M*	F	M†	F
SUD cases (135)	6·84 (0·16)	7·08 (0·20)	7·06 (0·17)	7·08 (0·21)	7·11 (0·34)	6·91 (0·39)
Matched controls (135)	7·23 (0·20)	7·11 (0·19)	8·19 (0·22)	7·49 (0·24)	8·24 (0·37)	7·09 (0·28)

*Difference in means = 1·13 ($t = 3{\cdot}96$, D.F. = 55, $P < 0{\cdot}001$)
†Difference in means = 1·13 ($t = 2{\cdot}15$, D.F. = 29, $0{\cdot}05 > P > 0{\cdot}01$

TABLE X

MEAN AGE-SPECIFIC WEIGHTS (lb) AT NECROPSY OF SUD SINGLETONS AND THOSE OF POPULATION SAMPLES OF LIVING INFANTS

Age (mths) (1)	SUD Cases		Population Series*		(5)–(3) / (5)–(4)
	No. (2)	Mean (3)	10th Percentile (4)	50th Percentile (5)	(6)
Birth	129†	7·02	6·21	7·52	—
1	20	8·60	7·87	9·45	0·54
2	31	9·63	9·36	11·04	0·84
3	26	11·11	10·61	12·27	0·70
4	18	12·85	11·90	13·76	0·50
5	9	13·84	13·32	15·06	0·70
6	8	14·98	14·33	16·40	0·69
7	4	16·78	15·31	17·61	0·36
8 and 9	5	17·14	16·70	19·18	0·82
10–12	7	18·13	18·25	21·14	1·04
14	1	23·00	19·00	22·25	—

*Unweighted average of series of Tanner (1958) and Stuart and Meredith (Watson and Lowrey, 1967)
†135 singletons minus 6 with inadequate necropsy data

For twins, mean weight gain of cases is 1·39 lb (0·61 kg) per month, which compares with Drillien's (1964, Appendix IIa) 'healthy twin' estimates of 1·66 lb (0·71 kg) per month from birth to 6 months and 1·27 lb (0·56 kg) per month from birth to 12 months. These results suggest normal postnatal thriving of SUD cases.

POSTNATAL HEALTH Arbitrarily dividing the period between birth and death (of an SUD case) or interview (of a control) into (1) from birth to one week before death (or interview), which may be relevant to the child's underlying fitness, and (2) the week preceding death (or interview), which may be relevant to the terminal event, and dealing exclusively with illnesses for which medical attention was sought, we obtain the following experience for 148 cases and their matched controls.

During period (1), and omitting twins and premature baby unit admissions, 25 cases and 19 controls were admitted to hospital at least once. The principal cause of the most recent admission was: pneumonia, bronchitis, and other pulmonary conditions (10 cases, 8 controls); failure to thrive (5 cases, 0 controls): rhesus incompatibility (2 cases, 2 controls); gastrointestinal conditions (4 cases, 4 controls); and others (4 cases, 5 controls). For other medical consultations and omitting twins, two cases with infantile eczema, and the episodes leading to hospitalization as above, 62 (46·6%) of the remaining SUD cases had at least one episode of illness compared to 57 (38·8%) controls. The episode rate (episodes per person sick) was approximately 1·3 for cases and 1·4 for controls, and 'upper respiratory infections' accounted for the majority (70% among cases, 60% among controls). There were no unusual diagnoses. These findings confirm the weight increment results (Table X) indicating basic fitness.

During period (2), seven SUD cases were discharged from hospital after treatment for pneumonia (3 cases), otitis media (1 case), and negative investigation of failure to thrive, breathless episodes, and intermittent vomiting (1 case each). None was admitted other than the six *in extremis* and who died, and no controls were in hospital during the period. In addition, a doctor was consulted or was sought for 30 other SUD cases (other than those *in extremis*) compared to 15 controls ($\chi^2 = 5{\cdot}61$, D.F. = 1, $P < 0{\cdot}05$), the cause being respiratory infection (17 cases, 12 controls), gastrointestinal conditions (10 cases, 3 controls), and general pyrexia, listlessness, and convulsions (1 case each). Furthermore, an additional 42 SUD cases had been allegedly 'unwell' (mostly minor coryzal or digestive symptoms)—though medical advice was not sought—during this period compared to zero controls. Assuming less than the grossest recall bias in this latter class, the picture is very definitely of increased minor illness during the week, particularly the 24 hours, before death. This confirms the findings of some authors (Ministry of Health, 1965; Vaughan, 1968) but not of others (Steele, 1970); but the literature is unreliable since surveys seldom include interviews or appropriate control data.

FEEDING AND MEDICAMENTS For the last decade hypersensitivity to cow's milk proteins has been a popular hypothesis in SUD causation even though some results have been equivocal and characteristic SUD cases, exclusively breast-fed, have been documented (Parish, Barrett, and Coombs, 1960a; Valdés-Dapena, 1967, 1970; Bergman, 1970; Houstek, 1970). SUD cases have often seemingly differed from controls in feeding regimens (Ministry of Health 1965; Valdés-Dapena, 1967), and breast feeding, especially during the first two weeks (to avoid sensitization), has been strongly advocated (Ministry of Health, 1965).

In the present study 18 SUD cases were wholly breast-fed for at least one week, 8 were partially breast-fed from birth, and 121 were never breast-fed. Corresponding frequencies for matched controls were 22, 6, and 119 ($\chi^2 = 0{\cdot}70$, D.F. = 2, $0{\cdot}98 > P > 0{\cdot}95$). One further case and control had been wholly breast-fed for five and three days respectively. Two of the 18 cases above were exclusively breast-fed throughout life, and among the remaining 16 the time interval between the first introduction of other types of feeding and death ranged widely (1–38 weeks; mean = 11·1; median = 7). The strengths and formulae of feeds were not markedly dissimilar for cases and controls, and in only five instances did the last feed contain a previously untried substance, *viz.*, Lucozade, glucose, Ostermilk 2, Farex, and a cereal. Furthermore, there were no detectable milk antibodies (using the coated tanned red cell haemagglutination technique) in 70 of 95 cases tested, titres up to 64—which can occur in healthy infants—in 18, a titre of 128 in four, and of 256+ in three: these are similar to findings among a group of children dying from 'explained' causes (Marshall, 1970). Two infants died suddenly while being fed and one child was found dead 30 minutes after taking a normal feed. No other case was known to die or collapse within one hour of feeding. These findings are not conclusive but they do not seemingly indicate an important numerical role in SUD for hypersensitivity to cow's milk protein.

Most infants are given medicines at some time. Among the SUD cases 10·8% allegedly received none, 46·6% allegedly received only household medicaments—aspirin, gripe water, nose drops, teething powder, etc.—while 42·6% received other drugs, usually antibiotics. Corresponding frequencies for matched controls—10·1%, 53·4%, and 36·5%—are not significantly dissimilar to these ($\chi^2 = 1{\cdot}40$, D.F. = 2, $0{\cdot}50 > P > 0{\cdot}30$).

TERMINAL FINDINGS Necropsy findings, including the position of the deceased when found and his relation to bedding and pillows, and such biological data as blood groups, immunoglobulin and blood urea levels, urinary chromatogram patterns, and virus and bacteria isolations, are described elsewhere (Froggatt, 1970a, b; Froggatt *et al.*, 1971). We consider the findings generally unimportant to elucidating the causation of SUD.

EVIDENCE OF HEREDITY

PARENTAL CONSANGUINITY No pair admitted kinship: the expected random figure in Northern Ireland would be about 1% (Kilpatrick, Mathers, and Stevenson, 1955). Ignorance or wilful denial of blood relationship with the spouse has not been a feature of surveys in Northern Ireland into non-fatal (Froggatt, 1960) or even serious (Fraser, Froggatt, and James, 1964) conditions.

FETAL LOSS Mothers' statements indicated no important difference between SUD cases and matched controls.

AGGREGATION OF CASES IN SIBSHIPS Sibships with two SUD singleton members have occasionally been documented (Porter, 1966; Valdés-Dapena, 1967; Vaughan, 1968; Houstek, 1970). (The six sibs originally reported as SUD by Valdés-Dapena (1967) died of other causes (Valdés-Dapena, 1970)). Omitting the twin-set with both partners SUD, the present study yields a minimum of four sibships with two, and a maximum of six sibships with two and one with three, SUD members, and probably only one sibship with an SUD singleton sib of a control group infant (Table XI). These give case rates per 1,000 live births of 11·1–22·1 among sibs of propositi compared to 2·3 for the control group sibships and 3·0 population incidence. (The rate for twins—11 surviving and one SUD partner of 12 SUD propositi—is probably not exceptional in view of their lower mean birthweight (5·1 lb; 2·3 kg)). This aggregation is insufficient for any coherent Mendelian interpretation; it may simply reflect the anticipated within-family association of weak 'risk' factors or perhaps indicate different aetiological mechanisms in some few families, e.g., those containing the sisters M.M.H., G.M.H., and that containing T.G.M. (see Table XI), where recurrent cyanotic attacks were a feature.

CONGENITAL AND FAMILIAL DISEASE IN PARENTS AND SIBS One (female) SUD case had three maternal uncles with Duchenne-type muscular dystrophy, the mothers of two others have respectively dystrophia myotonica and idiopathic epilepsy, the father of another had a cerebral aneurysm, and, among the 360 surviving sibs of cases, two (brother and sister) are low-grade mental defectives, three have 'fits', two have structural heart lesions, and there are single cases of asthma, spina bifida, and severe milk allergy. These are considered unremarkable survey findings.

SEX CHROMATIN Buccal smears showed the sex chromatin content always to be normal and consistent with the phenotypic sex. Karyotyping was not done: recent work (Weinberg and Purdy, 1970), however, suggests that some karyograms may be abnormal (deletions, telemeric associations, chromatid breaks) though the significance is not clear.

SPACE-TIME CLUSTERING

We have shown that SUD cases are commonest in Belfast in the colder months and that in the two 'winters' (November to April 1965–6 and 1966–7) cases seemed randomly distributed in time (Table IV). We now examine, by the 'sum of empiric clusters' method of Ederer, Myers, and Mantel (1964) and the 'points-on-a-plane' approach of David and Barton (1966), whether cases clustered in space and time when taken together. Only Knox, using his 2 × 2 contingency table approach (Knox, 1963) on 32 cases from Cameron and Asher's (1965) series, has previously sought such epidemicity in SUD, but he was unable to detect significant space-time clustering (Knox, 1970, unpublished data).

METHOD OF EDERER *et al.* (1964) Table XII summarizes the results obtained for three years' data (1 August 1965 to 31 July 1968) on the method of Ederer *et al.* (1964), as described and applied (to multiple sclerosis) by Ashitey and MacKenzie (1970). The areas used were the six counties and two county boroughs, and the time-units were calendar years in order to avoid distortion by the known seasonal variation in SUD. In none of the eight areas is there an important difference between observed and expected yearly maxima, and on the value of the test statistic ($\chi^2 = 0{\cdot}45$, D.F. $= 1, 0{\cdot}70 > P > 0{\cdot}50$) the null hypothesis of randomness (as measured by the test) cannot be rejected.

METHOD OF DAVID AND BARTON (1966) This treats the space co-ordinates as a randomization set and postulates that all possible allocations of a given time-space point are equally likely. The test criterion (Q) is the ratio of the average squared distance between space points within time-clusters to the overall average. This method requires *a priori* the definition only of the time-units—a considerable advantage when, as in SUD, choice of units must be arbitrary because of the unknown aetiology. In fact several time-units can be selected, and this further reduces the chance of obtaining a fortuitous result.

We decided to examine 'city' and 'country' groups separately as well as the combined data. (The five presumptive cases from 'approved pathologists' are now included, making 167 in all.) These groups comprised cases in (*a*) greater Belfast, i.e., the area embraced by the municipal boundary or postal district, whichever was wider (84 cases), and (*b*) the rest of Northern Ireland, though excluding the nine from Londonderry C.B. (74 cases). For the former group the space co-ordinates were those of the address where death occurred as plotted exactly on a 1 inch = 0·2 mile street map; for the latter, corresponding co-ordinates were plotted on the 1 inch =

TABLE XI

DETAILS OF SIBS, OF SUD AND CONTROL GROUP SINGLETON PROPOSITI, WHO DIED SUDDENLY AND UNEXPECTEDLY AGED 4–51 WEEKS

Reference (and Sex)	Age at Death (mth)	Clinical Information	Certified Cause of Death	Necropsy	Necropsy Findings	Likely Diagnosis from Available Data
Sibs of SUD propositi:						
M.M.H. (F) } Sisters	4	Found dead in cot. Well when last seen. One previous cyanotic attack noticed.	Interstitial pneumonia	Yes	Consistent with SUD	SUD
G.M.H. (F) }	4	Found dead in cot. Well when last seen. Several previous cyanotic attacks. Thorough hospital investigation—N.A.D.	Pneumonia and cerebral gliosis	Yes	Consistent with SUD	Probably SUD
R.H. (M)	3	Found dead in bed shared with two other children. Well when last seen.	Interstitial bronchopneumonia	Yes	Consistent with SUD	SUD
A.W. (M)	2	Found dead in cot. Well when last seen.	Virus pneumonia	No	—	SUD
C.E.McC. (F)	3	Collapsed and taken to hospital. Resuscitation unsuccessful. Well since birth	Bronchopneumonia	No	—	Possibly SUD
T.G.M. (M)*	1	Found dead in cot. Slight cold previous day.	Bronchopneumonia	Yes	Consistent with SUD	SUD
M.M. (F)	4	Died suddenly while taking bottle feed.	Statement 'choked on bottle'	Yes	Not available	Possibly SUD
M.P.R. (F)	3	Found collapsed. Died 4 hours later in hospital.	Pneumonia	Yes	Consistent with SUD	Possibly SUD
Sibs of control propositi:						
P.J.H. (M)	4	Found dead in cot. Healthy since birth.	Bronchopneumonia	Yes	Consistent with SUD	SUD
R.M.P.C. (M)	1	Found dead in cot. Healthy since birth.	Virus pneumonia and sagittal sinus thrombosis	Yes	Not consistent with SUD†	Not SUD
E.C.O'R. (F)	5	Found dead in cot. Rubber undersheet stuck to and occluding mouth and nose.	Suffocation	Yes	Consistent with SUD	Not SUD

*One other brother found in bed aged 16 months during cyanotic attack. Resuscitation by father by mouth-to-mouth breathing
†The sagittal sinus thrombosis would have excluded this case from our study

one mile Ordnance Survey map (3rd series, 1967) using Irish grid kilometre square references and to the nearest 0·2 km. The time reference point was the date of the presumptive or estimated (as described above) day of death.

Summarized results are given in Table XIII. Assuming Q to be approximately normally distributed, the statistic d may be referred to the normal probability scale. In all instances and for all time-units, $+2{\cdot}0 > d > -2{\cdot}0$ (specifically $d > -2{\cdot}0$) and the null hypothesis of no clustering cannot therefore be rejected in any group on any time-unit criterion. If clustering (or 'contagion') exists, there is no evidence of it from this test which is in fact quite powerful (Barton *et al.*, 1967) and can readily demonstrate clustering of such infective diseases as measles and poliomyelitis (Barton, David, and Merrington, 1965) as well as of some which may have only an infective component, e.g., Burkitt's tumour (Pike, Williams, and Wright, 1967).

Discussion

The results provide an epidemiological and clinical profile of SUD. They have, however, only limited value in assessing the relative merits of the current theories of causation, and then only in the general case. Specific hypotheses must be tested by more appropriate disciplines: to provide relevant epidemiological data would require formidable planned enquiries necessarily beyond the scope of this study. Nevertheless, we can adduce some evidence on the coherence of certain general theories of SUD production.

Though strict proof is lacking, we can confirm the consensus view (Bergman *et al.*, 1970) that SUD victims do not have some underlying 'disease' as yet unrecognized: the unrevealing special necropsies, the lack of evidence for the segregation of abnormal genes, the satisfactory thriving and absence of significant clinical findings (other than terminally), and the narrow age range all argue against 'disease'

TABLE XII

SPACE-TIME CLUSTERING OF SUD CASES: RESULTS OF METHOD OF EDERER *et al.* (1964) ON THREE-YEAR DATA (1 AUGUST 1965 TO 31 JULY 1968)

Area	No. of Cases (1)	Maximum No. of Cases		Variance of Estimate in Col. 3 (4)
		Observed in any Year (2)	Expected in any Year (3)	
County Borough:				
Belfast	99	42	37·98	8·73
Londonderry	11	5	5·34	1·08
County:				
Antrim	41	15	16·87	3·53
Armagh	16	6	7·31	1·30
Down	34	12	14·29	3·12
Fermanagh	3	1	1·89	0·32
Londonderry	11	6	5·34	1·08
Tyrone	14	5	6·52	1·28
Total	229	92	95·54	20·44

$$\text{Test statistic } (\chi^2) = \frac{(\,|\,92-95{\cdot}54\,|\,-0{\cdot}5)^2}{20{\cdot}44}$$

$$= 0{\cdot}45, \text{ D.F.} = 1, \; 0{\cdot}70 > P > 0{\cdot}50$$

TABLE XIII

SPACE-TIME CLUSTERING OF SUD CASES: RESULTS OF METHOD OF DAVID AND BARTON (1966) ON TWO-YEAR DATA (1 AUGUST 1965 TO 31 JULY 1967)

Interval between Time Clusters (days)	No. of Clusters			Q			$d\dagger = (Q-1)/\sqrt{\text{var } Q}$		
	A*	B*	C*	A	B	C	A	B	C
3	45	51	59	0·94	0·87	0·92	−0·48	−0·79	−1·13
6	36	36	31	0·91	0·84	1·00	−0·91	−1·46	0·01
9	24	26	17	0·88	0·88	0·98	−1·73	−1·48	−0·74
12	19	17	12	0·93	0·97	0·98	−1·25	−0·53	−0·69
15	16	14	7	0·91	0·96	0·99	−1·70	−0·82	−0·79
18	12	13	2	0·93	0·97	0·99	−1·59	−0·69	−1·07
30	4	4	1	1·03	0·95	—	1·44	−1·95	—

*A = Greater Belfast (84 cases); B = rest of Northern Ireland omitting Londonderry County Borough (74 cases), C = combined group A + B (158 cases)

†When (approximately) $+2{\cdot}0 > d > -2{\cdot}0$, as in every instance here, the corresponding value of Q does not differ significantly from its expected value (= 1·0) on the assumption of randomness

in the ordinary sense. Cases appear in fact to be essentially 'normal' infants, and the social and biological characteristics so far examined and which (on average) distinguish them from random samples drawn from the same age-specific population, i.e., characteristics of the 'at risk' child, can be shown to have poor predictive power (Froggatt, 1970a). The characteristic age range is the most important factor, and there seems little doubt that these infants die because, while passing through this period of increased physiological vulnerability, some critical combination of intrinsic and extrinsic factors proves lethal: what *is* in doubt is the mechanism, or 'final common pathway', of death, and here epidemiology can play only a minor role.

Any orthodox interpretation of our results must ascribe some role to infection, mainly respiratory infection. The greatest incidence is in Belfast among the lowest socio-economic groups and the most crowded houses, in the coldest months, with serial correlation between SUD frequency and documented major virus epidemics, and with 'season'/'city' contingency—cases in Belfast in the winter being disproportionately prevalent; a history of minor symptoms, usually coryzal or respiratory, in the week and notably the 48 hours before death is common; there is increasing relative incidence with increasing parity, at least in mothers under 30 years of age; the clinical picture is of seeming respiratory infection in those few cases seen *in extremis* by a doctor; when both twin partners are SUD, death is simultaneous;* and the necropsy findings, though conventionally accepted as 'normal', usually show in common with other studies (Valdés-Dapena, 1967; Beckwith, 1970) some alveolar neutrophils and lymphocytic infiltration of peribronchial tissue and throughout the lung interstices (Marshall, 1970). Furthermore, virus and bacteria isolations, unremarkable in our study (Marshall, 1970; Froggatt, 1970b), have been considered relevant in others (see Bergman *et al.*, 1970). As against this is the failure to demonstrate space-time clustering—though available tests will not invariably detect epidemicity especially if, as seems likely, there be several partly independent infective agents (Ray *et al.*, 1970)—and the fact that some of the above findings could be expected on other hypotheses, e.g., minor coryzal symptoms are not unusual premonitory findings in milk allergy (Goldman *et al.*, 1963), and the terminal symptoms in those few cases admitted to hospital *in extremis* are not unlike those which have occurred in cases of documented cow's milk allergy (Bower, Stanley-Roose, and Wolff, 1958).

The precise role played by any such infection is more equivocal. It may be primary, *viz.*, in overwhelming the infant during an innate vulnerable immunological state, in sensitizing (by a first challenge) then overwhelming (in a second challenge) the now sensitized child, in inducing lethal pulmonary reflexes or occlusive laryngospasm, or by other mechanisms (Valdés-Dapena, 1967; Froggatt *et al.*, 1968; Dawes, 1968; Bergman *et al.*, 1970; Ray *et al.*, 1970); or it may be secondary, increasing the child's susceptibility to some other, perhaps unrelated, lethal process or making such a process itself more likely (James, 1968). Whatever the mechanism, even quite trivial respiratory infections may seemingly trigger SUD in a child aged 1 to 6 months.

Sleep seems also to be an important component. There is no certainty that an unobserved infant is asleep at any particular time, but the characteristic distribution of cases over the 24 hours—unless time of day is itself a factor in SUD—and the rarity of the terminal event while the child is being handled are supportive findings. This does not help towards establishing the 'final common pathway' of death: bodily changes during sleep are theorized to increase the likelihood of SUD by, specifically, laryngospasm (Bergman *et al.*, 1970, p. 210), cardiac conduction disturbance (James, 1968), respiratory centre failure (Guntheroth, 1970), and lethal cardiopulmonary reflexes (Steinschneider, 1970).

The age distribution (Table II) is characteristic: any viable hypothesis of causation must explain it. It is the main cornerstone of the concept of developmental physiological vulnerability in SUD, and the many relevant mechanisms in the dynamics of normal development—anatomical, autonomic, immunological, physiological—by which an infant in this age range could be vulnerable have been extensively reviewed (Wedgwood and Benditt, 1965; Valdés-Dapena, 1967; Froggatt *et al.*, 1968; Dawes, 1968; James, 1968; Bergman *et al.*, 1970). This general concept receives support from the case histories and family data. One aspect should be emphasized: the occasional history of previous 'fainting', cyanotic or apnoeic episodes, or periodic breathing, perhaps especially in multi-case sibships (Table XI). Such a history could be reliably elicited in several of our cases (only twice did it lead to hospital investigation —which was negative) and has also been documented by, for example, Stevens (1965) in the terminal episodes in four cases, and by Steele (Bergman *et al.*, 1970, p. 74) in the routine histories of several. It may

*Even allowing obvious ascertainment bias against twin partners who died as SUD cases but not coevally, the more or less simultaneous death is striking. This is not paralleled by non-related like-aged infants in institutions (Geertinger, 1968). Infection is an obvious possibility, especially if heredity or common uterine environment be a predisposing factor.

be even more common than retrospective enquiry reveals since such episodes may easily go unnoticed (or unrecorded) in the very young infant. Episodes of this type occur in infants generally and for variously interpreted causes (James, 1968; Steinschneider, 1970; Guntheroth, 1970); if they are more common in SUD victims than in others, then, whatever their cause or frequency, they should be considered a more sinister symptom than at present and, furthermore, investigation of the child may be informative. They may, on the other hand, indicate causal heterogeneity (Froggatt *et al.*, 1971): if so, the mechanism of SUD in such infants may be different from that in others. The study of these and other conditions with death simulating SUD may provide information on possible terminal mechanisms.

Undoubtedly the outstanding problem is to identify the 'final common pathway' of death, which has so far proved elusive; a subsidiary and related one is to distinguish sub-types in the entity (or entities) SUD. Meanwhile SUD will remain a disease of theories with investigators continuing to favour explanations in their own speciality, and unfortunately tests, which may, for example, discriminate 'pulmonary' from 'cardiac' death, e.g., terminal blood-gas composition (Mithoefer *et al.*, 1967), seem not to be unequivocal in interpretation (Bergman *et al.*, 1970, pp. 130–2). Epidemiological studies would not normally help in this elucidation: the answer must ultimately come from experimental and basic scientists though perhaps aided by planned field studies.

In the present state of knowledge case reduction would seem to depend upon a general realization of the vulnerability of the infant between, say, 1 and 5 months—especially if he be an underweight twin or a child with respiratory symptoms—and the possibility that the crucial episode, whatever its mechanism, is not irreversible and that a proportion of infants could be saved by cardiopulmonary resuscitation. Such resuscitation methods may not need to be by machine; simple handling and first-aid techniques may arrest or reverse the process long enough to allow emergency hospital admission. Prevention of known environmental trigger mechanisms, e.g., respiratory infection, would have only a slight effect, but round-the-clock surveillance (or monitoring) of *all* infants would certainly reduce case incidence and could elucidate causation; in view of the infrequency of SUD and the weak predictive power of the currently recognized 'risk' factors (Froggatt, 1970a), anything short of this would have a numerically small effect. Such a procedure is impracticable, but further studies may disclose factors which would allow surer identification of 'at risk' children and so make such a surveillance scheme feasible. Anyone working for a reduction in the incidence of SUD must hope that this will prove to be the case.

Summary

One hundred and sixty-two cases of 'cot death' (SUD) were ascertained by special methods in Northern Ireland from 1 August 1965 to 31 July 1967. The families of 148, and of 148 matched controls, were interviewed. The main findings are:

(1) an incidence of 2·5 to 3·0 per 1,000 live births with a male excess in Belfast;

(2) a male predominance of cases but no greater than for infant mortality generally;

(3) a characteristic age distribution, 75% of cases being aged 4 to 25 weeks and less than 1% over 1 year;

(4) a marked seasonal distribution, cases being commonest in the winter months and serially correlated with influenza (A_2 and B) cases;

(5) an excess of cases in twins, in families at socio-economic disadvantage, in crowded dwellings, among younger mothers in higher parities, and, possibly, in premature infants;

(6) an increase in minor illness in the week before death but no unusual experience of other morbidity, feeding or medicaments in the child, or of maternal health or obstetric factors during pregnancy;

(7) some five times the population and control group SUD incidence among sibs of propositi but no evidence for postulating specific inheritance mechanisms; and

(8) an absence of epidemicity as measured by temporal and space-time clustering methods.

Discussion concentrates on examining how these, and some other findings, accord with and elucidate the major current hypothesis of causation and how a reduction in case incidence may be attained. It is concluded that the age range represents a period of enhanced physiological vulnerability in which some critical combination of extrinsic (e.g., infection and sleep) and intrinsic (not yet unequivocally identified) factors can prove lethal.

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