SUDDEN UNEXPECTED DEATH IN INFANTS ('COT DEATH') REPORT OF A COLLABORATIVE STUDY IN NORTHERN IRELAND*

by

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INFANTS HAVE always been known to die suddenly and unexpectedly in bed, their deaths being formerly ascribed to 'mechanical suffocation' by clothing or by 'overlaying' – of which there are presumptive examples from early literature (I Kings, 3:19). Early investigators (e.g. Templeman, 1892) stressed this danger and in Ireland the powerful temperance lobby obtained a clause (sect. 13) in the 1908 Children's Act under which an adult, if 'at the time of going to bed [be] under the influence of drink', could be prosecuted for 'overlaying' a child. Current views are different: sudden unexpected death in infants ('cot death') is now considered to be a clinical syndrome and the majority of cases are thought to have an identical – though as yet unidentified – 'final common pathway' of death. Victims, essentially healthy throughout life, die seemingly because during a developmental stage of physiological vulnerability some combination of intrinsic and extrinsic factors proves fatal. Among the many hypotheses advanced those postulating (i) asphyxia from laryngospasm or nasal obstruction, (ii) cardiac conduction disturbance, and (iii) some hypersensitivity or aberrant immunological reaction, are currently tenable.

Little was know about 'cot death' when we initially planned this study; in fact the report of the 'First Conference on Sudden Death in Infants' (Wedgwood and Benditt, 1965), which first brought together pertinent findings from diverse disciplines, was not then published. Accordingly, we aimed for breadth of knowledge through wide fact-finding; we neither specifically tested formulated hypotheses nor restricted our enquiry to a detailed study in any one discipline. Furthermore, because of the general dearth of data on this condition we described our results piecemeal as they became available (Froggatt, Lynas and Marshall, 1968; Froggatt, 1970a, b; Marshall, 1970; Froggatt, Lynas and MacKenzie, 1971). Some of the findings, however, have not yet been reported; documenting these, and presenting a coherent synopsis of our study are the purposes of the present paper.

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*Members of the working party were Dr. T. K. Marshall (chairman), Professors I. J. Carré, K. B. Fraser and P. Froggatt, and Drs. W. Bamber, D. J. L. Carson, Margaret Lynas, J. A. McLaughlin and A. L. Walby. We thank our colleagues for their confidence in entrusting us with the description of this study.

To minimise citation of the now extensive literature we reference specific work only when essential or when not covered in recent thorough reviews (Valdés-Dapena, 1967; Froggatt *et al.*, 1968; Bergman, Beckwith and Ray, 1970; and Froggatt *et al.*, 1971). For brevity these four publications are not always cited when they are the source for unreferenced facts. 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 per cent of repeated trials. χ^2 is everywhere calculated on absolute numbers and, where appropriate, corrected for continuity.

Many terms and acronyms describe this condition: 'sudden unexplained death in infancy' (SUD), 'sudden unexpected infant death' (SUID), 'sudden unexpected, unexplained death in infants' (SUUD), and 'sudden infant death syndrome' (SIDS) – and their variants – are all used and in practice are synonymous with the colloquial 'cot death' ('crib death' in U.S.A.). In this article we use for convenience the acronym SUD.

Ascertainment

Selection of Cases

Ascertainment was through the Northern Ireland Forensic Pathology Service (NIFPS) – a government service run exclusively for the use of the country's 16 coroners – and covered the two years 1st August 1965 to 31st July 1967. Strictly, SUD infants would be coroners' cases under law (Coroners Act, 1959), but to maximise ascertainment we apprised general practitioners and the Northern Ireland General Health Services Board and one of us (T.K.M.), as State Pathologist, asked the coroners to demand an autopsy on young children as a routine. As a result, 297 children aged under five years were autopsied by one of five similarly-trained forensic pathologists in the NIFPS to a standard routine.

Since there are no recognisable positive autopsy criteria of SUD we reached our study group by exclusion. From the 297 children we excluded 78 who died from unnatural causes, e.g. violence and drowning; 29 in which there was an adequate natural cause for death other than respiratory inflammation (which some consider to be the cause of SUD), e.g. peritonitis; 21 in which respiratory inflammation co-existed with other lesions, e.g., mongolism, renal vein thrombosis, and congenital heart disease, which were considered adequate to explain death; and five which were difficult to appropriately allocate because of administrative problems. All but two of the remaining 164 children were in the 'conventional' age group 2–103 weeks (respectively four days and 144 weeks), and these were excluded leaving 162 'unexplained' cases for study. These are termed below 'index cases'. Interviews were conducted by one of us (M.A.L.) with the families (nearly always the mother) of 148 (91.4 per cent) of these index cases: of the 14 failures, eight families refused, two were untraced, three had left the country, and one case was *sub judice*.

Selection of Controls

There is no satisfactory control group for SUD. Accordingly two (Groups A and B) were selected each to serve in the analyses where appropriate. Group A comprised the (chronologically) next like-sexed birth (identified from birth notifications) in the same administrative area or sub-area division as that of each of the 148 index cases whose families were interviewed. Matching was therefore by

sex, county or county borough of domicile – or (in two counties) sub-area division – and date of birth. Only two second-choice controls were necessary. No family declined interview. Group B comprised the 42 infants, aged 2–103 weeks, from among the 107 (78+29) children under five years, mentioned above, whose death was unnatural or due to certain natural causes. A third control group was selected for some multivariate analyses the results of which are described elsewhere (Froggatt, 1970a).

Completeness and Bias

The nature of SUD precludes an accurate assessment of the completeness of the ascertainment, but we can reach a working estimate as follows. The records of children of Belfast-resident mothers dying in Belfast C.B. aged under one year yielded, for the study period, 91 infants aged 2–51 weeks with principal and, when documented, also contributory certified cause of death 'pneumonia' or associated conditions *viz.* ICD (Seventh Revision) categories 470–475, 480–483, 490–493, 500–502, 525 and E921. Because the NIFPS certify SUD in one or other of these categories, these cases should contain the Belfast index cases. Of these 91 infants, 13 had died in hospital with clinical bronchopneumonia (confirmed in eight at autopsy) and five had died (none autopsied) either at home, in the admission ward, or in transit to hospital in each case being under treatment for at least 12 hours for respiratory symptoms, often severe. None of these 18 was considered as notifiable to the coroner. We found that the remaining 73 comprised 72 of our index cases and one other infant death reported to the coroner on which an autopsy had been carried out by a pathologist not in the NIFPS. No child who died suddenly and unexpectedly for an 'unexplained' cause was missed and our Belfast ascertainment is therefore some 94–100 per cent 'complete' depending on whether only 13, or all 18, of the non-notified 'bronchopneumonias' above be accepted as 'explained'. Similar information is not available outside Belfast: but from the NIFPS figures (90 SUD outside Belfast) and the numbers of registered death 4–51 weeks in the Registrar General's tabulations under the above ICD categories (98 in Belfast C.B.; 151 in other areas), and accepting the Belfast ascertainment as 94 per cent complete, we can, *certeris paribus*, estimate the ascertainment outside Belfast as at least 83 per cent complete $\left(\frac{94 \times 98 \times 100}{151 \quad 73}\right)$ with an overall figure of, say, 85–90 per cent for Northern Ireland.

With this high level of 'completeness' important bias would be introduced only by the mechanism of ascertainment and the criteria themselves. The following are the most pertinent.

(a) Due to the selection criteria – whereby respiratory inflammation as a sole finding was not a criterion of exclusion – index cases are biased towards displaying pathology of the respiratory as compared to other systems. The respiratory inflammation was, however, slight (see below) and in only some 10 per cent would death have been considered 'explained' or 'possibly explained' in the terminology of Beckwith's (1970) rigorous criteria.

(b) Some index cases were ill for (usually short) periods pre-mortem yet their deaths were 'unexplained' at autopsy. These could have been excluded on the strict interpretation of the term 'unexpected' in SUD, but in fact few investigators exclude

such cases since they judge them as sufficiently 'sudden' and 'unexpected'. Bias and over-ascertainment should therefore be small.

(c) Some children who were excluded because of autopsy findings considered adequate to 'explain' death, may have actually been SUD cases. This bias operates in all surveys and leads to universal under-ascertainment of an unknown degree.

(d) Ascertainment through the NIFPS could bias selection against neonates. An autopsy on a neonate dying 'unexpectedly' in a maternity hospital would be carried out by a *hospital* pathologist. In addition the death of a neonate at home would be less likely to be reported to the coroner – death in a neonate being more common and less remarkable than in an older child. On the other hand, neonatal deaths are generally unlike SUD, and autopsies usually show presumptive non-SUD conventional causes of death. We consider, therefore, that missed cases should be few.

Materials and Methods

We contacted the families of the bereaved and control group A children through local health authority staff. The interviews, timed optimally for two weeks after the death, were conducted by one of us (M.A.L.) to a set scheme. Information, recorded on a standard schedule using mostly pre-coded responses, specified (index cases and controls are collectively designated 'subjects'): essential ante-natal, birth, and medical data on subjects and their sibs and the medical data 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 cases; sleeping and feeding routine of subjects; state of housing, maternal care, and indices of domestic crowding; and electro-cardiograms (bipolar limb leads) of parents of index cases. A two-month pilot study preceded the main survey, cases ascertained being later discarded.

Only those results not previously documented, pertinent to the more plausible hypotheses of causation, or which are essential to coherently define the entity SUD are presented here: other findings are detailed elsewhere (Froggatt *et al.*, 1968; Froggatt 1970a, b; Marshall, 1970; Froggatt *et al.*, 1971).

Autopsy Results

Gross pathology

Most of the 162 infants seemed well-nourished (see later). A nappy rash, rarely severe or extensive, was found in 47 (29 per cent). None had any internal injury and only seven (4.3 per cent) bore external marks of trauma and these were always trivial. Hypostasis was unremarkable and it was rare to find any contact pallor over the nose and mouth such as could have indicated occlusion by pressure on the pillow or mattress.

The deaths of 35 infants (21.6 per cent) were associated with some escape of fluid from the nose or mouth and fluid of one kind or another – watery, mucus-like blood-tinged froth, milk curds – generally in very small amounts was also found in the trachea of 112 cases (69 per cent). Sometimes the fluid came from oedematous lungs; sometimes it had been regurgitated. However, there was no indication that

fluid from the stomach played a role in causing death; and microscopy neither revealed aspirated foreign material in the medium sized bronchi nor areas of aspiration autolysis. It probably entered the air passages in the agonal period or even post-mortem.

Petechial haemorrhages were present on the thymus, heart and lungs, in 48 cases (30 per cent); in 29 (18 per cent) they were on two of these organs and in 33 (20 per cent) on only one, most commonly the lungs (17 cases). This frequency (110 of 162 cases) is significantly greater than that of group B controls (12 of 42 cases) – $\chi^2=21.46$, d.f.$=1$, $P<0.001$ – confirming the experience of notably Beckwith (1970). These petechiae were more common in cases found unequivocably dead (83 of 109) than in those allegedly seen to die or 'collapse' (20 of 39) – $\chi^2=7.26$, d.f.$=1$, $P<0.01$ – but they are unrelated both to age at death and whether or not the subject had symptoms or was allegedly perfectly well during the week before death. Their role in SUD is discussed later.

Microscopic findings

The main changes concern the respiratory apparatus, the typical appearance of which is briefly described, more details being in Marshall (1970).

The submucosa of the trachea and main bronchi were often infiltrated by lymphocytes and plasma cells but neutrophils were uncommon. Peribronchiolar mononuclear cells were present, sometimes amounting to 'cuffing'. This picture, however, is often seen in infants who die from injuries or carbon monoxide poisoning and so it was considered unspecific as was also the 'fibrinoid necrosis' of the vocal cords carefully studied by Pinkham and Beckwith (1970).

The lung parenchyma showed a variable degree of patchy oedema and areas of alveolar collapse often affecting only a few alveoli in each locus and in such a way that what on cursory examination seemed normally aerated tissue really consisted of strands of collapsed tissue interspaced with large air spaces comprising alveoli and alveolar ducts which had undergone compensatory dilatation. Such collapse can produce an apparent increase in cellularity of the alveolar tissue, a change usually seen in SUD lungs, but in our cases there were parts where thickening and cellularity could be shown to involve single alveolar septa thus favouring a true reaction rather than an artifact. Even so, the significance of an increased cellularity is difficult to assess. The lungs of like-aged infants dying suddenly from carbon monoxide poisoning or head injury are not obviously different. However, a detailed comparison showed SUD lungs to contain more alveolar cells (pneumocytes and septal cells) and their nuclei more often vesicular and deformed. Many of these cells had entered the alveoli where some had ruptured and provided much of the granular material within the alveoli. This picture is consistent with a reaction of the lung to some local or bloodborne stimulus.

Special Examinations

Blood groups

A syndrome causing sudden death in children shows, in Northern Ireland, segregation of the rare C^w allele in two families (Fraser, Froggatt and Murphy, 1964) and possible linkage of the abnormal gene with the Rh locus. Accordingly,

TABLE I

Blood group phenotype frequencies. Observed numbers of SUD cases and expectations based on stated controls

Phenotype	*Belfast*		*Extra-Belfast*		*Phenotype*			*Phenotype*		
	Obs.	*Exp.*[1]	*Obs.*	*Exp.*[2]		*Obs.*	*Exp.*[3]		*Obs.*	*Exp.*[4]
O	26	33.01	53	54.45	M	46	41.15	R_1r	46	47.44
A	24	19.82	29	28.05	MN	76	71.88	rr	28	21.61
B	8	5.67	11	9.35	N	23	31.97	R_1R_2	22	20.97
AB	2	1.50	1	2.14				R_1R_1	18	23.43
								R_2r	18	18.13
								Other	13	13.43
χ^2 (d.f.)	3.49 (3)		0.97 (3)			3.32 (2)			3.26 (5)	
P	0.30–0.50		0.80–0.90			0.10–0.20			0.50–0.70	

[1]Kopec (1970), pp. 98-99. [2]Kopec (1970), pp. 98-99 and Dawson (1964).
[3]Race and Sanger (1968), p. 91. [4]Heiken and Rasmuson (1966).

SUD cases were grouped for Rh (and also ABO and MNS) phenotypes and the frequencies compared with expectation derived from controls (Table 1). (Weighting the expectations on regional or 'postal district' frequencies seemed an unnecessary refinement). The differences were nowhere significant though the ratio $A_1/A_2 = 1.7/1.0$ is lower than that (3.7/1.0) suggested for southern England by Ikin, Prior, Race and Taylor (1939). Only one child had the C^w gene. These findings should be interpreted with caution because of the geographic variation in phenotype frequencies and the small number of SUD cases.

Serum proteins and immunoglobulins

In SUD cases and group B controls age-specific levels of serum albumin, α_1-globulin, and β-globulin were unremarkable but α_2-globulin was consistently elevated – which we interpret as due to autolysis. Immunoglobulin (IgA, IgM, IgG) levels, which had not previously been measured in SUD, were estimated using Hyland immunoassay plates to a standard technique (Collins-Williams, Toft, Generoso and Moscarello, 1967). The readings of two observers, and replications, were taken and, for IgG and IgA (where dispersion should *a priori* be minimally affected by freezing and thawing) the results were averaged, but for IgM (where such dispersion could be marked) the first reading was taken. Non-systematic inter- and intra-observer variation, the dependance of the real level on such factors as maturity and post-natal experience (Hobbs and Davis, 1967), the disproportionate effect of a few aberrant experiences, and the effect on molecule dispersal of repeated freezing and thawing, could all influence the results, but nevertheless the age-specific levels show reasonable concordance with those of other series of which the results of Stiehm and Gold (1968) are representative (Table II). Collation of individual readings with e.g. case history was not attempted because of the high error of the individual estimates.

TABLE II

Age specific immunoglobulin levels in mgm. per cent. SUD cases and results from Stiehm and Gold (1968)

Age (months)	*Immuno-globulin*	*N. Ireland SUD cases (median)*	*Stiehm and Gold* (1968) *SUD cases (mean)*	*Living infants (mean)*
1–3	IgA	28.5	17±12	21±13
	IgG	530.0	388±138	430±110
	IgM	41.0	27±14	30±11
4–6	IgA	38.5	44±31	28±18
	IgG	580.0	659±370	427±186
	IgM	57.0	42±19	43±17
7–12	IgA	49.0	36±18	37±18
	IgG	850.0	694±207	661±219
	IgM	44.0	43±17	54±23

Amino-acid chromatograms

'Nephrosis peptide' and increased excretion of sulphur-containing amino-acids have been described in SUD (Stowens, Callahan and Clay 1966). We attempted two-dimensional chromatography on 57 subjects but protein autolysis reduced confidently interpretable papers to 12 SUD cases and three group B controls. Of the former, six were normal, three showed cystathionine (or, possibly, phosphoethanolamine), two β-amino isobutyric acid, and one taurine; of the controls, one was normal, one showed 'nephrosis peptide' (in a child with left atrial agenesis), and one cystathionine. All abnormal constituents were in small quantities. Indole papers showed, in both groups, occasional aspirin metabolities, the tryptophan metabodities kynurenic acid and kynurenine, and (in one SUD case) 5-hydroxyindole acetic acid*. It is unlikely that these results are significant to the problem of SUD.

Blood urea

This was estimated on later cases in the series. The levels varied considerably but there were many over 100 mgm. per cent in both SUD cases and group B controls. In some it may have been agonal, and in some again it probably reflected a metabolic disturbance during the last few hours of life. The highest figures are usually associated with dehydration from vomiting or diarrhoea. This field might re-pay further study.

Bacteriology

This is described in Marshall (1970). Briefly, tracheal swabs were examined from 159 SUD cases and, after exclusion of contaminants, growths were obtained in 24 per cent compared to 20 per cent among control group B. Predominant

*We thank Dr. N. A. J. Carson for conducting and interpreting these tests.

organisms in the former were coagulase positive *Staph. aureus* (21 cases), haemolytic *Streptococcus* (12 cases) and *Pneomococcus* (5 cases). The controls produced mainly haemolytic *Strept.* Pleuropneumonia organisms were also sought in 76 SUD cases. None was detected: in 65 cases the results were negative while in 11 bacterial contamination made the plates uninterpretable.

Virology

This was restricted to a search for respiratory syncytial virus (RSV) and is described in Froggatt (1970b). Briefly, using tracheal swabs, impressions of lung, heart and kidney, and a fluorescent antibody technique, there was no single positive finding. This result must be considered at least in part artifactual – a few positives would have been expected irrespective of the cause of death and total failure is perhaps partly ascribable to antigen distintegration over the period (up to 18 months) of tissue storage. Other workers (e.g. Ray, Beckwith, Hebestreit and Bergman, 1970; Brandt, 1970) have described higher levels of successful isolation of most strains of virus from SUD cases than from various 'controls'; but interpretation is equivocal.

Other examinations

Other gross and microscopic examinations, e.g. otitis media, and special tests, e.g. presence of milk antibodies and nuclear sex chromatin content of buccal mucosal cells, are generally uninformative and have been described elsewhere (Froggatt *et al.*, 1968; Froggatt, 1970a, b; Marshall, 1970; Froggatt *et al.*, 1971).

Epidemiology

General Factors

Incidence

Adjusting the first estimate on the basis of overall 90 per cent ascertainment gives a 'corrected' incidence of SUD as 2.8 per 1,000 live births, 11 per cent of total infant (<1 year) mortality, and 33 per cent of postneonatal (4–51 week) mortality. These accord generally with the consensus urban experience in North America, Europe, Scandinavia and Australia; disparities with some series can probably be attributed to differences in diagnostic criteria, population structure, and survey methods. An incidence of 2.0–3.0 per 1,000 live births can therefore be accepted for Europeanised communities in temperate zones. Nothing is known of SUD in 'underdeveloped' countries: no surveys have been published and cases would most likely be swamped by the high infant mortality rates.

Regional variation

Authors differ as to whether or not there is an urban excess in SUD. Table III summarises our results which are confined to post-neonatal deaths to allow population comparisons. (This restriction excludes only nine cases). Columns (a)–(c) show our ascertainment and columns (d)–(f) are the rates per 1,000 live births based on our finding (above) that a 'complete' ascertainment in Belfast would yield not more than 75 post-neonatal SUD cases. Columns (g)–(i) are the estimates for SUD cases based on registered deaths in combined 'respiratory' ICD (Seventh Revision) categories, again on the Belfast experience, and columns (j)–(l) give

TABLE III

Regional incidence of SUD per 1,000 live births. Post-neonatal (4-51 weeks) cases

Administrative Area	Number of Ascertained Cases (1 Aug. 1965—31 July 1967)			Incidence of SUD based on 'Adjusted' Numbers of Ascertained Cases†		
	Males (a)	Females (b)	Total (c)	Males per 1000 Male Live Births (d)	Females per 1000 Female Live Births (e)	Total per 1000 Total Live Births (f)
County Borough						
Belfast	47	23	70	5.79	3.09	4.49
Londonderry	5	3	8	3.24	2.08	2.66
County						
Antrim	14	14	28	1.94	2.14	2.03
Armagh	4	6	10	1.39	2.29	1.80
Down	14	9	23	2.44	1.72	2.09
Fermanagh	0	1	1	—	1.09	0.53
Londonderry	4	5	9	1.36	1.83	1.58
Tyrone	4	5	9	1.26	1.71	1.47
Total	92	66	158**	2.82	2.21	2.54

† Adjustment factors, based on Belfast experience, are: Males=50/47; Females=25/23; Total=75/70 (see also text).

**Includes 5 cases ascertained outside the NIFPS.

the corresponding rates per 1,000 live births. Except for Belfast the two sets of rates are independently reached.

Th overall rates (colums (f) and (l)) are disparate only for Fermanagh, Londonderry County, and Tyrone. Taking the estimate in column (l) we reach, for the six counties, a weighted average of 2.29 per 1,000 live births (χ^2 of heterogeneity= 0.80, d.f.=4, $0.95>P>0.90$) which is significantly lower than the Belfast figure of 4.49 ($\chi^2=20.13$, d.f.=1, $P<0.001$) but not that (2.61) for Londonderry C.B. This Belfast excess is significant for males ($\chi^2=35.9$, d.f.=1, $P<0.001$) but not for females ($\chi^2=1.63$, d.f.=1, $0.30>P>0.20$), and it seems not to be a general factor of urbanity since there is no difference in the rates per 1,000 live births for pooled rural districts (2.35), and for pooled urban districts and metropolitan boroughs (2.25).

Sex

Males predominate in only four of some 60 post-war series (Froggatt *et al.*, 1971). Our study has 95 (58.6 per cent) males and 67 (41.4 per cent) females, the male excess being ascribably mainly to the atypical Belfast experience (Table III). We show elsewhere (Froggatt *et al.*, 1971) that this overall male excess probably patterns that for deaths in infants generally.

TABLE III—*continued*

Administrative Area	Estimated Number* of Cases based on Registered Deaths (1 Aug. 1965—31 July 1967)			Incidence of SUD given Estimated Number of Cases based on Registered Deaths		
	Males (g)	Females (h)	Total (i)	Males per 1000 Male Live Births (j)	Females per 1000 Female Live Births (k)	Total per 1000 Total Live Births (l)
County Borough						
Belfast	50.00	25.00	75.00	5.79	3.09	4.49
Londonderry	3.23	4.86	8.42	1.96	3.09	2.61
County						
Antrim	17.00	15.28	32.91	2.20	2.16	2.23
Armagh	6.45	7.64	14.54	2.10	2.67	2.45
Down	17.00	7.64	24.49	2.77	1.34	2.08
Fermanagh	0.81	2.79	3.83	0.80	2.79	1.91
Londonderry	6.45	8.33	15.31	2.06	2.82	2.50
Tyrone	8.09	8.33	16.84	2.37	2.64	2.57
Total	109.03	79.87	191.34	3.14	2.47	2.85

* Calculated by applying factors, based on Belfast experience, to number of registered deaths in pooled ICD (Seventh Revision) categories 480-483, 490-493, 500-502, 525, and E921. The factors are: Males=50/62; Females=25/36; Total=75/98. Thus in Londonderry C.B. there were 8.42 x (98/75)=11 deaths 4-51 weeks in the above categories. (See also text).

Age

This study confirms the unique age distribution, similar for each sex, which characterises SUD, *viz.* 75 per cent of cases between four weeks and six months, a mean of 18 weeks and a median of 14 weeks, and only 5 per cent of cases under one month and 15 per cent aged 6–11 months. This is highly dissimilar to overall infant mortality where the decrement curve is negative exponential.

Seasonal variation

SUD is commonest in the colder, rarest in the warmer months, again different to the distribution of other causes of infant death (Froggatt *et al.*, 1971). This winter peak, present also for the 40 per cent of cases described as symptom-free over the week pre-mortem, is more marked in the first year of the study (Fig. 1) – coinciding with an epidemic of type B influenza in January and February and type A2 in February and March 1966. This suggests epidemicity; we have not, however, been able to confirm this by time-series analysis nor by space-time clustering techniques (Froggatt *et al.*, 1971).

Social and economic status

Most authors have noted that SUD is commonest among underprivileged children. Our data confirm this: compared to four acceptable control groups (no

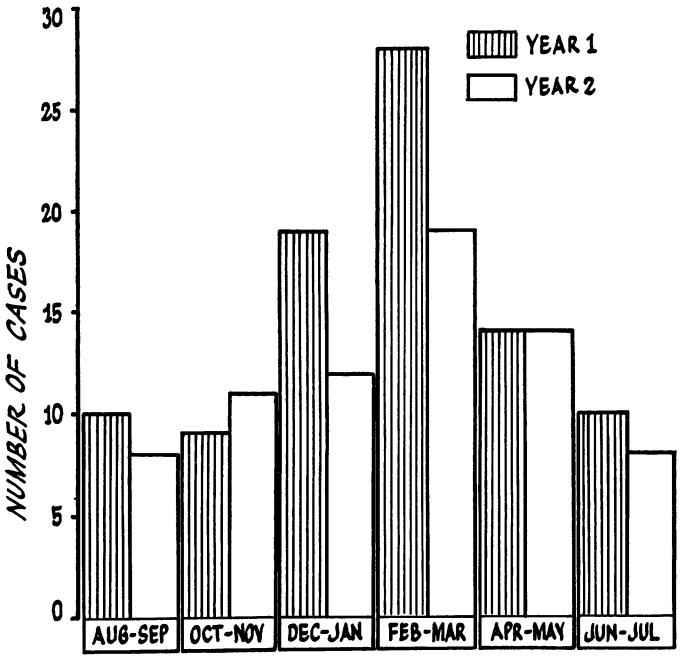

FIG. 1. *Seasonal incidence of 161 cases of SUD in Northern Ireland during the periods 1st August, 1965—31st July 1966 (Year 1) and 1st August 1966—31st July 1967 (Year 2). Reproduced by courtesy of the Editor from Amer.J.Cardiol.*, **22**, 457-468

single group is wholly appropriate for families ascertained through a SUD child) families of SUD cases are deficient in social classes I and II and over-represented in class V. Moreover, the fathers of 21 per cent of SUD cases compared to 8 per cent of group A controls ($\chi^2=8.51$, d.f.$=1$, $P<0.01$) were unemployed, or off work through sickness for more than six months; 7.4 per cent of SUD cases but no group A controls were illegitimate ($\chi^2=9.44$, d.f.$=1$, $P<0.01$); while room occupancy – 'crowding' - within social class was generally higher for the families of SUD cases than for those of group A controls. (Details are in Froggatt *et al.*, 1971).

To assess the independent importance in SUD of the above and other factors, we used a discriminant analysis, the two groups being Belfast singleton SUD cases and a random sample of Belfast surviving singletons, and the factors being sex, social class, parity, number of sibs claiming family resources, father's and mother's ages, and birthweight. Results (Froggatt, 1970a) showed a significant ($F=3.38$, d.f.$=7$ and 1,000, $P<0.01$) though unimportant difference between the mean discriminant scores but predictive power was too weak to be of practical importance.

Day of the week and time of the day

Cases occurred equally on each day of the week, but over the 24 hours the percentage distribution of the 'estimated' (Froggatt, 1970a) time of death in the three eight-hour periods from midnight, is 50.0, 36.4 and 13.6 (tested against equal frequencies, $\chi^2=32.93$, d.f.$=2$, $P<0.001$) which is similar to that (51.7, 33.3, and 15.0) for the sub-group of 60 index cases allegedly symptom-free throughout the week before death. More significantly, most infants were supposedly asleep at

TABLE IV

Distribution of SUD cases and Group A 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	—	—	—	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

*(Number of previous livebirths, stillbirths and miscarriages)+1.
†Birth order of one child unknown.

the time of death; certainly very few were being handled or patently awake at the time of the terminal event.

Maternal age and parity

These highly correlated factors entered the discriminant function (mentioned above) – where neither proved to be a significant determinant of SUD – but they were also examined, as follows. Table IV sets out the appropriate data and, on testing the null hypothesis that the two bivariate distributions are not discordant, we obtain a large sample χ^2 of 117.67 (d.f.=29, $P<0.001$) and the two distributions are thus significantly different. Partitioning this χ^2 value into its interaction components we find 10.43 (d.f.=4, $0.05>P>0.02$) ascribable to differences in parity, 9.50 (d.f.= 2, $P<0.01$) to differences in maternal age, 99.29 (d.f.=8, $P<0.001$) to the age/parity interaction, and a negligible component due to the second-order interaction. Though the differences are small SUD cases are on average of significantly higher parity and born to younger mothers; but inspection suggests that these are particularly marked in mothers under 30. These results parallel findings on infant mortality in Belfast for all categories other than congenital malformations (Elwood, 1969, pp. 96-7).

Factors Related to Birth and Pregnancy

Birth weight and gestation period

Most authors note a lower average birth weight or gestation period in SUD than

among surviving live births though not generally than among infants dying in the first year. These are found also in the present study, but when birthweight is more rigorously tested by the multivariate methods of discriminant function (Froggatt, 1970a) and multiple regression (Froggatt *et al.*, 1971) it appears less important. We conclude that birthweight *may* be a correlate with, but is not an important *determinant* of, SUD: as such it is likely to be merely a manifestation of general vulnerability of the premature since binary multiple regression shows birthweight to be a comparatively powerful determinant of all infant deaths (Elwood, 1969, ch. VI).

Multiple births

SUD is common among twins, equally so for mono- and dizygous pairs. When both partners are SUD cases their deaths have usually been coeval (Geertinger, 1968). In the present study 11 index cases were twins and two others were members of one like-sexed (female) but presumptive dizygous (by blood grouping) twin-set who died on the same day aged 10 weeks. Of the 12 sets, five were FF, four MM, and three MF; and the SUD twin was the heavier at birth in six. We argue elsewhere (Froggatt *et al.*, 1971) that this high representation of twins may be ascribable to their low birth weight (mean is 5.1 lb.) and the coeval death in twins (when both die) possibly interpretable in terms of a common environmental agent. We may also speculate that it is the direct effect on one twin by the death of his partner possibly mediated through shock or fear, factors known to cause sudden death (Engel, 1971).

Maternal health during pregnancy

During the pregnancies producing the 148 SUD cases with family interview data and the group A controls, respectively 27.7 and 23.6 per cent of mothers had conditions which could have endangered pregnancy, e.g., pyelitis, PET, APH, respectively 52.7 and 58.1 per cent alleged that their health throughout was good, while the remainder (19.6 and 18.3 per cent) had complaints either minor or conventionally unassociated with risk to the foetus. These differences are unimportant.

X-ray exposure

During the above pregnancies respectively 83.8 and 85.8 per cent of mothers had no pelvic or abdominal X-rays, and the number, and stage in pregnancy, of X-irradiation to the remainder were approximately equal.

Presentation and mode of delivery

Of the 148 SUD cases and group A controls, respectively 94.5 and 94.0 per cent were vertex presentations, most others being breech; while respectively 80.3 and 78.3 per cent were spontaneous deliveries, equal numbers (12) were induced, and 11 and 13 per cent respectively were delivered in other ways, about half being by Caesarian section.

Evidence of Specific Inheritance

A recessive Mendelian hypothesis would require sibship aggregation (within Mendelian expectations) and increased parental consanguinity, while an inherited autosomal anomaly would likely be recognisable on karyotyping and would produce

increased foetal loss. We show elsewhere (Froggatt *et al.*, 1971) that (i) the SUD case rate amongst sibs of singleton propositi is 11.0–22.0 per 1,000 live births, i.e. 4–7 times the population and control group A figures, but still far too weak an aggregation for a Mendelian interpretation, (ii) no parents of SUD cases admitted kinship, and (iii) there was no unusual foetal loss. (Tissue for karyograms was at the time difficult to culture: subsequently Weinberg and Purdy (1970) have shown some minor chromosomal abnormalities in SUD though of uncertain significance). From this, and autopsy evidence, we conclude that specific inheritance must play at most a small part in SUD.

Post-Natal Health and Environment

Post-natal weight increment

Drillen's (1964) work shows parallel population weight increment curves over the first year of life for each sex and all birth weights: thus Figure 2 validly compares weight increment of pooled SUD singletons with combined population series (Tanner, 1958; Watson and Lowrey, 1967). (Each SUD autopsy weight is 'corrected' to an estimate for exactly 1, 2, ... months, whichever is nearest, on the basis of Stuart and Meredith's tables (Watson and Lowrey, 1967)). The curve for SUD cases lies between the 10th and 50th percentile and, allowing for small-number instability at older ages, at a probably constant relationship to both. For twins, mean weight gain was 1.39 lb. per month which compares reasonably with Drillien's (1964, Appendix IIa) figures for weight increment in 'healthy' twins. These results suggest that SUD cases thrived normally.

Post-natal health

Arbitrarily dividing the period between birth and death (of an SUD case) or interview (of a control) into (i) from birth to one week before death (or interview) – which may be relevant to the child's underlying fitness, and (ii) 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 SUD cases and group A controls.

During period (i), 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 (ten cases, eight controls); failure to thrive (five cases, no controls); rhesus incompatability (two cases, two controls); gastro-intestinal conditions (four cases, four controls); and others (four cases, five controls). For other medical consultations and omitting twins, two cases with infantile ecezema, and the episodes leading to hospitalisation (as above), 62 (46.6 per cent) of the remaining SUD cases had at least one episode of illness compared to 57 (38.8 per cent) of 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 per cent among cases, 60 per cent among controls). There were no unusual diagnoses. These findings confirm the weight increment results (Fig. 2) indicating basic fitness.

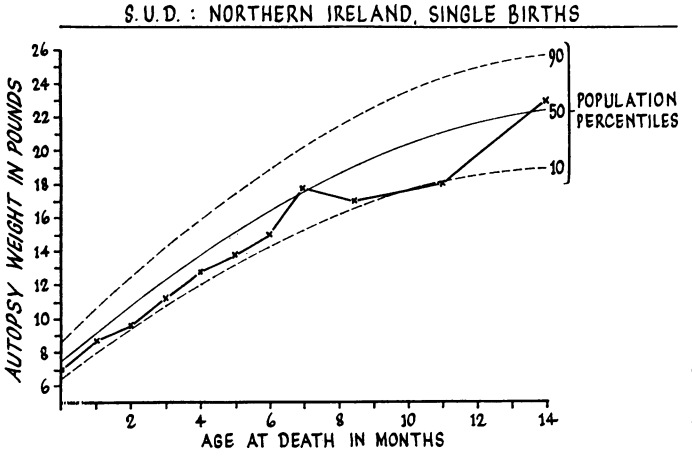

FIG. 2. *Mean weights at death of singleton SUD cases in the present study compared with population limits for mean weight of normal singletons at birth, 1, 2 . . . months of age. (See also text).*

During period (ii), seven SUD cases were discharged from hospital after treatment for pneumonia (three cases), otitis media (one case), negative investigation of failure to thrive (one case), breathless episodes (one case), and intermittent vomiting (one case). Six SUD cases were admitted *in extremis* and died. 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 with 15 controls ($\chi^2=5.61$, d.f.$=1$, $P<0.05$), the cause being respiratory infection (17 cases, 12 controls), gastro-intestinal conditions (10 cases, 3 controls), and general pyrexia, listlessness, and convulsions (one 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. Unless there was gross re-call bias the picture is of increased minor illness during the week, particularly the 24 hours, before death.

Feeding and medicaments

SUD cases have often seemingly differed from controls in feeding regimens, and breast feeding, specially during the first two weeks (to avoid sensitisation), has been advocated (Ministry of Health, 1965).

In the present study 18 SUD cases were wholly breast-fed for at least one week after birth, eight were partially breast fed from birth, and 121 were never breast-fed. Corresponding frequencies for matched controls were 22, six and 119 ($\chi^2=0.70$, d.f.$=2$, $0.98>P>0.95$). One further case and control had been wholly breast-fed for five and three days respectively. Two of the 18 cases 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 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. Only three infants were known to die or collapse within one hour of feeding. Generally milk antibody titres were unremarkable (Froggatt *et al.*, 1971). These findings were 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 per cent allegedly received none, 46.6 per cent allegedly received only household medicaments – aspirin, gripe water, nose drops, teething powder, etc. – while 42.6 per cent received other drugs usually antibiotics. Corresponding frequencies for group A controls – 10.1, 53.4, and 36.5 per cent – are not significantly dissimilar to these ($\chi^2=1.40$, d.f.$=2$, $0.50>P>0.30$).

Sleeping position

Suffocation by bed clothes and 'overlaying' were long accepted as major causes of sudden death in infants (Templeman, 1892; Froggatt *et al.*, 1968). Most authors now accept that suffocation by external agencies or by aspiration of gastric contents is unimportant, but some recommend discontinuance of soft pillows (e.g., Ministry of Health, 1965).

Though we cannot interpret the relevance of the results, we record that there were significant differences between SUD cases and group A controls in their 'normal' sleeping position, i.e., the position in which the mother allegedly 'usually' finds the child (Froggatt, 1970a), but in the 111 cases found unequivocally dead there was no difference, in as many as 68 per cent, between 'normal' sleeping position and position found. Where there was a difference the terminal position was: face down (nine); face up (eight); face to side (five) – i.e. there is no evidence of an excessive 'face down' position. Among 144 cases, 55.4 per cent slept without a pillow (25.3 per cent with neither bedding nor pillow) and only 17.6 per cent of those found dead or *in extremis* were face down on a pillow or with nose and/or mouth covered by bedding. Again there is no strong evidence for smothering. Other terminal findings are described by Marshall (1970).

Discussion

These results provide a pathological, epidemiological, and clinical profile of SUD. They have, however, only limited value in specifically assessing current hypotheses of causation though we can adduce some evidence on the coherence of certain general theories.

We can confirm the consensus view (Bergman *et al.*, 1970) that SUD victims do not have some underlying 'disease' as yet unrecognised: the unrevealing special autopsies, 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 it. Cases appear in fact to be essentially 'normal' infants, and the social and biological factors correlating with SUD can be shown to have very poor predictive power (Froggatt, 1970a). The characteristic age range is the most important factor and there seems little doubt that these infants die during a period of increased physiological vulnerability because some critical combination of intrinsic and extrinsic factors proves lethal: what *is* in doubt is the mechanism, or 'final common pathway', of death.

Our results must ascribe some role to infection, mainly respiratory infection. 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 and 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 pre-mortem 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 autopsy findings, though conventionally accepted as 'normal' (except perhaps for the petechiae – see below), usually show in common with other studies (Valdés-Dapena, 1967; Beckwith, 1970) an increased cellularity of the lungs sometimes with cellular infiltration of peri-bronchial tissue (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 the tests will not always detect epidemicity especially if, as seems likely, there be several partly independent infective agents (Ray, Beckwith, Hebestreit and Bergman, 1970) – and the fact that some of the above findings could be expected on other hypotheses (Froggatt *et al.*, 1971).

The precise role played by any such infection is 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 e.g. cardiac conduction disturbance, or making such a process itself more likely (e.g. James, 1968). Whatever the mechanism even quite trivial respiratory infections may seemingly predispose to SUD in a child aged 1–6 months.

Apart from findings in the conduction system of the heart (James, 1968) the only significant autopsy finding is the presence of numerous petechiae on the lungs, heart and thymus. They occurred on one or more of these organs in two-thirds of cases. These haemorrhages, formerly interpreted as 'asphyxial', were largely responsible in the past for the diagnosis of suffocation and recently they have been interpreted as evidence of terminal laryngospasm by Beckwith (1970) who argues that the strict intrathoracic distribution of the petechiae provides compelling evidence of markedly elevated intrathroracic negative pressure due to a terminal episode of high airway obstruction. We are reluctant, however, to accept this argument; petechial haemorrhages occur in many kinds of death in adults and whatever the cause of death, they favour certain sites of which the lungs and heart are prominent; and they are not particularly numerous in children suffocated by a plastic bag over the head or by a foreign body in the larynx, when elevated intrathoracic negative pressures ought also to operate. Whilst we are unwilling to ascribe any diagnostic significance to intrathoracic petechiae, we recognise that they are found more regularly and more conspicuously in SUD than in other infant deaths and that interest in them should be maintained.

Sleep seems also to have significance. It is impossible to be certain that an unobserved infant is asleep, 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 suggestive. This does not help towards establishing the 'final common pathway' of death: bodily changes during sleep are theorised 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 is characteristic and is the main cornerstone of the concept of developmental physiological vulnerability in SUD. This concept receives support from the case histories and family data. One aspect should be emphasised: the occasional history of previous 'fainting', cyanotic or apnoeic episodes, or periodic breathing, perhaps especially in multi-case sibships (Froggatt *et al.*, 1971). Such a history could be elicited in a few of our cases (only twice did it lead to hospital investigation – which was negative) and has also been documented by e.g. Stevens (1965), and Steele (Bergman *et al.*, 1970, p. 74). It may in fact be even more common 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 be more common in SUD victims than others then they should be considered a sinister symptom requiring investigation of the child. They may on the other hand indicate causal heterogeneity: if so the mechanism of SUD in such infants may be different to that in others.

Undoubtedly the outstanding problem is to identify the 'final common pathway' of death; a subsidiary 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 specialty. Thus virologists see the importance of respiratory viruses, immunologists the dangers of immature immune mechanisms, cardiologists the hazards of the unstable infantile conduction system or myocardial electrolyte disturbance, and cardiopulmonary physiologists the role of the baby's labile autonomic system. Tests which may, for example, discriminate 'pulmonary' from 'cardiac' death e.g. terminal blood-gas composition (Mithoefer, Mead, Hughes, Iliff and Campbell, 1967) unfortunately seem to be equivocal in interpretation (Bergman *et al.*, 1970, pp. 130-2). Nevertheless experimental and basic sciences offer now the best avenues to advance knowledge. Case reduction would at present seem to depend upon general realisation of the vulnerability of the infant between one and six months – especially if he be an underweight twin or a child with respiratory symptoms – and the possibility that the crucial episode is not irreversible and that a proportion of infants could be saved by cardiopulmonary resuscitation. Such methods may not need to be by machine; simple handling and first-aid techniques may arrest or reverse the process long enough to allow hospitalisation. Prevention of known environmental trigger mechanisms e.g. respiratory infection, would have only 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 recognised 'at 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 reduction in the incidence of SUD must hope that this will prove to be the case.

Summary

This article describes a collaborative study of sudden unexpected death in infants ('cot death') in Northern Ireland based on the 162 cases ascertained through the Northern Ireland Forensic Pathology Service from 1st August 1965, to 31st July 1967. These represent some 90 per cent of an estimated complete ascertainment, and clinical, epidemiological, and pathological data are presented on them. After full discussion of theories and interpretation of the data it is concluded that 'cot death' victims are essentially healthy throughout life; they die because during a developmental stage of physiological vulnerability – mainly between one and six months – some combination of intrinsic and extrinsic factors proves fatal. Despite intensive research the 'final common pathway' of death is still unknown though social and biological risk factors have been identified. Basic scientific and experimental studies now offer the best opportunities for further work.

Acknowledgments

We are grateful to our colleagues on the working party for entrusting us with describing this collaborative study. Among the many others who helped we are particularly indebted to: the Medical Officers of Health and County Medical Officers and their staffs who facilitated the field work and ascertainment of group A controls; Dr. J. A. Taggart and Dr. Kathleen Corbett for making available the extensive records on births and infant deaths in Belfast, and Dr. J. H. Elwood for additional information on them; members of the Northern Ireland Forensic Pathology Service who facilitated the work in every way; the Registrar General for supplying many special tabulations; and the coroners and the Northern Ireland General Health Services Board for helping to maximise ascertainment. Grants were received from the Northern Ireland Hospitals Authority and the Faculty of Medicine, The Queen's University, Belfast.

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