SUDDEN UNEXPECTED DEATH IN INFANTS
Evidence on a Lethal Cardiac Arrhythmia

by

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THE incidence of sudden unexpected death of infants (‘cot death’ – ‘crib death’ in USA – ‘sudden unexpected and unexplained death in infants’, ‘sudden infant death syndrome’), termed below cot death, is 2.0 – 3.0 per 1,000 live births in ‘developed’ countries of Europe and North America\(^1\), less than 1.0 in Israel\(^2\) while no data are available for underdeveloped countries. In Northern Ireland the ‘corrected’ figure is 2.8 and represents 10 per cent of total infant, and 33 per cent of postneonatal, mortality\(^4\). The condition is considered sufficiently homogeneous to constitute a distinctive syndrome and most cases are thought to have an identical —though unidentified—‘final common pathway’ of death\(^5\).\(^6\) Despite intensive research the cause (or causes) is unknown; but the consensus holds that victims, mostly healthy throughout life, die because while passing through a period of enhanced physiological vulnerability some critical combination of intrinsic and extrinsic factors proves 'suddenly' and ‘unexpectedly’ fatal yet produces at autopsy no identifiable abnormality acceptable as being a ‘cause’ of death. Though certain ‘risk factors’ have been identified\(^8\)–\(^9\) it is not known through what ‘final common pathway’ (or ‘pathways’) death occurs. Of the many theories adduced that which now commands the widest support and which the data are alleged to favour is that these infants die a respiratory death—in the sense that death is mediated through a respiratory (rather than a cardiac) primary mechanism—due possibly to asphyxia secondary to laryngospasm, to apnoea with or without laryngospasm and mediated through some aberrant or immature reflex possibly impeding recovery from ‘normal’ sleep apnoea, or to respiratory failure as part of an immunological collapse or hypersensitivity on challenge with an appropriate antigen presumed to be a virus.

These explanations are reached mainly by inductive inference: lethal laryngospasm has not been demonstrated; aberrant or immature reflexes have been indicted\(^10\) but their role (if any) in cot death is unknown; no basis for an immunological mechanism has been established. Where deductions as to respiratory death are made either from animal models\(^11\) or from study of selected infants ultimately
being cot deaths\textsuperscript{12} the data do not exclude other interpretations. In this article we examine another hypothesis seemingly consonant with the facts—namely, that these infants (or at least a significant number of them) die not a respiratory but a \textit{cardiac} death—in the sense that death is due to a lethal arrhythmia produced by failure or disturbance in the normal electrical activity of the heart. This hypothesis was little considered until 1968\textsuperscript{13} and receives only modest attention now despite its plausibility in any form of sudden, unexpected, and ‘unexplained’ death.

This hypothesis will be examined below as a general theory of causation. Infants sometimes die from documented cardiac arrhythmias and at conventional autopsy no anatomical explanation is found, e.g. the QT interval prolongation syndromes either with\textsuperscript{14, 15} or without\textsuperscript{16, 17} deafness, but we will not suggest that these or other conditions with \textit{documented} electrical instability of the heart play a major role in cot death though we will draw inferences from them in developing the argument.

Many of the data below are from our own studies, some from other surveys. It is unnecessary to describe these here; full details appear in works as referenced.

\textbf{SALIENT CLINICAL AND EPIDEMIOLOGICAL FACTS}

We first establish that this cardiac hypothesis is consonant with the data. Salient facts, the consensus of recent work\textsuperscript{4, 5, 8, 9, 18} are as follows and as summarised in Table 1: (i) death is sudden and silent; (ii) routine autopsy fails to identify a lethal mechanism; (iii) there is no important heritability; (iv) throughout life victims appear healthy and thrive normally; (v) there is enhanced risk in boys, low birth-weight infants, dwellers in poorer urban areas, and winter months—though there is no time/space epidemicity\textsuperscript{9}; (vi) upper respiratory, febrile, or coryzal symptoms, usually mild, are frequent (50 per cent of cases) during the week, especially the 48 hours, pre-mortem; (vii) being asleep at the onset of the fatal episode is a presumptive finding in most cases; and (viii) there is a characteristic age distribution with 90 per cent of cases 1 – 6 months and a peak incidence at 2 – 4 months.

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\textbf{TABLE I}
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\textit{Sudden (Unexpected) Death in Infants—Salient Facts}
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\begin{tabular}{l}
1. Sudden and silent death \\
2. Routine necropsy normal \\
3. No important heritability \\
4. Infants thrive normally \\
5. Increased risk in boys, low birth-weight infants, colder months, poorer urban areas \\
6. Mild systemic or febrile symptoms in 50\% cases during 48 hours pre-mortem \\
7. Sleep \\
8. Characteristic age distribution \\
\end{tabular}
\end{center}
Factors in (i) – (iv) are clearly compatible with a cardiac hypothesis in an otherwise healthy heart, though (iii) will be discussed later. Factors in (v) are general to infant deaths though there is a possible role for cold environment on the hypothesis. Factors in (vi) are, with the seasonal variation, commonly adduced as evidence of a key role for infection in the chain of events leading to cot death and therefore (illogically) as evidence that death itself is ascribable to an infective process. These, together with factors (vii) and (viii), which are crucial findings in cot death (the ‘eligibility factors’ of Beckwith6) are not uniquely explicable on any theory and are discussed later.

The cardiac hypothesis is thus clearly not discredited by the major facts, a prima facie case has been established, and we can now legitimately proceed to consider the theory in detail (including discussion of factors in (v)–(viii) above) recognising that logical inference will only allow one to accept or discard the hypothesis—more strictly to discard a null hypothesis— with a particular degree of certainty and that this is independent of the outcome of testing any other theory.

**Examination of the Hypothesis**

It is axiomatic that the postulated electrical instability of the heart must be capable of being lethal. Cot death cases however present unique difficulties since there cannot be any direct evidence for a terminal arrhythmia: sudden and unexpected death by definition precludes terminal examination. Nor do we know the normal ECG status of these infants: being mostly healthy from birth there is rarely call for medical investigation; and since there is no marked family aggregation of cases6,9 there is no demand for family screening to establish any ‘at risk’ status of members. To examine the hypothesis we must reason inductively—as have those who have examined other theories—and this requires consideration of all relevant data.

**Hypothesised nature of the cardiac problem**

We first consider possible mechanisms by which a lethal arrhythmia might arise in cot death infants recognising their essentially non-familial distribution, the negative clinical and (routine) autopsy findings, and the thorough neonatal examination and surveillance of most infants (e.g. all the 162 in our series4,8,9 in which 90 per cent were hospital births) which fail to disclose any significant anomalies. We may therefore exclude for the generality: (i) overt heart blocks with or without structural heart defects; (ii) most of the (rare) familial cardiac arrhythmias or conduction abnormalities and (iii) such overt vascular, infective, or myopathic processes, or drug ingestion, which could affect cardiac rhythm lethally. Included *ad interim* is any condition truly or seemingly symptom-free and with clinically and histologically normal cardiovascular system but with a conduction system prone to produce potentially lethal arrhythmias through some mechanism—possibly neural aberration or metabolic disturbance at a cellular level—unidentifiable at autopsy.

Apart from occasional sporadic (e.g. James *et al*19) and familial (e.g. Green *et al*20) cases of sudden death in healthy young people with or without explanatory histo-pathological changes (demonstrable on special examination of the conduction system as the sole discernible anomaly21) QT interval prolongation syndromes are
acceptable for inclusion. These conditions viz. the cardio-auditory\textsuperscript{14, 15} and Romano-Ward syndromes\textsuperscript{16, 17}, are characterised by repeated syncope often in infancy and frequently fatal and due to ventricular arrhythmias—usually ventricular fibrillation though rarely asystole\textsuperscript{22, 29}—arising from an innate cardiac electrical instability of uncertain aetiology but involving conspicuously abnormal myocardial repolarisation (Fig. 1) with sinus bradycardia as a frequent salient feature. Their immediate relevance is that the patient until the first syncope appears healthy (he may be deaf but this is unascertainable in an infant) and careful routine autopsy fails to uncover any significant lesion: in fact, the syndromes manifest several documented electrophysiological mechanisms which can produce a sudden cardiac death in infancy and are not immediately incompatible clinically and pathologically with cot death. We must therefore consider whether this mechanism either as part of, or independent of, these syndromes could provide an acceptable model and be consistent with cot death data.

\textit{Basis for an aberrant repolarisation model}

Given the facts of cot death and postulating aberrant ventricular repolarisation expressed through a prolonged QT interval as the model, we can theorise three main mechanisms of its genesis: (i) inheritance as a Mendelian autosomal trait—as in the QT prolongation syndromes\textsuperscript{24, 25}; (ii) arising as an autosomal mutant characteristic (subsequently following Mendelian law); or (iii) origin as an extreme quantitative value of the normally occurring continuous range of QT intervals.

Under (i) above, inheritance may be (in conventional terms) either ‘dominant’ or ‘recessive’, the characteristics of which are well-known. Briefly, ‘dominant’ law requires (a) one or other parent affected, (b) in complete ascertainments about one half of sibs of propositi affected or an equivalent foetal loss, and (c) many other cases among the affected parent’s kin. None of these obtain. No parent in our series of 148 (visited) families had a history of pertinent syncopal attacks and the ECGs (238 of a possible 296 were taken) showed neither significant arrhythmias nor an enhanced number with a prolonged QT interval as compared to random (normal) expectation (8 as against an expected of 6.5 at $t=2.0$); and, while ECG tracings on sibs are not uniformly available, sibship aggregation of cot death or of pertinent symptoms, fraternity foetal loss, and suspicious symptomatology in more distant kin, are minimal\textsuperscript{9}. ‘Recessive’ law on the other hand requires (a) increased parental consanguinity, and (b) as (b) above substituting one-quarter for one-half. Again neither of these obtain: (b) is already considered; while under (a) no parents professed kinship whereas random expectation in Northern Ireland for third cousin and closer consanguinity is 2 per cent to 3 per cent\textsuperscript{25}. Furthermore, taking cot death as a single and exclusive ‘recessive’ genotype with population incidence of 3 per 1,000, then on Hardy-Weinberg (with $q^2=3/1000$) and Lenz-Dahlberg (putting $\alpha=1\%$) assumptions first cousin parent marriage should be some 1.4 per cent and total ascertainable cousin marriage perhaps some 3 per cent; and these estimates would increase with the number of postulated genotypes. There is, therefore, no supportive evidence for a Mendelian hypothesis on the pooled sibship data either for cot death or the generating model, though this does not exclude Mendelian segregation in some families or polygenic or other mechanisms.
Fig. 1. Electrocardiogram of an 11-week-old boy with unequivocal cardio-auditory syndrome showing prolonged QT interval and TU wave changes. These also occur in the Romano-Ward syndrome and they characterise the two conditions. (Each small square represents 0.04 secs.)
Concerning (ii) above, heritability would not be expected since the genotype does not reproduce. Mutations in both the QT prolongation syndromes probably occur—difficult to demonstrate in the 'recessive' cardio-auditory syndrome but possible in single-case ("dominant") Romano-Ward families (e.g. that of Karhunen et al.\textsuperscript{26} and probable in the family of Sandra C\textsuperscript{27}—a victim of unequivocal Romano-Ward syndrome—where ECG examination of 109 blood relatives and 233 of their spouses and in-laws covering all age groups showed no significant differences especially relevant to QT interval. But if we postulated 'dominant' gene mutation as the exclusive 'cause' of cot death we would have to accept a mutation rate equal to the population incidence since there is complete selection against the genotype, i.e. a rate many hundreds of times greater than any yet postulated for man—an unrealistic assumption.

The third possibility ((iii) above) can be stated as follows. Under (i) and (ii) QT prolongation has been considered as a qualitative change in that, irrespective of degree, it is abnormal and potentially lethal as judged by the resultant clinical stigmata (syncope, ventricular arrhythmias, sudden death) characterising the syndromes. But in the interpretation under (iii) above we are judging whether a QT interval prolongation, which might arise occasionally on population sampling as an extreme value on a continuous scale of QT\textsubscript{c}* measurements, could \textit{per se} be potentially lethal. This is now discussed.

\textit{Consideration of minimal 'quantitative' QT lengthening in sudden death}

We have shown\textsuperscript{24} that the QT\textsubscript{c} interval among healthy school-children is normally distributed. (This is after the cot death age range when victims have already died: however, there is no detailed information on the form of the distribution in infants—in fact the QT interval in the neonate is very labile\textsuperscript{28}—and for the present argument we will accept that the neonatal QT interval is also normally distributed). We would expect therefore about 0.5 per cent of infants to have 'long' QT\textsubscript{c} intervals (at \(t = 2.58\), \(P = 0.01\))—which is, incidentally, the approximate cot death population incidence. Most will be only slightly prolonged: but even slight statistical prolongation could be \textit{biologically} important—in the two QT prolongation syndromes though there is usually a correlation between degree of QT prolongation and severity of clinical expression especially age of onset\textsuperscript{15} nevertheless Tables II and III, compiled from the literature, show that minor or even nil QT prolongation can be associated with lethal arrhythmias in the presumed absence of other heart disease.

Accepting then the credibility of this genesis of the model we would expect three corollaries. \textit{First,} that the QT\textsubscript{c} distribution among children over one year would be truncated at its upper bound due to previous removal (by cot death) of infants with the longer QT intervals. Such demonstration would require measurements on very large samples: on our smaller series (random sample of 369 from 82,000

\* This is the length of the QT (QT\textsubscript{o}) interval corrected for heart rate using one of the many available regression formulae. In random population samples QT\textsubscript{o}—QT\textsubscript{c} (\(= QT\textsubscript{d}\)) will be normally distributed so that statistics based on normal theory are appropriate\textsuperscript{24}.
### Table II

**Romano-Ward Syndrome (QT prolongation without deafness)**

*Cases from the Literature distributed by Degree of QT Prolongation*

| \( \frac{QTo - QTc}{SE(QTc)} \) | Number of cases (N=62) |
|-----------------------------|-----------------------------|
|                            | with syncope ± VF and/or sudden death | without symptoms |
| 0–2.6                      | 16                           | –                |
| 2.6–                       | 16                           | 5                |
| 4.6–                       | 11                           | 5                |
| 6.6–                       | 4                            | –                |
| 8.6–                       | 1                            | –                |
| 10.6–                      | 3                            | –                |
| 12.6–13.6                  | 1                            | –                |

*Compiled from cases with adequate data in 18 families. Facts supplied on request to one of us (P.F.)

**\( \frac{QTo - QTc}{SE(QTc)} \)** is distributed as \( t \) (see text). 99% limits are -2.6 to +2.6: thus 16(25%)—with values < +2.6—had "normal" QTc intervals but had syncope attacks with or without VF and/or sudden death.

### Table III

**Cardio-Auditory Syndrome**

*Univocical Cases with Minimal QT Lengthening*

| Source                        | Statistic* | Syncope | Affected Sib | Sudden Death (and age) |
|-------------------------------|------------|---------|--------------|------------------------|
| Jervell and Lange-Nielsen¹⁴   | 4.0        | +       | Yes          | Yes (4)                |
| Fraser, Froggatt and James¹⁵ | 3.1        | +       | Yes          | No (20)                |
| Lamy et al²⁹                  | 2.4        | +       | Yes          | No (10)                |
| Fauchier et al³⁰              | 3.2        | ?       | No           | No (2)                 |
| Pernot et al³¹                | 3.2        | +       | Yes          | No (6)                 |

* \( \frac{QTo - QTc}{SE(QTc)} \). Upper range of normality (99% limit)=2.6
children 5–15 years in Belfast\textsuperscript{24}) truncation is not evident (9 expected against 9 observed with $QT_o - QT_c$ greater or equal to 2 SE ($QT_c$)) but would in fact be unexpected with this sample size and an incidence of only 3 per 1,000 live births. Second, that many infants known to have long QT intervals would themselves have been cot death cases. Though some children with documented or presumed QT\textsubscript{c} prolongation have died suddenly in the cot death age range—notably the original cases of Romano et al\textsuperscript{16}—the majority have been older at death or have survived childhood. And third, by postulating lethal arrhythmias in infants with slight QT prolongation we must accept a fortiori such arrhythmias in infants with gross QT prolongation, unless the latter (but not the former) are free of associated factors (e.g. sinus bradycardia and premature beats). The literature shows only a few children under one year with gross QT prolongation and syncope\textsuperscript{16, 24, 30–34} but transient potentially lethal arrhythmias could be missed without monitoring. Only one example of QT prolongation syndrome (a boy with unequivocal cardio-auditory syndrome) has been ascertained in the perinatal period and monitored through the first six months\textsuperscript{35}. During this time he remained well, had no syncope, but had marked sinus arrhythmia with occasional runs of AV nodal bradyarrhythmia (Fig. 2) and had his first documented syncopal attack ironically just after hospital discharge aged 6 months i.e. within the cot death age range though after its peak. (Monitoring of subsequent syncopal attacks showed tachyarrhythmias including ventricular fibrillation). This slow rate of the escape AV junctional rhythm may be especially important for four reasons: (i) sinus bradycardia is a feature of the disease clinically; (ii) histopathology of the sinus node is one of the distinctive abnormalities at necropsy\textsuperscript{15}; (iii) there is normally a consistent mathematical relationship between sinus rhythm and escape AV junctional rhythm\textsuperscript{36}; and (iv) AV junctional rhythm is more dependent than is sinus rhythm on intact adrenergic neural tone abnormalities of which may in turn be a partial explanation for the QT prolongation\textsuperscript{37}.

In summary: the role of this model in cot death cannot be established from the data. But the facts are necessarily limited: e.g. we have accepted the QT interval as an invariant parameter whereas it shows within-person variability even in normal infants\textsuperscript{38}, and markedly in QT prolongation syndromes (e.g. cases in Fraser et al.\textsuperscript{15, 24} and in Phillips and Ichinose\textsuperscript{39}). If variation approaching this relative order (with reference to QT prolongation syndromes) occurred in infants with 'normal' QT intervals then transient prolongations (which may be lethal) are possible without disturbing the form of the population QT\textsubscript{c} distribution even in very large samples. Again, it may not be synchronous but asynchronous prolonged myocardial refractoriness which predisposes to ventricular tachyarrhythmia and this need not manifest a prolonged QT interval at all. And there are other mitigating factors. (Theories of causation of the QT prolongation are outside the scope of this paper: they are well summarised by James\textsuperscript{40}). These, and others, are legitimate variants of the main hypothesis: they further emphasise the difficulty of establishing or discrediting this model by a necessarily inductive approach.

**ALTERNATIVE MECHANISM OF SUDDEN CARDIAC DEATHS**

Explanatory histopathological changes in the conduction system in some QT prolongation cases\textsuperscript{16} and in sporadic sudden deaths in healthy young people\textsuperscript{19} and
FIG. 2. Continuous strip monitor tracing of the boy whose ECG is shown in Figure 1. Note the run of bradycardia and supraventricular (AV nodal) rhythm before return of sinus rhythm. The relevance of this and associated rhythms to the hypothesis under discussion is considered in the text. (Each small square represents 0.04 sec.)

the clinical facts of cot death, led James\textsuperscript{13} to examine the regions of impulse formation and conduction in hearts, and age-matched controls, from the Northern Ireland cot death material. The basic findings, confirmed by Anderson \textit{et al}\textsuperscript{41} and Ferris\textsuperscript{42, 43} but questioned by Valdés-Dapena \textit{et al}\textsuperscript{44} are present in all the postnatal hearts including controls but in none of the foetal ones examined. These are a ‘quiet’, orderly, focal resorptive degeneration of portions of mainly the left part of the undivided His bundle (Fig. 3) and also of the AV node. The process is interpreted as a first step in the production of the thin, smooth, regular, densely collagen-encased ‘adult’ bundle of older children and adults. There is no associated inflammation, haemorrhage, or massive necrosis. Such orderly cell death is not unusual in morphogenesis: it accompanies digit formation and without it for example all babies would have imperforate ani\textsuperscript{45}. James\textsuperscript{13} speculates that the relatively large foetal His bundle can allow for some loss of (surplus) tissue during the normal postnatal fibrosing process in the central fibrous body and that the resultant ‘adult’ bundle is more efficient in maintaining stable longitudinal conduction than is the large, shaggy, ‘infantile’ bundle—which is electrophysiologically unsafe. The process is postulated to be normal and ubiquitous, to start at or soon after birth, to progress episodically with variation in phase and rate from child to child, and to be more or less complete at about one year of age. James\textsuperscript{13} argues that this critically located process could have a dysrhythmic potential: certainly cell death (at least in the myocardium) releases intracellular potassium and other substances—such as adenosine and other nucleosides and nucleotides—with a
negative chronotropic and inotropic action\textsuperscript{46, 47}; produces local acidosis—which can act on the numerous ganglia and nerve endings in the conduction system; and, with other mechanisms, may depress differentially surviving conduction tissue, and all of these could augment the dysrhythmic potential of episodic hyperexcitability of degenerating pockets of tissue. Some specific electrical events may be: longitudinal dissociation of AV conduction, partial block and abnormal re-entry mechanisms, unifocal ectopic tachycardia, and reciprocating tachycardia beginning in, or recycling through, parts of the His bundle and AV node. Thus by maturing to the 'adult' conduction system—which is highly efficient in maintaining stable longitudinal conduction—the infant heart temporarily becomes somewhat electrophysiologically unsafe. These changes occur in all infant hearts: cot deaths (on this hypothesis) would be the 2 or 3 per 1,000 in which the above hypothesised electrical disturbances occur and prove fatal. By providing an anatomic basis for an enhanced
likelihood of ventricular arrhythmias in the 'normal' infant in the first year of life
is this work provides an alternative to QT prolongation as a model for a cardiac
dconduction role in cot death. It is to be noted that concomitant delayed repolarisation
or other myocardial vulnerability—which would of course compound lethal proclivity especially from 'benign' electrical events hypothesised above—need not be postulated.

Certain facts are immediately supportive of this anomalous conduction model:
(i) ectopic rhythms are documented in infants with for example 'breath-holding' or
apnoeic episodes48; (ii) supraventricular arrhythmias are not uncommon in 'healthy'
babies49; (iii) asystole50 and ventricular fibrillation51 are easily induced in young
mammals; and (iv) the nearly random choice of a cot death from among “eligible”
in Beckwith's6 p.29 term) children—though this is not exclusive to this model.
Contrary evidence is that potentially lethal ventricular arrhythmias are seldom
documented in normal infants28—possibly because only short and infrequent ECG
runs are taken on small samples, possibly because such disturbances are themselves
brief terminating either in quick recovery or sudden death (either way they would
be missed), or possibly because they don’t occur. Without further large scale
monitoring studies and ongoing surveillance on relevant groups of infants to a
standard prospective design, or relevant animal work, additional useful evidence
on this hypothesis is unlikely.

FURTHER TESTING OF THE MODELS

Additional to the above evidence we must consider the following for any general
tory implicating cardiac electrical instability in cot death:
(a) why do long QT interval children rarely die or manifest syncope as early as
the peak cot death age (2 – 4 months)?
(b) why do cot death infants rarely have a history of previous syncopal episodes
given that ventricular arrhythmias in QT prolongation children generally revert
spontaneously the child rarely succumbing to the first attack and sometimes
surviving hundreds?; and
(c) how successful is the general cardiac hypothesis in explaining factors set out
as (5) – (8) in Table 1?

As regards (a), on James's13 findings we would expect a high mortality in long
QT interval syndromes in the first year of life consistent with the dysrhythmic
potential of the anatomic changes described. Some such infants do have documented
arrhythmias or syncope (see above) or related episodes (e.g. those described by
Lipp et al82 and Johansson and Joring53) in the first year, but most do not.
Admittedly, cases may die suddenly in infancy before diagnosis; nevertheless we
must accept that the initial episode is usually after the cot death age. We have no
ready explanation for this.

As regards (b), careful histories will elicit in perhaps 5 per cent of cases6 evidence
of previous suspicious episodes (faints, cyanotic attacks, fits, severe breath-holding
etc.) or overt syncope or collapse4, 6. 8. 9. 54-56—often termed 'near misses'. Though
less common in 'sporadic' than familial cases4, 9, 12—whose aetiology may be dif-
ferent—they are not negligible. Their cause is unknown but usually ascribed to
severe primary respiratory apnoea, an exaggeration of the apnoeic episodes common

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in immature infants\textsuperscript{57} though, as discussed below, other interpretations are possible. Even careful history-taking will underestimate their frequency in cot death infants since many episodes must go unnoticed or unrecorded (especially since they are commonest during sleep) even if due to potentially lethal ventricular arrhythmias e.g. a 9-year-old monitored boy with Romano-Ward syndrome had spells of ventricular tachyarrhythmia/fibrillation during sleep unnoticed by ordinary ward staff and without awakening him\textsuperscript{53}. Nevertheless we must suppose that most cot death infants die during their first serious attack whereas QT prolongation syndrome cases rarely do. Again, we have no ready explanation for this.

As regards (c), we take the relevant points in order.

\textit{Points (5) and (6), Table 1.} The (slight) male excess is unimportant merely patterning the general infant decrement in the male; while the lower birth weight (without obvious smallness for dates) and the evidence of socio-economic disadvantage as measured on the usual parameters and as analysed by single and multi-factor methods\textsuperscript{9, 58} are generally unexceptional compared to most other classes of infant death. We need not therefore explain them specifically on our hypothesis: they would be general to most. Increased prevalence in colder months and in crowded homes producing ‘season’/‘city’ contingency—though without demonstrable time/space epidemcity—is however greater than with relevant comparison groups\textsuperscript{9}. Together with the clinical facts listed under (6) in Table 1, the pathological evidence of respiratory inflammatory infiltration albeit minor, and the classical interpretation of the intrathoracic petechiae (‘Tardieu Spots’)—which on Beckwith’s\textsuperscript{59} evidence may be more dense and widespread than in other infant deaths (but see however Marshall’s\textsuperscript{60} findings)—these have understandably been adduced by adherents to ‘respiratory theory’ schools in their own support. This is reasonable; but we can question any exclusiveness. Reasons, admittedly speculative, can be advanced to show consistency of these findings with a theory based on electrical instability of the heart: (a) viraemia and mild general toxicity could influence the functional behaviour in portions of the AV node and His bundle although the infection itself may be innocuous; (b) excess vagal activity caused by coughing or sneezing (though these are not generally recognised as clinical features of the terminal cot death episode) could in an infant disorganise or disrupt normal AV conduction or sinus pace-making or produce a sudden bradycardia which could compound dysrhythmic potential of the actively changing conduction system; and (c) the documented increased frequency of prolonged apnoeic spells during sleep\textsuperscript{12}—itself a potentially dysrhythmic factor in normal hearts (see (ii) below) and in post-infarct or ischaemic situations\textsuperscript{62, 63}—and with the cardiac impulse originating in an ectopic focus possibly compounding the dysrhythmic potential\textsuperscript{48}. (See also argument below).

\textit{Point (7), Table 1.} The presumption that the infant is asleep at the onset of the fatal episode is much emphasised: certainly it is a common\textsuperscript{6, 9} or even allegedly a universal finding\textsuperscript{6}. With the typical age distribution (see below) it characterises the syndrome and these two data powerfully and independently discriminate cot death from other causes of infant death. Any successful hypothesis must explain them.

Reasoning inductively from the known physiological changes during sleep so as to discriminate between likely explanatory cot death hypotheses is necessary but
Unfortunately unlikely to be conclusive due to their pleiotropic and fundamental nature. On the sudden cardiac death model we may note the following phenomena during sleep:

(i) the concomitant decrease in blood pressure and tissue pH\(^50\) may trigger abnormal activity in the infant’s (unstable) conduction system;

(ii) the decrease in heart rate may \textit{per se} induce ventricular aberrant rhythms in a normal myocardium\(^64,65\) and \textit{a fortiori} in a vulnerable one, or permit the emergence of escape rhythms by ectopic pace-making foci;

(iii) the increased accelerative heart rate response to stimuli\(^66\) may precipitate abnormal cardiac rhythm if there is a pre-existing basic conduction vulnerability;

(iv) asphyxia—as frequently postulated in cot death either by external\(^67\) or internal means e.g. nasal blockage in obligate nose breathers\(^68\), or apnoea—as documented in ‘rapid eye movement’ (REM) sleep and with respiratory tract inflammation\(^12\)—could if not reversed clearly cause sudden death consonant with cot death findings. Beckwith\(^6\) considers that apnoea “with or without myotonic occlusion of the upper airway” could be the “final common pathway” leading to cot death; and others\(^11\) suggest that failure to interrupt a prolonged apnoeic spell, however produced, is crucial. These are reasonable assertions; what is not known, since no terminal episode has been fully monitored in cot death, is whether the apnoea proves fatal \textit{directly} through respiratory failure or \textit{indirectly} through some concomitant lethal mechanism. We have already mentioned the dysrhythmic potential of the concomitant bradycardia (though in monitored prolonged apnoeic spells in monkeys ended by interventionary resuscitation French \textit{et al}\(^11\) failed to demonstrate a lethal ventricular rhythm on tachometry); in fact in the so called ‘diving reflex’—a complex pattern of apnoea, bradycardia, and vasoconstriction by which diving animals conserve oxygen for vital centres and which can be demonstrated in humans\(^69\)—vagally mediated bradycardia, often severe, is an early and marked finding. This reflex can be easily induced in young monkeys\(^11\) and in man\(^70\) by cold and/or wet non-occlusive facial stimuli; and it may be relevant that mucus on the face is common in cot death, exposure to low ambient temperatures was marked in Steele’s\(^65\) first Ontario study, in all surveys cases are commoner in colder rather than warmer months, and in hotter surveyed areas e.g. Israel\(^2,3\) and California\(^18\) the incidence (respectively 0.3 – 0.73, and 1.55, per 1,000 live births) is less than that from most other comparable North American and European studies\(^9\). Furthermore, though ventricular arrhythmias in QT prolongation syndromes are classically triggered by emotional shock—which in fact may itself prove lethal in ‘healthy’ adults\(^71\) and which can \textit{per se} produce the ‘diving reflex’ changes in man and certain animals\(^72\)—syncope and death while bathing are described in these syndromes\(^39,73\) perhaps due to the ‘diving reflex’ changes and an electrically vulnerable heart. Even our own material discloses three instances: a 9-year-old boy with Romano-Ward syndrome and AV dissociation\(^74\) had his first syncopal attack in an outdoor unheated swimming pool in Castlerock, Co. Antrim; Sandra C., an unequivocal Romano-Ward case\(^27\), had her first attack aged 7 years in a YWCA swimming pool; while Paul de la C, with severe cardio-auditory syndrome\(^35\) had his first, and 4 years later his fatal attack, while bathing at sea;
repeated self-limiting attacks of ventricular tachyarrhythmia/fibrillation with syncope have been described in an otherwise symptomless child exclusively on sudden arousal from sleep by auditory stimuli. Resting ECG showed anomalous repolarisation changes (marked U waves) but only equivocal QT lengthening. The auditory stimulus e.g. alarm clock, produced QT prolongation, ventricular premature beats and ventricular fibrillation. In QT prolongation syndromes bradyarrhythmias and AV junctional rhythms and ventricular tachyarrhythmias without patient arousal have been documented; and monitoring would undoubtedly disclose dysrhythmias more frequently. We have analysed monitored tracings in three cases and in one (Sandra C) further QT prolongation and therefore enhanced dysrhythmic potential, during sleep was marked (Table IV). (This could either be due to sleep per se or as a circadian phenomenon: either would accord with cot death data where most deaths are during the night as well as in sleeping infants). These (i)–(v) above and associated data could, on the cardiac hypothesis, imply an important role for sleep in cot death.

### TABLE IV

**Romano-Ward Syndrome (QT Prolongation without Deafness)**

_Degree of QT Prolongation while Asleep and Awake: ECG Tracings over Four Consecutive Days (Sandra C., age 8 years)_

| Day, and time of day (24 hour clock)** | Sleep status |
|---------------------------------------|--------------|
| Day 1                                 |              |
| 1700                                 | Awake        |
| Day 2                                 |              |
| 0100                                 | Awake        |
| Day 3                                 |              |
| 1100                                 | Awake        |
| Day 4                                 |              |
| 0015                                 | Asleep       |
| Mean of averages: asleep=11.9; awake=6.3  |              |

* See Table II, foot-note.

** Tracings taken in the domestic situation in USA by a relative of the patient: this explains the irregular time intervals and numbers of complexes measured.
Point (8) Table 1. The age distribution characterises cot death and is grossly disparate to the negative exponential of infant mortality generally where most deaths are earliest after birth. Even allowing for an artifactual underestimate in the first month of life\textsuperscript{a}, \textsuperscript{b} cot death seems commonest during the 2–4 month period and is rare after 6 months. No simple explanation for this age distribution is possible because of the number and spectrum of contingency factors producing the critical combination presumed to produce lethality, but on the cardiac hypothesis the His bundle and AV nodal changes in the first year are described\textsuperscript{13}, \textsuperscript{42}, \textsuperscript{43} as being least marked in the neonatal period (when cot death mortality is lowest) while the same holds for the bradycardia in the ‘diving reflex’\textsuperscript{69} and for sleep-apnoea spells in immature babies\textsuperscript{12}. The age distribution would appear discordant with obligate nose-breathing-induced apnoea\textsuperscript{68} which is present from birth and may in fact disappear at 3–5 weeks\textsuperscript{76} rather than at 5–6 months i.e. much earlier than the cot death peak incidence. Further argument is on present knowledge speculation and unhelpful to hypothesis discrimination.

**CONCLUSION**

In a rationale of this type where inference is inductive and no precise probability can be attached to rejection or acceptance of this or any other hypothesis of cot death put under test, only general likelihoods are possible. Individual preference or experience therefore weigh disproportionately: thus virologists espouse virological theories; immunologists immunological theories; cardiologists cardiological theories. As regards a theory based on electrical instability of the heart we can say that on the evidence it appears neither more nor less likely than a respiratory one—which currently finds general support. All the facts of cot death adduced in favour of the latter may, on the evidence of this article, equally favour the former, and since the logic is identical scientists should not reject (or accept) one at the expense of the other. More data are required from many disciplines before discrimination can be legitimately made, but describing these is beyond the scope of this paper. Epidemiologists and cardiologists are no less human than are other scientists and so we will permit ourselves to say that since cot death infants typically die suddenly and silently without external insult or discernible autopsy anomaly ‘causing’ death, the credentials of an alternative theory would have to be strong before one should dismiss a cardiac cause for the ‘final common pathway of death’.

**SUMMARY**

The cause of sudden unexpected death in infants (‘cot death’) is unknown. This article reviews extensively evidence on the hypothesis that an electrical instability of the heart is a component in the ‘final common pathway of death’ in a significant number of cases. The conclusion is drawn that on available data, much from our own previous work, this hypothesis is no less likely than others currently in favour, particularly those in which cot death is ascribed to respiratory causes. Emphasis is placed on the nature of the evidence and the need for caution in its interpretation.
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