Sudden Infant Death Syndrome (SIDS): An Integration of Ontogenetic Pathologic, Physiologic and Epidemiologic Factors

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Abstract

Sudden Infant Death Syndrome (SIDS) is the most prevalent cause of death in infants between one and six months of age. Epidemiologic pathologic and physiologic data suggest the mechanism of SIDS is complex, characterized by interactions at many levels of the neuroaxis, between the organism and the environment and spanning both pre- and postnatal life. Details of one such model are presented here. The model is based on 1) systematic physiological studies of two groups of infants at statistically increased risk for SIDS: subsequent siblings and near-miss for SIDS. 2) An epidemiological study of approximately 800 SIDS in Los Angeles County, and 3) clinical perinatal data and fetal heart rate recordings of a subset of these 800 SIDS. Data from other investigators are incorporated as well.

Factors unique to SIDS are: Age of death, association with sleep, seasonal distribution and increased risk for the second born. The proposed core deficit consists of mild hypoxia, sustained during pre- and postnatal life, for which the majority of infants successfully compensate. Previously not fully appreciated changes between one and three months of age in development and integration of the central nervous system, give rise to increased vulnerability to endogenous and exogenous deleterious influences at this time. Altered sleep state distributions consisting of an increase in Quiet sleep (QS) and a decrease in Active sleep (AS), are temporally and functionally associated with alterations in respiratory and cardiac regulation. Some infants pass through this age period sooner, at a faster rate and with less reserve and thus are more susceptible to additional stress. Although the etiology of the core deficit is unknown, many factors can potentiate an existing mild hypoxia. One such potential mechanism is the influence of ambient pollutants. Other mild deficiencies of varied origin operate as predisposing factors to risk or precipitating events causing death. A large number of infants would be expected to be stressed but only an unfortunate intersection of prior vulnerability and one or more aggravating conditions encountered during a discrete limited age of risk would result in death. Many nonspecific factors associated with SIDS are identical to those associated with perinatal morbidity and mortality. Programs aimed at reducing the latter should substantially reduce the rate of SIDS as well.

Introduction

Sudden Infant Death Syndrome (SIDS), the most prevalent cause of death between one and six months of age (Beckwith 1973), has baffled physicians and laymen alike. An ostensibly normal infant suddenly dies without identifiable prodromal clues or an adequate pathological explanation. During the 1970's the U. S. Department of Health, Education and Welfare began a vigorous effort to identify the cause of SIDS and those infants at increased risk. Ten years have passed and, while our knowledge about this syndrome has advanced, we still do not know the cause nor the means for prevention.

At a time when no physiological data were available, epidemiological and pathological findings constituted the basis for a number of hypotheses. One striking aspect of each proposed mechanism, however, is the failure of a large number of cases to fit the proposed models. At present, a small number of infants has been carefully studied prior to death, and no one single mechanism can be discerned that can account for SIDS. Available data support a complex model, characterized by interactions at many levels of the neuroaxis, between the organism and the environment and spanning both pre- and postnatal life. This conceptualization is not new, Bergman et al (1970), pioneers in the study of SIDS, suspected an interaction of several factors and McGinty and Harper (1974) described a number of conditions that could contribute to SIDS. In the same year, Milligan (1974) wrote: "The consensus view is that throughout life SIDS infants are essentially healthy; they die while passing through a developmental state of physiological vulnerability. Some critical combination of extrinsic and..."
intrinsic factors proves lethal...". During the past decade numerous single factors have been proposed and rejected. A model postulating interactioning factors, however, remains appealing and consistent with available data. It is the objective of this paper to present such a model, based on an extensive body of data obtained between 1972 and 1980 in infants and kittens.

The first study consisted of a normal control group of infants (n=25), selected because of absence of maternal disease and family history of SIDS, a group of subsequent siblings (n=26) known to be at a 4 to 6 times increased risk for SIDS (Froggatt et al 1971, Peterson et al 1980), and a group of infants with unexplained apnea designated as near-miss for SIDS (n=26) (Gunteroth 1977). Subjects in the first two groups were identified prenatally and monitored during the last trimester of pregnancy, the first week of life and at monthly intervals thereafter until the age of six months. Near-miss for SIDS were monitored at variable intervals after the first apneic episode. Twelve-hour polygraphic recordings of cardiovascular variables and sleep from mothers and infants were submitted to computer and visual analyses and constitute the physiological data base. Clinical and developmental examinations were continued up to one year of age in all infants.

In a second study, 54 infants born at Los Angeles County-University of Southern California (LAC/USC) Medical Center who subsequently died of SIDS were identified. The perinatal clinical records of these infants were matched with those of infants born during the same week, of similar gestational age and from the same socioeconomic background (Hoppenbrouwers et al 1977). The fetal heart rate (FHR) recordings of 20 SIDS were compared with those from matched controls (Hoppenbrouwers et al 1978).

In a third study, the total incidence of SIDS in Los Angeles County between 1974 and 1977 was examined in relation to daily levels of air pollutants, temperature and barometric pressure (Hoppenbrouwers et al 1981).

Finally, studies in kittens were designed to examine the influence of altered ambient oxygen and temperature upon sleep states and respiratory behavior (McGinty et al 1980). Notably among these is the study by Baker and McGinty (1977) illustrating the physiological and behavioral adjustments to low ambient oxygen in freely moving kittens. Data from other investigators have been included.

**Study results**

Despite the comparability of controls and subsequent siblings in study group characteristics (Table I) and monitoring procedures, a number of significant differences were observed in the polygraphic tracings of these two groups during the first half year of life. With one exception, infants exhibited very similar sleep and waking patterns: subsequent siblings once asleep were significantly more likely to remain asleep than control infants (Hoppenbrouwers et al 1980). The most striking differences were observed in respiratory behavior. Contrary to expectations, subsequent siblings exhibited an increase in respiratory rates and an associated decrease in apnea counts (Figs. 1 and 2).

Subsequent siblings exhibited higher respiratory rates in all states at three months of age. The incidence of total breathing pauses between two and five seconds and six to nine seconds was reduced in subsequent siblings as well (Hoppenbrouwers et al 1980). Subsequent siblings also exhibited greater variability in breathing although significant differences were restricted to quiet sleep (QS) variability at one week of age and QS and indeterminate (IN) variability at three months of age. The tracings of near-miss infants were not significantly different from those of age and sex matched controls although there was a tendency toward increased respiratory rates and decreased apnea counts in a number of these infants as well (Hodgman et al 1978).

In a second study, 54 infants born at Los Angeles County between 1974 and 1977 was examined in relation to daily levels of air pollutants, temperature and barometric pressure (Hoppenbrouwers et al 1981). The fetal heart rate (FHR) recordings of 20 SIDS were compared with those from matched controls (Hoppenbrouwers et al 1978).

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**Table I. Characteristics of the study groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>Subsequent Siblings</th>
</tr>
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<tbody>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.10</td>
<td>26.45</td>
</tr>
<tr>
<td>SD</td>
<td>3.64</td>
<td>5.06</td>
</tr>
<tr>
<td>Maternal race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Asian American</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mexican American</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.64</td>
<td>3.13</td>
</tr>
<tr>
<td>SD</td>
<td>1.43</td>
<td>0.90</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>2.48</td>
<td>1.92</td>
</tr>
<tr>
<td>SD</td>
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</tr>
<tr>
<td>Birth weight (gm)</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3575</td>
<td>3594</td>
</tr>
<tr>
<td>SD</td>
<td>465</td>
<td>496</td>
</tr>
<tr>
<td>Range</td>
<td>2890-4550</td>
<td>2821-4593</td>
</tr>
<tr>
<td>Gestational age</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.78</td>
<td>40.06</td>
</tr>
<tr>
<td>SD</td>
<td>1.64</td>
<td>1.31</td>
</tr>
<tr>
<td>Range</td>
<td>37-44</td>
<td>38-42</td>
</tr>
<tr>
<td>Apgar at 1 minute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>8.52</td>
<td>8.14</td>
</tr>
<tr>
<td>SD</td>
<td>1.64</td>
<td>1.04</td>
</tr>
<tr>
<td>Apgar at 5 minutes</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.26</td>
<td>9.04</td>
</tr>
<tr>
<td>SD</td>
<td>0.54</td>
<td>1.04</td>
</tr>
</tbody>
</table>
those of Guilleminault et al (1980). The latter authors described instead an increased incidence of obstructive apnea in risk infants, again a finding not substantiated by our own data nor by those of Monod et al (1976). These discrepancies can be partially explained by the differences in measurements and the setting and duration of recording. In particular, the discrepancy in the near-miss data may be reconciled by the fact that monitoring in some of these laboratories occurred immediately following the near-miss event. These tracings, therefore, captured an acute phase of the illness whereas our tracings may well reflect a successful compensatory effort.

Heart rate and variability were also found to be different (Harper et al 1978). Subsequent siblings showed a higher heart rate at three months of age, particularly in the waking state. Heart rate in both subsequent siblings and controls declined after two months in every state; however, the risk infants lagged in the two to three months' decline seen in the controls. Heart rate variability during wakefulness was reduced in subsequent siblings compared to controls during the first two months of life. In near-miss infants heart rates also tended to be elevated compared to controls (Harper et al 1978).

The data are consistent with the hypothesis that risk infants were successfully compensating for a mild chronic hypoxic deficit. Indeed, in the study of Brück et al (1962) increased QS respiratory rates were observed in infants with congenital heart disease and documented hypoxemia. Recently QS respiratory rates were shown to increase following administration of 17 percent oxygen ($O_2$) to premature infants, whereas active sleep (AS) rates decreased (Rigatto 1979). Finally, kittens recorded under conditions of 10 percent ambient $O_2$ exhibited an increase in respiratory rates and a decrease in apnea (Baker and McGinty 1977).

The evidence that chronic mild hypoxia preceded death of SIDS is based on detailed studies of tissues obtained at autopsy. Naeye (1973) reported that approximately 60 percent of the SIDS infants exhibited medial muscle hypertrophy of the pulmonary arterioles, a finding confirmed by Williams et al (1979), but not found by Kendeel and Ferris (1977). A similar percentage had an increase in the weight of the right ventricle, persistent extramedullary hematopoiesis in the liver and retention of brown fat (Naeye 1980). Valdes-Dapena (1979) also found extramedullary hematopoiesis, but reported increased brown fat retention only in SIDS older than five months of age (Valdes-Dapena et al 1976), and no differences between SIDS and controls in weight of the right ventricle (Valdes-Dapena 1980). Carotid body abnormalities have also been observed (Naeye 1976, Cole et al 1977). As pointed out
by Cole et al (1977), it is unlikely that the observed degranulation in the carotid bodies from SIDS resulted from hypoxia because chronically hypoxic infants did not exhibit such degranulation. These authors favor the hypothesis of a chronic defect in the chemoreceptor cells of the carotid body, not primarily caused by hypoxia. Despite the discrepancies reported here, evidence is mounting that mild chronic hypoxia preced­ed SIDS. For the purpose of this model, hypoxia is designated as a core deficit.

Fetal and neonatal heart rates are shown in Figure 3. Comparisons of average fetal heart rates (FHR) during the last trimester of gestation did not reveal any statistically significant differences. The overall FHR variability in the siblings, however, was significantly elevated compared to control fetuses. The mean variability was “moderate” in controls with a difference of 6 – 10 beats per minute (bpm) according to Hon’s (1968) classification and “increased” in subsequent siblings (11 – 25 bpm). Although the number of FHR accelerations was not significantly different in the risk fetuses compared to the controls, an elevated number of accelerations was followed by heart rates below 120 bpm in siblings (Fig. 4). Careful scrutiny of individual FHR patterns indicated that the sibling fetuses were more likely to exhibit short episodes of bradycardia (> 3 minutes) although this pattern was not exclusively seen in this risk group (Hoppenbrouwers et al 1979, 1981). These differences must be interpreted cautiously. First, while maternal sleep stage distribution reflected a degree of insomnia characteristic of laboratory studies of pregnancy, mothers of SIDS exhibited an even higher degree of sleep disturbance (Hoppenbrouwers et al 1979). The findings in the fetus may therefore be an epiphenomenon of this maternal difference. Second, there was an uneven distribution of males and females in the study, with a preponderance of males in the control group. The traces were selected a posteriori on the basis of signal quality and therefore this imbalance is a puzzling finding.

Study group differences may also reflect physiopathologic differences between these fetal populations. Manifestations of increased lability such as enhanced beat-to-beat variability and increased incidence of bradycardia have been associated with intrauterine challenges, in particular hypoxia (Copher and Huber 1967, Hammacher et al 1968). The acceleration-deceleration pattern in siblings also suggests a degree of increased lability, which may reflect a mild hypoxic deficit. Whereas these are the first published data describing FHR patterns in infants at risk for SIDS, other reports in the literature suggest that intrauterine and perinatal factors bear on the genesis of SIDS (Vales-Dapena 1980). Some isolated physiologic tracings obtained in the neonatal period from infants who subsequently died of SIDS deviated from tracings obtained from normal controls (Salk et al 1974, McNamara 1976, Thoman et al 1977, Lipsitt et al 1979). Naeye (1977) found in SIDS an increased frequency of acute funisitis, acute chorioamnionitis, lymphocyte infiltration of the decidua and macrophages in the fetal membranes, all suggesting a less than optimal intrauterine environment.

We compared the intrapartum fetal heart tracings of 20 in-
Fetal Heart Rate Accelerations

Fig. 4 Examples of FHR accelerations. FHR in excess of 150 bpm lasting ≥10 seconds can be seen in each tracing. Subsequent decelerations to rates below 120 bpm were observed in A, B, E and F. This pattern was more common in tracings of subsequent siblings than in those from control fetuses.

fants that died of SIDS and 20 matched control infants, both drawn from a population at increased obstetrical risk (Hoppenbrouwers et al 1978). The composition of the SIDS and control group was quite comparable in terms of measured characteristics including gravidity, parity, Apgar scores, duration of tracings and the number of uterine contractions (Table II). Four infants in each group were delivered via Caesarean section and spontaneous and instrumental deliveries were comparable. FHR patterns examined included accelerations, early decelerations, variable decelerations (VD) and late decelerations (LD). Comparisons between the mean and median number of these patterns in each group, regardless of stages of labor, did not reveal any statistically significant differences. The incidence of both decreased and increased baseline variability was similar. There were three infants with bradycardic FHR levels (≥10 minutes) who all belonged to the SIDS group. Although FHR levels with both VD and LD patterns were seen in approximately half of the infants in each group, it should be emphasized that the SIDS and the control group could not be differentiated. It has been shown that the fetus manifests a recurrent quiet-active cycle in utero, comparable to the AS-QS cycle in the newborn infant (Sterman and Hoppenbrouwers 1977). Reported data suggest that AS as well as wakefulness affords the young organism more protection against hypoxia than quiet sleep (Baker and McGinty 1977). Labor, representing strong central nervous system activation comparable to wakefulness, could actually conceal manifestations of mild while enhancing those of severe hypoxia. Another interpretation of the data is that infants who subsequently died were not hypoxic before death but once without the protection of the utero-placental unit, suffered mild hypoxia. This interpretation, however, is not supported by FHR findings in siblings during maternal sleep. The relative increased incidence of bradycardia in the sibling fetuses is particularly interesting in light of the three cases with prolonged bradycardia seen in the intrapartum recordings of only the SIDS infants.

Charts from 50 infants born in our hospital who died of SIDS were scrutinized and compared with those of carefully matched controls. These data are summarized in Table III, together with data from Naeye et al (1976). These findings and reports from other investigators (Kulkarni et al 1978, Grether 1980, Valdes-Dapena 1980) indicate that the infant at risk cannot be reliably identified in the pre- or postnatal period. They confirm, however, that factors contributing to perinatal high risk status are similar to those associated with risk for SIDS. Notable among these are age of the mother, birth weight, short interpregnancy interval, lack of prenatal care and socioeconomic class (Valdes-Dapena 1968, Bergman et al 1972, Kraus and Borhani 1972). Maternal smoking was also found to increase the risk for SIDS (Bergman 1976, Lewak 1979).

Several epidemiological studies of SIDS refer to its seasonal incidence (Peterson 1966, Kraus et al 1967, Froggatt et al 1971, Bergman et al 1972, Borhani et al 1973, Bonser 1978). In the Western hemisphere the incidence increases in October, peaks in December and January, remains relatively high until the end of May, but then declines sharply in June and remains low through September. Year-to-year variations have been noted (Peterson 1972), but this pattern is well established. Since levels of environmental pollutants also show seasonal patterns, the study of the relationship between SIDS and
Table II  Characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gravida</th>
<th>Parity</th>
<th>Gestational Age</th>
<th>Birth Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDS</td>
<td>Mean</td>
<td>21.8</td>
<td>2.2</td>
<td>1.2</td>
<td>39.3</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.8</td>
<td>1.7</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>17-38</td>
<td>1-7</td>
<td>0.6</td>
<td>34-42</td>
</tr>
<tr>
<td>Control</td>
<td>Mean</td>
<td>24.1</td>
<td>2.5*</td>
<td>1.1</td>
<td>39.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>8.6</td>
<td>1.9</td>
<td>1.7</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
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<td>16-41</td>
<td>1-7</td>
<td>0.6</td>
<td>36-42</td>
</tr>
</tbody>
</table>

* One subject was excluded as significant outlier.

Table III  Infants and maternal factors in SIDS victims and matched controls

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>SIDS (n = 54)</th>
<th>Controls (n = 54)</th>
<th>p</th>
<th>SIDS (n = 125)</th>
<th>Controls (n = 375)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 19.9 yrs.</td>
<td>19 (35)*</td>
<td>12 (22)</td>
<td>NS</td>
<td>44 (35)</td>
<td>71 (19)</td>
<td>.001</td>
</tr>
<tr>
<td>Married</td>
<td>34 (63)</td>
<td>37 (70)</td>
<td>NS</td>
<td>85 (68)</td>
<td>260 (69)</td>
<td>NS</td>
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<tr>
<td>Single</td>
<td>17 (31)</td>
<td>14 (26)</td>
<td>NS</td>
<td>25 (20)</td>
<td>60 (16)</td>
<td>.01</td>
</tr>
<tr>
<td>Divorced</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>NS</td>
<td>15 (12)</td>
<td>53 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Prenatal visits</td>
<td>13 (38)</td>
<td>7 (21)</td>
<td>NS</td>
<td>33 (20)</td>
<td>60 (10)</td>
<td>.02</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>14 (26)</td>
<td>11 (20)</td>
<td>NS</td>
<td>51 (14)</td>
<td>101 (27)</td>
<td>.005</td>
</tr>
<tr>
<td>&lt; 10 gm/100 ml</td>
<td>5 (15)</td>
<td>7 (19)</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>7 (13)</td>
<td>2 (4)</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>over 140/90</td>
<td>7 (13)</td>
<td>8 (15)</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Venereal disease</td>
<td>35 (65)*</td>
<td>32 (59)</td>
<td>NS</td>
<td>84 (67)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mild Toxemia</td>
<td>3 (6)</td>
<td>0</td>
<td>NS</td>
<td>4 (3)</td>
<td>0</td>
<td>.025</td>
</tr>
<tr>
<td>Male</td>
<td>23 (43)</td>
<td>23 (43)</td>
<td>NS</td>
<td>19 (15)</td>
<td>26 (7)</td>
<td>.01</td>
</tr>
<tr>
<td>Positive Resp. pressure</td>
<td>10 (16)</td>
<td>16 (13)</td>
<td>22 (6)</td>
<td>.02</td>
<td></td>
<td></td>
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<tr>
<td>Resuscitation open oxygen</td>
<td>13 (24)</td>
<td>34 (27)</td>
<td>56 (15)</td>
<td>.005</td>
<td></td>
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<tr>
<td>Respiratory Distress Syn.</td>
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<td>0</td>
<td>NS</td>
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*( ) Percentage
Table III (continued)  Infant and maternal factors in SIDS victims and matched controls

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>LAC Study</th>
<th>Naeye et al 1976</th>
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<tbody>
<tr>
<td></td>
<td>SIDS (n=54)</td>
<td>Controls (n=54)</td>
</tr>
<tr>
<td>Received antibiotics</td>
<td>4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Feeding by gavage</td>
<td>5 (9)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>1st bottle feeding 4th day or later</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>9 (17)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Maximum serum bilirubin level 12 mg/100 ml</td>
<td>1 (4)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Abnormal Moro reflex</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Deformities</td>
<td>2 (4)</td>
<td>(2)</td>
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</tbody>
</table>

DEATHS (W)

TEMP

OZONE

CO

BP

Fig. 5  Plot of daily incidence of SIDS in Los Angeles County between January 1974 and December 1977. Abscissa: each increment represents 70 days, totaling 1460 days; ordinate: number of SIDS per day ranges between 0 and 4. Average daily temperature (range 47° to 86° F). Barometric pressure (BP) ranged from 29.54 to 30.27 inches of mercury. Notice that low temperature during the winter months tended to coincide with an increase in SIDS. Ozone levels were low during those months in contrast to levels of CO and BP, which were high.
pollutants seemed indicated. Investigators who have documented increased mortality and morbidity during episodes of elevated pollution in large metropolitan areas were primarily interested in the acute effects upon patients with cardiovascular complaints (Carnow et al 1969, Glasser and Greenberg 1971, Buechley et al 1973). Current knowledge of SIDS suggests that predisposing factors that lead to increased risk should be distinguished from the acute events that lead to death. Thus, acute stress from elevated levels of environmental pollutants may be less important than more prolonged exposure to modest levels. This conceptual framework led to a re-examination of the relationship between SIDS and environmental variables. To establish a relationship between any two variables, a correlation matrix is frequently obtained. This procedure is not suitable when the presence of a lag time between environmental events and mortality is suspected, as is the case here. Since both SIDS and environmental variables are characterized by seasonal and thus periodic variation, time series analyses such as auto and cross spectral techniques are uniquely suited to demonstrate a temporal relationship (Harper et al 1974, Cech et al 1977). Day-to-day mean levels of sulphur dioxide (SO₂), nitrous dioxide (NO₂), carbon monoxide (CO), hydrocarbons (HC) and ozone (O₃), and monthly lead levels were obtained. Figure 5 illustrates the daily rate of SIDS between 1974 and 1977, together with the data of daily CO, O₃ and meteorologic variables. The year-to-year seasonal variation in all variables is clearly seen in this figure. The troughs in temperature generally coincided with increased incidence of SIDS. Barometric pressure appeared to have an inverse relationship to temperature and therefore a positive one to SIDS. Visual inspection of the data in Fig. 5 reveals a lag in the peak levels of CO and the peak incidence of SIDS. Ozone levels fluctuated also but cycles appeared to be in phase with those of increased temperature, and therefore negatively correlated with SIDS. Auto spectra confirmed the seasonal peak of SIDS and the seasonal elevation in environ-
mental pollutants (Fig. 6). Not shown in this figure but apparent in Figure 5 was a dominant frequency also once per year in temperature, barometric pressure and ozone. An inspection of the coherence plots (Fig. 6) shows that at this yearly frequency SIDS was highly correlated (> .80) with CO, SO₂ and HC, and to a lesser degree with NO₂. The corresponding phase plots show a remarkable similarity among these pollutants at the yearly frequency. SIDS and these pollutants were approximately 50 degrees out of phase, with SIDS lagging by seven weeks. A rise in barometric pressure preceded a rise in SIDS by approximately one month. These observations explain why other investigators who were seeking an acute effect of pollution in the day of death failed to identify a relationship (Greenberg et al 1973). Similarly, the seasonal increase in barometric pressure occurred one month earlier than the peak incidence of SIDS, which explains why this relationship was not identified (Heany and McIntire 1979).

While the statistical relationship established here does not prove a causal relationship, theoretical considerations and evidence from studies in animals and man support such a hypothesis. Hemoglobin has an approximately 245 times greater affinity to CO (Aronow 1978); therefore, CO displaces O₂ from hemoglobin and decreases the amount of O₂ available to the tissues (Aronow 1978, Kurt et al 1978). Commonly occurring levels of ambient CO can cause significant acute physiological changes (Aronow et al 1972). An increase in fetal carboxyhemoglobin has been reported during maternal smoking (Longo 1977, Roels et al 1978), establishing that CO can cross the placenta and affect the fetus. Additional support for a functional relationship is derived from findings that the SIDS infants exposed to higher levels of pollutants for longer time periods died at a younger age (Hoppenbrouwers et al 1981).

In this study, the effects of temperature and pollution were confounded. Not only has incidence of SIDS been consistently higher in winter, but also it has been higher in communities with large seasonal temperature changes compared to those with small seasonal variations (Kraus et al 1967, Valdes-Dapena 1967). While additional studies in contrasting geographic locations would be useful to elucidate the contributions of temperature and ambient pollutants, the role of the latter, while not essential for occurrence of SIDS, cannot be summarily dismissed.

Summary of the model

The core deficit consists of mild hypoxia. This usually elicits successful compensatory behavior but over a period of time may render the infant more vulnerable to other risk conditions. The core deficit is mild, and established as a result of influences during pre- and postnatal life. These influences include conditions in utero, mild perinatal insults, premature delivery, and postnatal environmental conditions. Successful compensatory behavior in an infant may be challenged by a number of aggravating conditions each of which alone, or in combination, can trigger decompensation resulting in death. Such an outcome is extremely rare, but the risk increases when the vulnerable infant enters a rather discrete period between one and four months of age. This is the time of integration of functional systems. It marks the end of the grace period of maternal immunological protection and is characterized by changing regulation of sleep organization and functional interaction with the environment. These profound alterations create instability and an organism which transiently can be more easily affected by internal or external influences. Finally, the model postulates a structural and functional "overshoot" in the development of forebrain areas as a compensatory response to an oxygen deficit. This accelerated maturational responsibility for a transient exaggerated inhibitory influence upon brainstem respiratory centers and for the elaboration of QS.

Mild deficiencies of varied origin as well as successful compensation are central to this model. A large number of infants would be expected to encounter challenges. Only an unfortunate intersection of prior vulnerability and one or more aggravating conditions encountered during a discrete limited age of risk would result in death. Evidence of mild hypoxia need not be discernable at autopsy if the infant has successfully compensated for the hypoxic deficit but has been compromised by an abnormal response pattern which produces little pathological evidence such as altered chemoreceptor sensitivity or altered thermal control. The abnormal response pattern should predict which aggravating condition would constitute the greatest challenge to an individual infant.

Details of the model

A. Age of risk

Few variables that have been associated with SIDS bear an exclusive relationship to SIDS. Age at risk is a notable exception and any model for SIDS must take this into account (Fig. 7). In Los Angeles County between 1974 and 1977, more than half of the deaths occurred between one and three months of age, with the highest incidence at eight and nine weeks, as reported by others (Beckwith 1973, Kraus and Borhani 1972). Infants are clearly at reduced risk prior to one month of age and after six months.

One characteristic of normal functional maturation not previously stressed is the non-monotonic development of a number of physiological, immunological, metabolic and hematological variables (Fig. 8a and 8b). Data were derived from our own studies and those of other investigators. Inspection of developmental curves reveals that the time between four and fifteen weeks of age is a unique period. In some functions only the rate of maturation changes, as evidenced by fetal hemoglobin and respiratory rates during sleep. In other functions a complete reversal in direction takes place. Thus, heart rates increased up to one month of age and then began to decrease. An opposite trend was observed in EEG activity between 12 and 15 Hz. Motility in QS also exhibited a non-monotonic trend. These changes were not necessarily in phase. Beyond four months of age a relative stability ensued.
Food intake patterns begin to change in association with the transition from polyphasic sleep-wakefulness organization to a diurnal sleep-wakefulness pattern (Kleitman and Engelman 1953, Sterman and Hoppenbrouwers 1972). From four months of age onward considerable stability in function is observed.

These non-monotonic changes in functional systems suggest analogous non-monotonic changes in responses to specific stimuli. A pertinent example from animal studies is reported by Jilek et al (1966), where altitude hypoxia caused a higher degree of CNS acidity in 12-day-old rats as compared to either younger or older ones. Prenatal and postnatal morphologic changes are non-monotonic as well (Dobbing and Sands 1973). One growth spurt occurs between 32 and 36 weeks of gestation and a second one from one to five months of age, coinciding with the time of highest risk for SIDS.

Designation of discrete functional developmental phases should encompass both prenatal life and early infancy. In utero, both somatic and autonomic systems show evidence of activity, albeit with altered stimulus thresholds (Dawes 1973). Immediately after birth, despite evidence that the infant responds to its environment (Lipsitt 1977), stimulus-response patterns exhibit a high degree of predictability. From one month of age on, a new period where functional system integration appears to dominate, is reached. Reflexive behavior is replaced with increasingly purposeful interaction between infant and environment. This is also evidenced by the emergence of circadian influences upon autonomic functions.

![Age at Death: Sids vs Other Natural Causes of Infant Death](California, 1976-1978)

![Fig. 7 Age at death of SIDS compared to deaths from other natural causes. Courtesy Grether 1980](https://example.com/fig7.png)

![Fig. 8a Schematic representation of a number of physiological variables during QS. Note the non-monotonic rate of change](https://example.com/fig8a.png)

![Fig. 8b Non-monotonic changes in hematological and metabolic measures](https://example.com/fig8b.png)
established and behaviorally the infant begins to exert more and more control over its environment. Vulnerability to outside deleterious influences tends to increase in periods of rapid change. This rule applies for instance in the first trimester during organogenesis when fetal morphology changes rapidly and is easily compromised by toxic agents (Jilek et al 1966). It is quite likely that a system is also vulnerable when its physiologic and functional characteristics change rapidly, as in the period between 1 and 3 months of age.

B. Rate of maturation

Siblings during this 1 – 3 months age period developed at a similar rate as matched control infants except in two instances where they showed a transient acceleration which was followed by a deceleration. Siblings exhibited evidence of a circadian influence upon respiratory and heart rates earlier than control infants (Hoppenbrouwers 1980). In the development of the EEG between 4 and 8 weeks, siblings showed an accelerated increment in power of 12 – 15 Hz activity during QS and 4 – 7 Hz activity during AS (Sterman et al 1979). It should be emphasized that premature infants who are challenged to function at a more mature level develop faster in some respects and are at increased risk for SIDS (Beckwith 1973). A few recent reports suggest a developmental model in which a physiologic deficit can bring about a transient acceleration in maturation (Hollenberg et al 1976, Gould et al 1971, Gluck 1977, Minkowski 1978). An abnormal stimulus may upset the normal developmental schedule and transiently cause an “overshoot” in some functional systems. This may be initially adaptive, but ultimately cause a depletion of the infant’s reserve. It is tempting to speculate that accelerated maturation in EEG and circadian influences are indeed a response to an abnormal stimulus, such as hypoxia. Accelerated, morphologic or functional maturation need not be present simultaneously at all levels of the neuraxis (Timiras and Woolley 1966, Quattrochi et al 1980). The developing nervous system exhibits regional differences in metabolic rate and blood flow which are not constant across the entire developmental course even in the same structures. Himwich and Fazekas (1941) demonstrated that medullar metabolic rate in the one week old puppy was twice that of the adult dog. The metabolic rate of the cortex was only half of that in the medulla right after birth, but increased dramatically and exceeded that of the medulla by a factor of two in adulthood. It is reasonable to assume that a similar heterogeneity can be found prenatally. A transient selective accelerated maturation of the forebrain is of particular interest in light of a postulated inhibitory influence of this area upon brainstem respiratory centers (Tenney et al 1971) and the relationship of the development of the forebrain to the emergence of QS (Parmelee et al 1972, Hoppenbrouwers and Sterman 1975). Indeed, the hypothesis of a transient overshoot is consistent with the finding that siblings once asleep tend to maintain sleep longer than controls (Hoppenbrouwers et al 1980), a possible precursor of an arousal failure.

C. Sequelae of the core deficit

If increased respiratory rates in siblings reflect a compensatory response to mild chronic hypoxia in some infants this could be expected to result in an altered chemoreceptor sensitivity. Shannon et al (1977) reported a significant hyperventilatory response to CO₂ in near miss infants, a finding not substantiated by Brady et al (1980) or Haddad et al (1981). The latter authors advance three reasons for the discrepancy in results; monitoring over a prolonged period of time, use of a barometric method which avoids facial stimulation known to alter breathing (Askanazi et al 1980) and differences in CO₂ percentages administered. The last factor may be of more importance than previously appreciated (vide infra).

A synergistic effect of hypoxia and temperature control is manifested by a decreased defense against ambient cooling. This phenomenon has been documented in both young animals (Moore 1959) and premature infants (Brodie et al 1957, Brück et al 1962). Cornwall (1979) recently argued the relationship between SIDS and hypothermia, caused by a presumed deficiency in the catecholamine system. Although SIDS is associated with low environmental temperatures, Western child care practices are conductive to overheating as a response to cold. Retention of brown fat, while known to be associated with hypoxia, could also result from a reduced need to respond to a cold environment. In addition, an increased proportion of brown fat may enhance the capacity of an infant to generate heat (Hull 1966). Indeed, a recent report attributed several SIDS to either overheating (Stanton et al 1980) or dehydration (Herbert and Andrews 1979). An interaction between hypoxia and hyperthermia has not been studied systematically in infants. A study using kittens revealed that hyperthermia during hypoxia caused a significant increase in respiratory rates (McGinty 1980).

The response patterns to hypoxia available to the infant should determine conditions which pose the greatest challenge to an individual infant. For instance, if chemoreceptor control has been altered, cooling with the concomitant increase in QS (Baker and McGinty 1977) will increase hyperventilation. On the other hand, with retention of brown fat, heating especially in the presence of hypoxia, may induce hyperthermia. Additional stressors would produce variable results; for example, fever should reduce the risk in the first instance, but compound it in the latter.

D. Environmental conditions and high risk status

Despite the fact that SIDS is encountered at all socioeconomic levels, a majority of SIDS occurs in inner cities of large metropolitan areas. A recent study compared census tracts in Philadelphia in which one or more SIDS had occurred with those without SIDS. A multiple regression analysis identified six factors that predicted SIDS frequency: size of population, total live births, median family income, percent crowded housing, inadequate prenatal care, and percent premature birth (Fullcomer et al 1980). These unfavorable conditions are also associated with perinatal mortality and morbi-
dity, and can be supplemented with a number of others: male
gender, young maternal age, birth order, short pregnancy in-
terval, and low birthweight (Grether 1980, Valdes-Dapena
1980). Ambient pollutants tend to be higher in the inner ci-
ties. They probably interact with respiratory dynamics and do
not selectively contribute to SIDS. Some constituents of smog
can cause mild hypoxia; others may impair the ability to ward
off infections (Ehrlich 1966). The striking similarity of the
many variables related to both SIDS and other causes of mor-
tality and morbidity suggests at least a partially common eti-
ology. These non-specific factors resulting in impaired host de-
fenses should not be dismissed as contributing to SIDS.

E. Multiple aggravating or triggering stimuli

No single event or stimulus has been identified as the
precipitating event causing SIDS. Nonetheless, a few reports
in the literature describe patterns that by their close time asso-
ciation to the death suggest a functional relationship. These
include obstructions (Guilleminault et al 1980), laryngo-
spasms (Beckwith 1970), prolonged apnea (Steinschneider
1972), gastroesophageal reflux (Leape 1979), dehydration
(Herbert and Andrews 1979), and immunizations (Hutches-
on 1980). Parents, after scrutinizing the days prior to death,
add to this list. They report listlessness, fever, upper respira-
tory infections, vomiting, labored breathing, failure to eat,
sleeping through the night, a change in routine, or sleeping in
a changed environment. The heterogeneity of these behaviors
is far more impressive than the severity. It is conceivable that
the trigger is indeed mild and can vary from infant to infant so
that only the intersection of age, level of vulnerability and
trigger determines the fatal outcome.

Discussion and conclusions

Two issues deserve further emphasis. First, with increasing
knowledge about the process of maturation, it has become
clear that some characteristics are unique to the developing
organism and not just immature copies of adult mechanisms.
Purpura (1964), for instance, described the unique qualities of
immature neurons. Pertinent to the model described here are
data reported by Hays et al (1978), showing that during con-
tinuous exposure to high altitude (3500 m) calves activated
the circulatory system, whereas oxen activated the erythro-
poietic system. Upon exercise at high altitude hemoglobin,
haematocrit and blood viscosity increased in oxen, but de-
creased in calves (Hays et al 1978a).

Second, a distinction must be made between the morpholo-
gic and functional sequelae of mild versus severe hypoxia.
Studies of brain asphyxia suggest how hypoxia may have act-
ed in SIDS. In monkeys, total perinatal asphyxia for more
than 10 – 15 minutes resulted in a typical pattern of brain
damage which always involved brainstem structures (Myers
1972). With few exceptions, damage followed the blood sup-
ply with most damage to those structures that received the
most flow per unit time. By contrast, partial asphyxia left
much less permanent damage. Tissue necrosis, while never
involving the brainstem, seemed to be related to a compres-
sion or obstruction of small parenchymal blood vessels. The
majority of monkeys recovered spontaneously. Since the hy-
poxic insult in SIDS is believed to be mild, it is surprising that
evidence of brain damage, particularly brainstem damage,
can be found at all (Naeye 1976, Takashima 1978). Studies
by Nyka (1976a) may provide a clue. He contrasted hypoxia
due to toxemia present during the last trimester of pregnancy
with asphyxia at birth. Early hypoxia caused brainstem
damage in humans. This suggests that the onset, duration and
relative intensity of hypoxia are relevant variables. Nyka re-
lated his finding to the rate of cell division and the resulting
large energy demand of maturing cells in the brainstem. In
light of these studies, the brainstem astroglial proliferation de-
scribed in a number of SIDS is probably, not a result of as-
phyxia at birth. In our studies, labor and delivery did not re-
veal a significantly different pattern in SIDS infants. More
likely the hypoxic stimulus is initiated earlier during preg-
nancy and maintained for a longer time.

Functionally, severe hypoxia will cause insomnia and rest-
lessness in infants, while mild hypoxia induces sleep (James
1957). Increased sleep can be seen as a means to reduce
metabolism and oxygen consumption (Stothers and Warner
1977). This is an example of a compensatory response, initial-
ly adaptive, which when used under conditions of diminished
reserve can have deleterious consequences. Indeed, a second
variable uniquely related to SIDS is its relationship to sleep
(Valdes-Dapena 1962). Under hypoxic conditions, kittens
manifested a failure syndrome in QS which was transiently
reversed in AS. In addition, QS percentages were increased
(Baker and McGinty 1977). The relative immunity of human
neonates to SIDS may result from prevalence of AS in new-
borns.

The role of apnea in SIDS is still equivocal. Etiology of ap-
nea varies and has been discussed recently by Rigatto (1977).
Our own data suggest strongly that apnea is not a significant
contributor to the presumed mild hypoxia in full term infants.
Infants at risk exhibited increased respiratory rates and less
apnea both central and obstructive than control infants, while
the incidence of periodic breathing was indistinguishable from
respiratory rates have been seen up to six months of age in
premature infants who had RDS (Dittrichova and Patal 1975).
Apnea in preterm infants while in the nursery are frequently
accompanied by severe heart rate decelerations and hypoxe-
mia. However, the association between apnea of prematurity
and SIDS has never been adequately explored. Apnea of var-
ied origin probably constitute one of many triggering stimuli;
clearly, it is the one which brings the near-miss infant to the
attention of the physician. Epidemiological studies suggest,
however, that only a very small percentage of SIDS exhibited
a recognizable and documented apneic attack prior to death
(Froggatt et al 1971). During careful monitoring of approxi-
mately 35 near-miss infants, only two infants exhibited either
an excessive heart rate deceleration following an apnea of nor-
El Síndrome de Muerte Subita en la Infancia es la causa más prevalente de muerte en infantes entre uno y seis meses de edad. Los datos epidemiológicos, patológicos y fisiológicos sugieren que el mecanismo de El Síndrome de Muerte Subita en la Infancia es complejo, caracterizado por interacción a varios niveles del neuroaxís, entre el organismo y el medio ambiente involucrando ambas, la vida pre y postnatal. Detalles de tal modelo son presentados aquí. El modelo es basado en 1) Estudios fisiológicos sistemáticos de dos grupos de infantes que estadísticamente tienen riesgo aumentado para El Síndrome de Muerte Subita en la Infancia: hermanos subsecuentes y los casos abortados de El Síndrome de Muerte Subita en la Infancia. 2) Un estudio epidemiológico de aproximadamente 800 casos del Síndrome en Los Ángeles County, y 3) Datos clínicos perinatales y registro de frecuencia cardiaca fetal, de un subgrupo de estos 800 casos. Datos de otros investigadores también han sido considerados. Factores característicos para El Síndrome de Muerte Subita en la Infancia son: edad de muerte, asociación con el sueño, distribución estacional y aumento del riesgo para el siguiente hijo. La alteración fundamental propuesta consiste en hipóxia leve presente durante la vida pre y postnatal, la cual es compensada satisfactoriamente por la mayoría de los infantes. Cambios no previamente apreciados, que ocurren entre el primero y el tercer mes de edad, en el desarrollo e integración del sistema nervioso central dan lugar a una vulnerabilidad aumentada a influencias deletéreas endógenas y exógenas durante este tiempo. Una distribución alterada de los estados del sueño consistente en un aumento del sueño tranquilo (ST) y una disminución en el sueño activo (S. A.) están temporal y funcionalmente asociados con alteraciones en la regulación cardiaca y respiratoria. Algunos infantes llegan a este periodo (de edad) más pronto, lo pasan más rápidamente y con menos reservas haciendo más susceptibles a stress adicional. Aunque la etiología de la causa principal es desconocida, muchos factores pueden potenciar una hipoxia leve ya existente. Uno de tales mecanismos potenciales es la influencia de contaminantes ambientales. Otras deficiencias tóxicas de origen variado operan como factores predisponentes al riesgo o como eventos precipitantes causando la muerte. Podría esperarse en un gran número de infantes que estén estresados, pero solo una desafortunada intersección de vulnerabilidad previa y una o más condiciones agravantes, encontrada durante un definido periodo de edad, resultaría en muerte. Muchos factores no específicos asociados con El Síndrome de Muerte Subita en la Infancia son idénticos a aquellos asociados con morbimortalidad y mortalidad perinatal. Los programas dirigidos a reducir estos últimos debieran también reducir substancialmente la frecuencia de El Síndrome de Muerte Subita en la Infancia.

Palabras claves: El Síndrome de Muerte Subita en la Infancia, hipoxia, sueño, respiración, apnea, contaminantes ambientales.

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