Regular Review

Recent theories on the cause of cot death

A D MILNER

In 1985, 1480 babies died in Britain from the sudden infant death syndrome. As deaths from other conditions, particularly infections, have fallen this syndrome is now responsible for more deaths than any other cause in childhood after severe prematurity and lethal congenital abnormalities.

Over the past 10 years several new hypotheses have been introduced to explain the cause of the sudden infant death syndrome. These may be loosely classified into four separate groups: (a) overwhelming stress in the previously normal baby; (b) a functional or anatomical defect present from birth; (c) maturation failure; and (d) a critical phase of development during which babies are especially vulnerable.

Overwhelming stress

INFANT BOTULISM

Infant botulism is a well recognised cause of sudden infant death in the United States.¹ Unlike classic botulism, the disease occurs as a result of colonisation of the bowel by *Clostridium botulinum*. Those affected often die with fulminating paralysis; the condition usually occurs between 2 and 6 months—an epidemiological pattern resembling that of the sudden infant death syndrome. Infant botulism has been claimed to be responsible for 4% of sudden infant deaths in the United States and up to 16% in Sweden.² In Britain only one case has been described.³ Although some deaths categorised as the sudden infant death syndrome have probably been caused by infant botulism, the number attributable to this cause in Britain is probably extremely small. One suggestion put forward to explain the rarity of the condition in Britain is that—unlike American honey—British honey rarely contains *C botulinum* spores. Only about one third of American babies whose deaths are classified as the sudden infant death syndrome and who are then found to have botulism have, however, received honey. The differences in the incidence may be related purely to the extent of soil contamination in the two countries.

ENVIRONMENTAL TEMPERATURE

The peak incidence of the sudden infant death syndrome is in the winter, suggesting that cold might have a direct effect or perhaps act by producing conditions under which respiratory tract infections are more common.⁴ A recent study has shown that the peak incidence in the sudden infant death syndrome tends to precede the lowest average daily temperature by two to three weeks; there was, however, a significant negative correlation between the environmental

temperature and the incidence of sudden infant death syndrome four days later.⁵

HEAT STROKE

In 1979 Bacon and others proposed that the combination of excessive wrapping and mild infection could produce potentially fatal heat stroke in infancy.⁶ Five infants had presented with fever, shock, convulsions, and a bleeding tendency and no obvious cause; the only constant finding was they they had all been excessively covered with bedding or exposed to external heating.⁶ A year later Stanton and others reviewed the clinical and pathological data on 33 cases of sudden infant death syndrome and in eight they found histological changes in the small bowel previously described in children dying from heat stroke and also present in four of the five infants reported by Bacon and others.⁷ Fifteen of these babies were judged to be excessively dressed, and seven were described as hot to the touch at the time of death.

Sunderland and Emery reported that of 24 Sheffield babies who had died suddenly and who had rectal temperatures measured immediately before refrigeration 10 had temperatures in excess of 38°C and five greater than 40°C, again suggesting that hyperpyrexia might be an important factor in the aetiology of the sudden infant death syndrome.⁸ The association of the sudden infant death syndrome with the cold winter months does not detract from this theory as Nicoll and others found that the pattern of clothing and bedding selected by parents depended on the external rather than room temperature, so that on a cold night extra blankets would be put on the baby even though the room temperature was often warmer than in the summer.⁹

THE FEAR PARALYSIS REFLEX

The fear paralysis reflex has recently been advanced as a possible cause of the sudden infant death syndrome.¹⁰ This reflex, which is well described in animals, can be triggered off by an unfamiliar threatening environment, separation from parents (particularly in the dark), and physical restraint. In animals the response consists of immediate immobility, respiratory arrest, and profound vagal bradycardia, which sometimes proceeds to asystole. This theory can explain the excess of deaths at weekends, when the period of separation is often at its greatest,¹¹ and in the winter months, when the nights are at their longest. It can also explain the association between the sudden infant death syndrome and excessive bedding, which will inevitably restrict the baby's spontaneous movements.

Functional or anatomical defects present from birth**CARDIOVASCULAR ABNORMALITIES**

Congenital abnormalities of the conduction system of the heart may lead to sudden death from asystole or ventricular fibrillation.¹² Children with these abnormalities have a prolonged QT interval (Romano-Ward syndrome); they can be identified at necropsy only by highly sophisticated morbid anatomical techniques. Although this syndrome must be responsible for some sudden infant deaths, the incidence must be low since none of 29 infants who died suddenly and who were studied prospectively by Southall and others¹³ or the 17 studied by Kelly and others had this abnormality.¹⁴ The one abnormality Southall and others found was a tendency for the doomed babies to have more brief sinus tachycardia (greater than 190 beats/min), with seven of 16 babies who subsequently died exceeding the 95th centile quantity as defined by a group of age matched controls.¹⁴ The relevance of this finding has yet to be established, but interestingly Kelly and others found that babies dying tended to have higher mean heart rates during quiet breathing and a greater tendency to bradycardia.¹⁴

CONGENITAL RESPIRATORY CONTROL DEFECTS

Ondine's curse is a condition in which respiratory exchange is satisfactory when the child is awake or in rapid eye movement sleep, when respiratory drive is mostly under cortical control, but fails in deep sleep, when the rate and depth of respiration are determined by the central and peripheral chemoreceptors. This condition is responsible for a few deaths in infancy. One hypothesis under investigation is that some infants have a partial defect that could lead to unexplained death, particularly at a time of stress—for example, when the child has a mild viral upper respiratory tract infection.

Prospective studies investigating the breathing pattern of many neonates have not supported the suggestion that many babies dying from the sudden infant death syndrome have defective respiratory control from birth. Southall and others were unable to show that babies dying subsequently from the syndrome had more periodic respiration, short apnoea, or prolonged apnoea than gestation and age matched controls.¹³ A subgroup of babies may, however, have defects in their respiratory control mechanism that would become apparent only under stress.

METABOLIC DISORDERS

Many rare inherited metabolic disorders lead to death in infancy. One that has been particularly related to cot death is deficiency of medium chain acyl coenzyme A dehydrogenase. This enzyme is important in the metabolism of fatty acids in the liver, providing an alternative energy source when glycogen has been exhausted. This enzyme deficiency has been claimed to be responsible for 5% of all sudden infant deaths.¹⁵ Certainly some children have died suddenly and unexpectedly from this condition.¹⁶ Recently the livers of 200 consecutive cases of the sudden infant death syndrome were reviewed: 14 showed diffuse panlobular microvesicular fatty changes in the liver identical to those occurring in Reye's syndrome.¹⁷ Of the five cases in whom frozen liver samples were available two had a deficiency of medium chain acyl coenzyme A dehydrogenase activity. This has thus been

proposed as a cause of the sudden infant death syndrome, but all the children dying of this condition were very unwell for 24 to 48 hours before death and were also over 18 months, an age at which the sudden infant death syndrome occurs rarely.^{15 16}

SURFACTANT

Biochemical analysis of postmortem lung secretions has shown that the surfactant present in children who have died from the sudden infant death syndrome is usually quantitatively deficient and qualitatively abnormal, with profiles that are similar to those found in the lungs of babies dying from the idiopathic respiratory distress syndrome.¹⁸ Babies dying from the sudden infant death syndrome might therefore have a congenital or acquired metabolic defect in surfactant and be dying from massive atelectasis. But this is not supported by pressure volume studies carried out after death which show that the lungs of babies dying from the sudden infant death syndrome are no stiffer than those dying from non-respiratory causes.¹⁹ One particularly interesting finding was that the surfactant profiles were also virtually identical to those occurring in babies dying from lower respiratory tract infections, suggesting that the surfactant abnormalities are a marker of infection even at a stage when it is not always apparent from histological assessment alone.

PROLONGED EXPIRATORY APNOEA

Some infants have episodes of cyanosis that occur earlier in apnoeic episodes than can be explained from our knowledge of oxygen stores in the alveoli and blood. These episodes might represent apnoea close to residual volume similar to that occurring in whooping cough—that is, caused by expiratory efforts.²⁰ An alternative explanation put forward is that the low lung volume may be caused by atelectasis resulting from surfactant deficiency or abnormality. Further information is needed on the changes occurring during these episodes.

Development abnormalities

Organs do not mature at the same rate, and delayed development of one or more organ systems could put a child at risk of death at times of stress.

Quattrochi reported in 1980 that 17 of 19 babies dying from the sudden infant death syndrome had persistent dendritic spines on reticular neurones compared with only two of nine age matched controls.²¹ These spines are common immediately after birth but are soon lost; their persistence shows that the neurones in the reticular system of babies dying from the sudden infant death syndrome were failing to mature at the normal rate. The same group obtained further supportive data when they extended their studies to a group of 62 babies dying from the sudden infant death syndrome and compared the results with 34 age matched controls who had died from non-respiratory causes.²²

Critical phase of development

The striking age distribution for the sudden infant death syndrome suggests that there may be a critical phase of development during which either all or a subgroup of babies

are at increased risk of sudden death. Some physiological data support this. The corrected QT interval is generally accepted to be at its longest at about 3 months of age, although the changes are small compared with the electrocardiographic findings in infants with the Romano-Ward syndrome.

RESPIRATORY CONTROL MECHANISM

Complex analyses of the breathing pattern after a spontaneous sigh have shown that in the first few days of life the pattern before the sigh is re-established slowly but in a smooth progressive fashion and controlled by the central brain stem chemoreceptor organs.²³ Within one week of birth the response changes dramatically with rapid oscillations in the depth and rate of respiration thought to be caused by an imbalance between the central and peripheral chemoreceptors. The peripheral chemoreceptors are thought to be suppressed in utero but are gradually reset over the first few days of life. This oscillating response, described as unstable, is at its height between 2 and 4 months of age. By 6 months the resumption of steady state breathing is rapid but critically damped so that oscillations no longer occur. The oscillatory pattern could be exaggerated by various stresses leading to periods of apnoea.

THE UPPER RESPIRATORY TRACT

Some infants undoubtedly die from upper airway obstruction caused by collapse of the hypopharyngeal structures, which leaves no signs after death. How often these changes occur is unknown, but Guilleminault and others recently reported a high incidence of small upper airways in babies

with the near miss sudden infant death syndrome and their families.²⁴ At birth the larynx lies more cranially than in later life and descends during growth, and during swallowing the epiglottis may actually be above the soft palate. It has been claimed that babies are obligate nasal breathers, perhaps because of the high position of the larynx. Recent studies, however, challenge this finding, and babies, like adults, seem to be preferential rather than obligate nasal breathers.²⁵ There is no evidence to suggest that the descent of the larynx is particularly associated with an increase in obstructive apnoea, although this has been proposed as yet another cause of the sudden infant death syndrome.²⁶

RESPIRATORY TRACT COMMENSAL TOXINS

At 2 to 4 months of age the serum antibody titres reach their nadir as the maternally derived supply falls. The child might then be vulnerable to toxins produced by what would generally be considered to be respiratory tract commensals after viral upper respiratory tract infections.²⁷

Conclusions

This list of hypotheses to explain the sudden infant death syndrome is far from complete, but several are likely to contribute to some deaths. What has emerged over the past few years is that it is easier and cheaper to propose hypotheses than either to prove or disprove them.

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A D MILNER

Professor of Paediatric Respiratory Medicine,
University Hospital,
Nottingham NG7 2UH

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