New light on cot death

The death of a baby is a tragic enough event, but is perhaps made even worse for grieving parents if it is sudden and inexplicable and concerns an apparently normal child. Sadly, this sudden infant death syndrome (SIDS), also termed 'cot death', is the commonest cause of death in babies between the ages of 2 weeks and 2 years.

Generally, the infant appears normal; nothing suggests a problem. The child seldom makes any cry or sound at the time of death, and usually dies while sleeping.

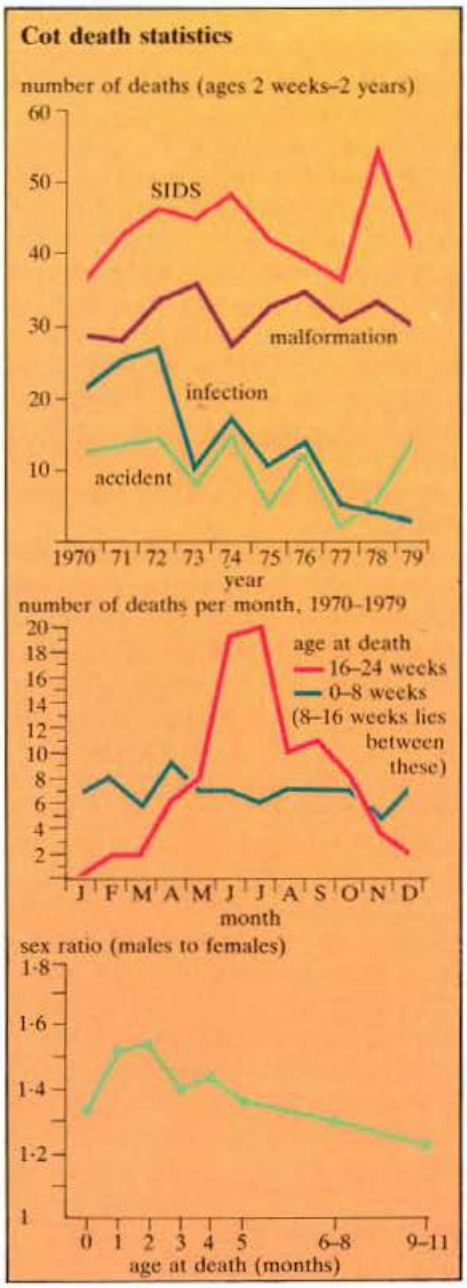
The exact cause (or causes) of SIDS still remains a mystery. That is not to say that we lack theories; a recent review of the problem cited 73 of them! But some features of the condition we do know for sure. It occurs at a rate of just over two deaths per 1000 live births, and about 50% more deaths occur in male than female infants. More cases of SIDS occur during the colder months, and the cooler times of day, with twice as many victims being found dead during the period midnight to noon as during the period noon to midnight. It appears that breast-feeding does not protect against SIDS.

Recently, some other points have emerged. Increasing evidence suggests that babies who succumb to SIDS might have had some difficulties at birth, or during labour. They might have had disturbances in their breathing, feeding, or temperature control immediately after birth. It is likely that somebody noticed that they had a poor colour when born, or were slow to start breathing. Afterwards, perhaps, they appeared normal.

Furthermore, it is now quite well documented that many SIDS babies had a history of some form of apnoea — that is breath-holding — most commonly during sleep. (Indeed, home monitoring equipment is now in use for apnoea-prone infants, which sounds an alarm if the infant's breathing becomes very irregular or stops.) Features noticed during autopsies of SIDS babies are often consistent with the idea that death was caused by apnoea.

But why does a baby, apparently quite healthy at the time, simply stop breathing? Nobody really knows, but scientists are homing in on an answer that involves the lungs and how they operate during breathing.

The ultimate cause remains elusive, and therefore so does a straightforward solution to the problem. What may be possible is to provide a relatively simple screening test to tell us which babies are most likely to be at risk so that parents and doctors can be warned, and monitor those infants accordingly. The research of Dr Ted McMurchie of CSIRO's Division of Human Nutrition in Adelaide, and his collaborator Dr Robert Gibson of Flinders Medical Centre, is suggesting a cause for SIDS and a means by which babies at risk can be easily identified.



Data for South Australia, compiled by Dr S.M Beal and Dr R.G. Carpenter, show SIDS is the main killer between the ages of 2 weeks and 2 years, the incidence is higher in the colder months, and males are more at risk than females.

Dr Gibson and Dr McMurchie provide an example of good collaboration between a very applied discipline like medicine and pure scientific research. The former is a paediatrician, while Dr McMurchie is a lipid biochemist more used to unravelling the intricate physics and chemistry of the cell membrane. What has this to do with SIDS?

Well-oiled lungs

We have in our lungs a marvellous substance called a 'surfactant', and it's made mainly of lipid. Although it's chemically complex, it really has a very simple function, and without it we couldn't breathe. The surfactant forms a thin coat throughout the inside of our lungs. We can think of it as being like an oil, and as such its job is to lubricate the movements of our thin, spongy lung tissue each time we breathe in or out.

Research is suggesting a cause.

Imagine two panes of glass, with a layer of water between them; it's difficult to pull them apart because of the surface tension of the water. (Sliding them resolves the problem!) The enormous moist area inside our lungs would suffer the same problem were it not for the surfactant, which lowers the surface tension, and so eases the work of breathing. As well as allowing the lung to expand with minimum effort, the surfactant is also important in preventing the collapse, during expiration, of the millions of alveoli — the lung's tiny sacs, or bubbles, where the gases are exchanged.

Humans usually start to produce functional surfactant in relatively large amounts about 4 weeks before birth, so that at birth they have sufficient to allow them to take the first and most difficult breath. Babies born prematurely may suffer a condition, called hyaline membrane disease, where the lung makes too little surfactant. The result is severe breathing difficulties — clinically termed 'respiratory distress'.

For lung surfactant to work it must form a monolayer — that is, a layer only one molecule thick — at the interface between

Dr Ted McMurchie operating the differential scanning calorimeter that enabled him to measure precisely the phase transition points of a variety of lung surfactants and lipid mixtures.

air and the fluid that lies on the outside of the lung's epithelial cells. It can do this because of the unique properties of the fats that compose it. Dr McMurchie has analysed human lung surfactant, and he and Dr Gibson are now proposing that in SIDS victims the surfactant may differ subtly in its chemical composition from that of normal babies. This implies that, although it may be present in sufficient quantity (unlike the situation in hyaline membrane disease), it may not do its job correctly all the time.

Fats consist mainly of atoms of carbon and hydrogen, with just a little oxygen. In our diet-conscious age most people now know that fats may be saturated or unsaturated. At its simplest this refers to whether or not a part of the molecule (called a fatty acid) contains the maximum number of hydrogen atoms that can possibly combine with the carbon atoms. If it does, the fatty acid is saturated. If it contains fewer hydrogens than the maximum possible, then 'double-bonds' form between the carbon atoms, and the molecule is unsaturated.

The principal component of human lung surfactant is called phosphatidyl choline (PC). The bulk of PC occurs in a disaturated form, which means that the phosphatidyl choline molecule has two saturated fatty acids connected to it. This is referred to as DSPC.

The crucial difference

In collaboration with Dr Rodd Carter at the Adelaide Childrens' Hospital, Dr McMurchie and Dr Gibson rinsed out the lungs of 40 babies that had died of SIDS, and obtained an extract that contained the surfactant. Using a technique called thin-layer chromatography, they separated the complex mixture of molecules in the extract. They then analysed these and compared them with material obtained in the same way from a control group of 12 infants of a similar age range that had died from other causes.

They found that the DSPC occurred in smaller amounts, on average, in SIDS victims' surfactant compared with that of the non-SIDS infants they used as a control. Of course, they found a range of variation within each of the two groups, but the overlap between them was small. So the difference in DSPC values seems to be sufficiently clear-cut to be of use as an indicator of SIDS. Significantly, DSPC is known to be the most active component of lung surfactant in terms of lowering surface tension.

Now DSPC has a complex molecule, which can take slightly different forms with different species of fatty acids. The researchers showed that DSPC in SIDS surfactant, although present in significantly lower amounts than that in controls, had a nearly identical nature. Furthermore, phosphatidyl choline as a whole occurred in the same amounts in the two groups. It was only the disaturated form of it that was lower in SIDS victims.

The Adelaide workers' initial findings broadly resembled those recently reported by a group in Cambridge University. Although some results differed, this corroboration is encouraging. Furthermore, the British researchers also demonstrated that SIDS surfactant is significantly less able to lower surface tension than is normal surfactant.

Finding a definite difference in the composition of surfactant between the groups, although exciting, only led to further questions. How does having less DSPC cause such a change in the lungs' functioning that it could lead to death?

Dr McMurchie, as a biophysicist, knew that alterations in a lipid's composition could lead to changes in what is termed its 'phase transition behaviour'. The physics of our schooldays taught that matter could exist only in three states (although we now know otherwise). These are, of course, solid, liquid, and gas. Changes of state, also known as phase transitions, can be brought about by changes in heat content or pressure.

When a substance is changing state an input of heat will not cause a rise in temperature (as it would normally) because the heat energy is being used to achieve the change of state. A different state is really a difference in the degree of order that molecules possess.

The temperatures at which changes of state occur differ for different substances. Ice changes to water at 0°C. Fats, such as butter, may solidify on cooling — much to the annoyance of those trying to spread butter straight from the fridge. A particular mixture of fats may even change state, for example, at the especially significant temperature of 37°C — our body temperature.

This is precisely what Dr McMurchie postulates may occur in lung surfactant during each breathing cycle of inspiration and expiration. On the basis of experiments with animal lung surfactant, he and others have suggested that, in order to perform its function, surfactant must undergo phase transitions from solid to liquid and back again. During expansion the surfactant could be in a liquid-crystalline phase (or fluid state), while upon contraction it becomes more solid and so helps to protect the lung from collapse when the air has been expelled from the alveoli.

But what would cause the phase transitions that accompany every normal breath? Temperature changes could not act so quickly. To help him find the answer, Dr McMurchie studied the effects that differing amounts of water had on the phase-transition temperatures of animals' lung surfactant lipids. He found that increasing the water content decreased the transition temperature, because the presence of water molecules affects the ordering and arrangement of the lipid molecules.

With sheep lung surfactant, he noticed that, at 37°C, a water content of 16% was a critical turning point. Very small changes in the ratio of lipid to water at this point would give rise to phase transitions. Possibly this could cause the changes of state postulated to occur during the breathing cycle in the lungs.

Changes of shape in each alveolus are known to accompany the breathing cycle, and may cause pressure differences that act to concentrate the water in a particular area of the alveolus, so making it more available

or less available for interaction with the surfactant. Subtle changes in the lipid composition of the secreted surfactant could affect the precise temperature at which a phase transition occurs, leading to a situation where surfactant is not performing its proper role at the temperature of 37°C normally found in the lungs. Perhaps failure of the surfactant to change phase during breathing is a factor in SIDS deaths.

Dr McMurchie's chemical analyses show that, other things being equal, lung surfactant with less DSPC than normal (such as in SIDS-type surfactant) should have a lower phase-transition temperature. At the usual body temperature, SIDS surfactant would be more fluid than it should be and therefore less efficient at preventing collapse of the alveoli during expiration.

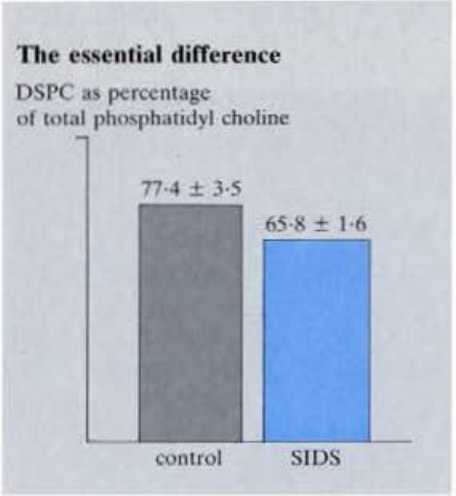
Temperature brings us back to the well-supported observation that cases of SIDS occur more often in the colder months of the year, and indeed in many of the cooler parts of the world. Could a situation arise in which both lung temperature and surfactant lipid composition were altered, with each factor actually aggravating the other's effects? A baby's core body temperature can change far more easily than an adult's.

Paradoxically, cooling would appear to aid a SIDS-type surfactant, by making it more solid! But an increased temperature (hyperthermia) would render it even more fluid, with possibly harmful consequences during expiration. The correlation of an increased body temperature with cool weather could perhaps result from anxious parents over-wrapping the infant, and placing it in a very warm room, or from a greater incidence of mild fever-inducing infections during the cooler months.

It's also possible that an infant possessing an abnormal surfactant, with altered physical properties, could succumb to SIDS if it were affected by any condition that would make breathing more laboured. This can happen with some colds, and could even be brought about by something as subtle as the baby's position in the cot.

The effects of water on surfactant behaviour are clearly important. Most lipid molecules have hydrophobic (water-repelling) and hydrophilic (water-attracting) regions. The hydrophilic parts of the molecules point towards (and probably lie within) the watery solution secreted by the epithelial cells inside the lung; the hydrophobic portions, like wax and oil — two very hydrophobic lipids — cannot mix with water, and point into the air. In this way the monolayer is formed.

The water content can critically affect the



The essential difference that the researchers uncovered between the lung surfactants of SIDS and control infants was in the amount of disaturated phosphatidyl choline (DSPC).

orientation and the physical properties of the lipid molecules. 'Wet' surfactant reduces surface tension less efficiently than 'dry' surfactant. High levels of water may cause the monolayer to break down; and, as noted earlier, water content affects the phase-transition temperature as well. Oedema, an accumulation of body fluid, may occur in the lungs under certain pathological conditions, although it is not always found in SIDS victims. As a SIDS baby has a less efficient surfactant, a slight amount of lung oedema, by making the surfactant too wet, would probably have a worse effect on it than on a normal baby.

The difference seems to be sufficiently clear-cut to be of use as an indicator.

A great problem in attempting to reduce the death toll from SIDS is that SIDS babies are often not recognisable as having any disorder until it is too late. Indeed, the very diagnosis of SIDS is not always clear-cut, and the name started as just an umbrella term for deaths that could not be attributed to anything else. Consequently, SIDS remains a very heterogeneous disorder, within which could exist a number of disorders of different origin. It is therefore all the more encouraging that Dr McMurchie and Dr Gibson think they have found a common thread.

Sadly, this does not mean that a 'cure' is in sight — in fact, we may never have that, especially if the surfactant difference has a genetic basis. However, the next best thing would be a means of identifying babies at risk when they are born, and then providing suitable care, as we do with so many other disorders. At least, with SIDS, the good news is that time provides a natural cure by carrying the baby past the age of susceptibility.

Using their discoveries about babies' lung surfactant, the two scientists are therefore trying to develop a simple risk-assessment method. Ideally, such a screening test should be simple, inexpensive, and easily applicable at birth. Direct measurement of lung surfactant would obviously give the needed information, but this can never be done in living children. Fortunately, mucus from the nose and the back of the mouth contains surfactant phospholipids from the lung, and can be relatively easily sampled, being obtained by aspiration of the upper-airways using a vacuum-cleaner-like tube. What still needs to be proved, however, is that the level of DSPC in mucus from the upper airways correlates well with the levels found in the lung washings from dead babies.

Accordingly, Dr McMurchie and Dr Gibson are planning a new study, with a grant from the SIDS Foundation of South Australia, who also supported their previous work. This would involve, firstly, establishing the range of variation in DSPC in aspirates obtained from normal infants and, secondly, comparing DSPC levels in lung washings with those aspirates, both from babies who have died from SIDS or hyaline membrane disease, and from babies who died from non-SIDS causes.

With the information they gather, it may be possible to issue doctors with a range of normal DSPC values found in mucus at the back of the mouth at birth; a significantly different value would indicate an infant 'at risk'. Obviously it would not mean the child will die of SIDS.

Environmental factors, which we have mentioned, and infection are both capable of influencing the incidence of SIDS. They are the precipitating factors that determine whether an infant with low levels of DSPC in its lung surfactant changes from being 'at risk' to actually succumbing. It is hoped that such a screening test will help to reduce the number of tragedies caused by this mysterious condition.

Roger Beckmann

More about the topic

Changes in lung surfactant lipids associated with sudden infant death (SIDS). R.A. Gibson and E.J. McMurchie. *Australian Paediatric Journal*, 1986, **22** (in press).

Decreased lung surfactant disaturated phosphatidylcholine in sudden infant death (SIDS). R.A. Gibson and E.J. McMurchie. *Paediatric Research*, 1986, **20** (in press).