Sudden Infant Death Syndrome (SIDS): An evolving hypothesis

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It has been previously proposed by Barry Richardson that toxic gas generated by fungi on fire retardant impregnated cot mattresses/covers could be the cause of SIDS. This theory was subsequently severely criticized by et al Lancet 1995 and in the editorial.

Whilst some of the specific points of Richardson's theory may have been incorrect (3)- i.e. incorrect identification of the fungus *Scopulariopsis brevicaulis*, and of gases generated by the microorganisms as stibine, arsine and phosphine, in broad terms the theory that an inhaled toxin that originates in the bedroom/cot environment has never been refuted. Indeed this seems to be the most likely explanation given that such candidates often leave little in the way of clues as to their presence and that inhaled toxins naturally affect breathing and this is central in SIDS.
In fact a study in mice by Anderson (67) finds evidence for toxic emissions from mattresses.

The only way to have tested the theory properly would have been to visit rooms where SIDS had occurred and assess the total environment and to carry out a wide range of post mortem and environmental tests. It would also be necessary to take account of additional cot factors- body heat, sweat, saliva, spilt drinks, urine etc.

It is feasible that if you take Richardson's 2 protagonists and consider them individually and take account of genetic predisposition, you may have an answer to most SIDS cases.

What are the possible candidates?

It's likely that a number of prime causes and contributory factors lie behind SIDS and one should start by looking at a broad range of potential causes.

1. Volatile organic compounds
VOCs are common in the home and are compounds of variable toxicity about which we know little, especially where infant exposure is concerned. They can out-gas into the atmosphere (without the involvement of microorganisms) often encouraged by heat and moisture. Most VOCs have been introduced over the last 30-40 years and fit the increasing incidence of SIDS from the early 1950s.

VOCs in the home are found in aerosol sprays, moth repellants, cleansers, disinfectants, air fresheners, dry-cleaned clothing and tobacco smoke.
Formaldehyde: is in pressed wood boards, tobacco smoke, durable press drapes and other textiles, and glues. The rate at which formaldehyde is released is accelerated by heat and may also depend somewhat on the humidity level.
Benzene: from cigarette smoke.
Perchloroethylene used in dry cleaning.
Methylene chloride is converted to carbon monoxide in the body
Fire retardants such as the anti carboxylesterase organophosphate (OP) Tri-O-Cresyl Phosphate (TOCP) were suggested by Richardson and have been added to mattress/covers since the early 1950s.

A number of other OPs are used as retardents ie. Triphenyl phosphate, Resorcinol bis(diphenylphosphate), Phosphonic acid, (2-((hydroxymethyl)carbamyl)ethyl)-, dimethyl ester.

Inorganic fire retardents include Aluminium trihydroxide, Magnesium hydroxide, Ammonium polyphosphate, Red phosphorus, Zinc Borate

Polybrominated diphenyl ethers (PBDE) retardents have been added to foam mattresses (some manufacturers such as Ikea are now substituting safer alternatives) and are released when the foam deteriorates and crumbles. SIDS has been associated with 2nd hand/older mattresses. These retardants, similar to PCBs, are highly persistent in the environment and biocentrate in fat cells and have various toxic effects (64,65, 66). The full nature of their low dose effects are poorly understood but they are thought to inhibit brain development. It would not be difficult to check for PBDEs in SIDS mattresses and postmortems.

Fabric softeners used to wash bedclothes are also plausible and have been suggested ie alpha-terpineol, benzyl acetate and benzyl alcohol.
www.coastalpost.com/99/5/4.htm

If one looks at research into many of these compounds and Organophosphate research in particular, the most common symptom of this type of inhaled chemical is laboured breathing sometimes leading to respiratory paralysis and death, which is what occurs in SIDS.

2. **Biological contaminants: Bacteria and Fungal spores.**

Fungi and bacteria can easily colonise the home environment : clothing, bedding and building materials and they thrive in damper conditions. Some diseases, like Humidifier fever, are associated with exposure to toxins from microorganisms that can grow in home heating cooling devices and humidifiers. Most Fungi flourish on open lattice structured materials, such as cotton where the spores can nestle safely. Some others require cellulose substrates for nutriment. It's possible that some cases of SIDS are caused by inhaling toxic spores which induce pulmonary hemorrhage and respiratory failure, a rare and poorly understood process, especially in infants. This diagnosis may have often been missed in past SIDS cases such as in Cleveland, Ohio 1994

Bacteria also seem to be involved in some SIDS cases.(58, 59) *Staphylococcus aureus* is a common pathogen found in around 50% of infants' lungs. However in some SIDS cases the bacterium has been found in the cerebrospinal fluid where it's very rare, such as in the well known case of Harry Clarke, Sally Clarke's second child to die of SIDS. This vital evidence was not disclosed at her trial and the eventual discovery of the bacterial presence, 3 years after her conviction for double murder, led to her life sentence being overturned. Infants with an immune deficiency would be much more susceptible to such infection. Matthew Cannings, a SIDS victim and son of Angela Cannings, was found to have virtually undetectable IgG antibody in his body.

Mechanisms.

Spores: Some domestic fungi can produce highly toxic allergenic spores.ie. *Aspergillus fumigatus,* (Greenberger PA.4,5,6,7) *Stachybotrys atra. (*Etzel RA*)*

One study found pathogenic fungi, including *Aspergillus fumigatus* more often on SIDS mattresses, with biofilms of theses organisms in the head area in every (22 cases) SIDS case studied. (Kelley J,)

SIDS has also been associated with 2nd hand/older mattresses (Tappin D.), which would be more likely to contain fungal colonies, and with mold growth in a cluster of damp homes in Cleveland, Ohio 1994 (Dearborn DG,)(Montana E,)

In this scenario the infant would be breathing in spores whenever it was in its cot over the few weeks of its life, once the moisture concentration had exceded the threshold for sporing. The spores would be at highest concentration when lying in the prone position. One possibility is that the infant becomes sensitised to the spores and develops an allergic inflammatory condition, similar to asthma, such as Allergic bronchopulmonary aspergillosis (Aba) Less toxic

spores may invoke an immune intervention when the person becomes sensitised, closer in mechanism to asthma which may involve mast cell release, cytokines and macrophages causing pulmonary inflammation.
Kamei K, *et al* found *Aspergillus fumigatus* at >1% could cause damage and eventual death to mouse macrophages in vitro via the release of toxins. Kurup VP, *et al* found that it was the synergistic activity of *Aspergillus* serine proteinases Asp f13 and Asp f2 that were allergenic.

The presence of intrathoracic haemorrhage is common in SIDS with a build up of haemosiderin containing macrophages (9. Stewart S.). This haemosiderotic build up within the phages takes at least 48 hours. The staining for iron however is not part of normal post mortems. In this study, macrophages, without evidence of fresh haemorrhage or inflammation, were only found in 13 SIDS younger infants (1-3 months). The remaining 11 older SIDS infants (4 months + at death) had no haemosiderin but had developed inflammatory lesions.

One would not necessarily expect death to occur at the point of initial haemorrhage because of the intervention of the macrophages at an early stage of poisoning. This scenario was in fact found in the cluster of 10 Cleveland cases and led to the local coroner re-examining the previous 2 years of SIDS cases to check for missed diagnosis.
5% (9 cases) of the re-examined cases had the haemosiderotic macrophage marker.

1 of these cases had involved well documented abuse and 2 others were known infanticides - actions consistent with the haemorrhage. The remaining 6 had no signs of abuse and were thus unexplained but were all found to have lived in the same 'damp' postal district as the original 10 cases of the cluster. This stongly suggests that all the damp cases were in fact caused by toxic fungal spores and demonstrates that topographical clustering can occur in SIDS.

Toxic Gases.

Toxic gas seems to be another plausible cause because of the esoteric pathological evidence that a gas would leave. The gas concentration would naturally be higher in the prone sleeping position which is an explanation for the finding that risk of SIDS is reduced for babies who sleep on their back. I think its plausible that they may cause subtle but serious affects in the brain - limbic/hypothalamus/brain stem in particular, accessed through the olfactory

nerves when inhaled.
The presence of a history of breathing difficulty for the infant is entirely consistent with a toxic condition that gradually worsens over weeks with the build up of the toxin.

There's evidence that some inhaled pesticides and toxic chemicals can produce respiratory failure with hemosiderotic laden macrophages often found in SIDS.(42,63)

Small molecular weight chemicals such as toxins, are potentially allergenic when bound to larger proteins and their capacity to irritate airways may be sufficient to cause haemorrhage. (14,15,17,18,19) These haptens would usually activate the immune system by inducing T cells with type I response. Some can induce type 2 response with allergic reactions. It may be that the immune involvement is delayed fitting the scenario mentioned above in (9. Stewart S.). Its feasible that such reactions in a susceptible infant could eventually result in a respiratory failure and death.

If specific anti esterase gases are involved these may work by directly inhibiting esterases in the pulmonary system leading to difficulty in breathing and possibly respiratory failure. Breathing difficulties are among the most common and severe symptoms of OP inhalation. Infant detoxification enzymes would also not be as fully expressed as in the adult. Susceptibility to these compounds would be greatly increased where the infant has a polymorphism in the PON I gene (Cherry N) and possibly the cytochrome P 450 gene. This would explain why only a very few infants die when these OP fire retardants are relatively common in bedding and the home.

Its also feasible that the toxin when inhaled follows the pathway from the olfactory nerve to limbic system to hypothalamus (40) and brain stem. It may thus be affecting some autonomic control centres leading to hypotension, cardiac and pulmonary inhibition that are found in SIDS(57).
Whilst SIDS infants may have minor cardiac rate and pulmonary abnormalities (49-57) it may be the low dose exogenous toxin that pushes these children's already weak systems too far and proves fatal.

Some research has found abnormality in the microsomal enzyme Glucose-6-phosphatase (G6Pase) in SIDS (35,36,37) which can be inactivated by lipid peroxidation. Ferritin is the principal human iron binding protein and the haemorrhage often evident in SIDS would release ferritin into alveolar tissues. Ferritin is a powerful catalyst of lipid peroxidation and thus the inactivation of G6Pase, increasing in the presence of pesticides (paraquat in this paper)(38).

The superoxide radical is implicated here and some toxic gases would up regulate this radical, therefore superoxide dismutase should be checked in SIDS.

Other symptoms? A baby suffering from chronic low dose anti esterase inhalation might be expected to suffer with other symptoms. Its feasible that many of the expected symptoms -salivation, urination, rhinitis, diarrhea would be disguised as they are part of a baby's normal repertoire of effluence.
It should also be noted that esterase inhibition should not be ruled out in infants if the classic muscarinic effects seen in adults are not present as OPs would not necessarily produce these same effects in infants (20)

One researcher, Ron Harper (46,47,48) has found hypotension to be a major factor in a sub set of SIDS deaths. Could this be caused by an OP exposure? Some research demonstrates bradycardia and hypotension as major symptoms in OP exposure (60,61,62).

There's anecdotal evidence that some SIDS infants had flown 1/2 days prior to death. An explanation for this could be exposure to pyrethroid insecticides such as permethrin that are often sprayed throughout the plane to combat insects. In addition it is now known that OPs from engine lubrication oils sometimes leak into the air-conditioning system. When this is of the recirculating type the exposure would be greater.

The case of the 4 SIDS cases near Porton Down experimental research station is another possible link with toxic OP gases. External gases are known to build up inside houses and at higher concentration inside than out.

Pesticides, vocs and other environmental contaminants may be causing more subtle epigenetic alterations and adduct formation to genes. These types of effects were not tested for when the products were tested for safety and the products would have 'got through' because they didn't cause direct changes to the genetic code. However epigenetic damage, which affects gene translation to proteins - enzymes, structural proteins etc, by affecting genetic neighbours such as chromatin, can be very serious and prevent some proteins from functioning properly. There's very strong evidence that this type of genetic damage lies behind the multi system illness CFS.

SIDS and Infanticide

Infanticide is sometimes invoked retrospectively as the cause of SIDS in multiple cases and there are people serving life sentences for this crime. (in the UK - Angela Cannings; Sally Clarke, until her conviction was quashed in January 2003). In some cases ie the 3 Cleveland cases there was little doubt about the cause because there was evidence of violence, and the presence of haemisiderotic macrophages at post mortem is consistent with violence.

However as we've seen pulmonary hemorrhage with hemisiderotic macrophages has known toxic causes and therefore this would seem the more likely explanation when there is no evidence of physical abuse. It also follows that in most cases where the charge is brought after 2 or 3 cot deaths that there was never evidence of violence in earlier deaths.

In cases where infanticide is the correct explanation there must have either been significant violence sufficient to cause pulmonary haemorrhage a minimum of 48 hours prior to death to obtain haemisiderosis. Where these infants have been admitted to hospital with breathing difficulties days/weeks prior to death, as is often the case with SIDS, then signs of bruising consistent with this degree of abuse would surely have been evident on examination if they had genuinely been abused. This time lag would also have given more opportunity to other family members, health visitors or friends to spot signs of abuse that must have existed in this scenario. Its very likely that there would also have been evidence of a history of violence or instability in such parents.
When this type of evidence is not found ie in Cannings and Clarke cases then what is the basis for prosecution.

SIDS is an under researched, poorly understood, relatively new multifactorial disease and the defence in these cases has to be built from this scant basis. Not really a fair start one might think.
Massive prosecutions are mounted against mothers of multiple SIDS children. Many of the mothers are found guilty because they understandably can't build up a decent scientific defence.

Calculating the 'odds'

Any calculation that cites enormous odds against multiple SIDS occuring in one family, such as are advanced by prosecution expert witnesses to support these cases are bogus as they are based on a false premise. This being that SIDS

is a very rare *chance* death and does not have an organic cause.ie the cases are independant of each other.
Firstly this has not been demonstrated. Secondly because nothing comprehensible to the investigating pathologist is revealed by the post mortem tests it doesn't follow that there isn't a scientific explanation for it. To jump from this point and say 2 or 3 SIDS cases in one family must be explained by infanticide because SIDS is so rare is flawed logic.
Another pathologist with different experience and interests might have called for different tests and found a cause. It doesn't mean there is no biological cause of SIDS.
It's axiomatic that an environmental disease with familial toxic bedding as prime cause and a genetic predisposition, as I believe SIDS to be, would actually be likely to produce some cases of familial or topographical clustering – it's not mysterious.
This situation highlights the need for pediatric pathologists together with other specialists ie mycologists and toxicologists to become involved. It's a medical matter and surely only a matter for the courts if substantial evidence of infanticide is produced.

Some of these statistics almost acquire a mythical status 'on the Clapham omnibus' and become quoted time and time again and no doubt influence juries. People remember them because they are powerful and easy to understand.
The truth behind the 1 in 73 million chance oft quoted in the Sally Clarke case was that it was a figure taken out of context of a full report, as the report authors are now keen to point out. Nevertheless it had considerable weight in the original court case when articulated by the powerful chief prosecution witness Professor Sir Roy Meadows.

By way of comparison I offer a personal example: my GP and Consultant investigating my fatigue syndrome said there was nothing wrong with me because the tests they had commissioned came back normal. And furthermore we would never find anything wrong if we continued with more tests.
I worked out what I suspected was wrong with me and commisioned what I considered the appropriate tests over several years. The results showed they were totally incorrect and revealed that I had numerous abnormalities. Needless to say my tests - the correct ones, were not carried out by my GP and consultant.

Conclusion

Whilst I accept genetic predispostion as a factor in SIDS the way to eradicate these tragic deaths is to study the environmental toxins and then to take action with advice and where appropriate ban or reduce the offenders.

One only has to look at some of the investigative and hypothetical work going on into SIDS abnormalities such as thyroid/selenium(30), lack of nerve fibres (31,32) mucosal immunostimulation (33), striatal and hypothalamic synapse (34, 40), hypoglycaemia /glucose 6 phosphatase (35,36,37,38), surfactant abnormality (41), and other various topics (46-59) to see that there are genuine biological mechanisms underlying the deaths.

Professor Bernard Knight, an eminent retired pathologist, who gave defence evidence in the Maxine Robinson SIDS case, when he saw the prosecution case commented as follows:
"This is so wrong as to be a travesty of pathological knowledge. . . . I consider this inference to be utterly speculative, pejorative and unjust . . . speculation tailored to suit a pre-conceived notion. . . . Absolute nonsense dressed up in scientific jargon. Nothing in the pathological findings in these cases is indicative of suffocation. Any findings - or their absence - are consistent with suffocation but equally consistent with Sudden Infant Death Syndrome."
Here, here!

Nigel Purdey , January 2002 ; purdeyenvironment.com

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