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Sudden infant death syndrome (SIDS): the search for the cause

An unexpected infant death for which there is no obvious explanation leaves the parents and medical staff with major questions to answer. Could the death have been prevented and will it happen again with future children? Was the death from natural causes or could some form of abuse have taken place? This situation is unsatisfactory and it is not surprising that considerable effort has been put into trying to elucidate the cause or causes of SIDS and that some of the work has provoked controversy.

In the past decade sleeping position, body temperature, and parental smoking have been linked to SIDS, and the impact of this knowledge on infant care has led to a major reduction in deaths in many countries. The evidence from which these linkages were made was epidemiological and it is still not known what makes a particular infant susceptible to SIDS. Theories proposed include anatomical abnormalities of the respiratory tract, infections, immunisation, nutritional deficiencies, environmental toxins, and metabolic disorders. The latter two hypotheses are particularly attractive as they lend themselves to experimental testing.

The hypothesis that inherited metabolic disorders, in particular inborn errors of fatty acid β oxidation, were a major contributor to SIDS resulted from necropsy studies showing excess fat in the livers and hearts of SIDS babies.[1] The suggestion that 10% of SIDS could be related to these disorders, especially medium chain acylCoA dehydrogenase deficiency (MCAD), was disproved by both metabolic and genetic studies and it is now believed that less than 1% of SIDS cases are caused by these disorders. Other inborn errors suggested as causes of SIDS include glycogen storage disease type I, defects of gluconeogenesis, and mitochondrial DNA mutations. While the presence of an appropriate DNA mutation is almost certainly diagnostic it is very important in metabolic studies to use age matched control data. It is unlikely that inborn errors are a major contributor to SIDS but it is important to diagnose even these small numbers for genetic counselling and prevention of future cases.

Toxic environmental factors in SIDS have been the subject of several studies. Chlorinated pesticides, polychlorinated biphenyls, and metals have all been measured in SIDS cases. Particular metals that have been studied are lead, cadmium, mercury, manganese, iron, copper, zinc, antimony, and arsenic. In most reports the data either show no difference between SIDS and controls, or conflicting information is found. Studies of low concentrations of trace elements are complicated by contamination and require a high degree of technical skill and attention to detail.

Two chemists, Sprott in New Zealand and Richardson in the United Kingdom, developed the hypothesis that SIDS resulted from the production of the toxic gases arsine, stibine, and phosphine from fire retardants and other chemicals in the PVC plastic covers of infant cot mattresses.[2] Historically it was well known that arsine could be produced from copper asenate pigment by the fungus *Scopulariopsis brevicaulis* and that it could have toxic effects, and this observation was extended to include antimony and phosphorus. These gases can act by inhibiting cholinesterases. It was suggested that the increase in SIDS observed in the United Kingdom after 1950 was caused by the use of these fire retardants. The hypothesis was treated with some scepticism but was testable.

Reports that increased antimony concentrations were found in the blood and tissues of SIDS patients received massive publicity in the United Kingdom through two television programmes in 1994, leading to withdrawal from sale of cot mattresses containing the suspect materials. As a result of the public pressure caused by the programmes several studies were designed to seek evidence for the production of stibine, arsine, and phosphine from cot mattresses. Those that were unsuccessful were criticised for not following Richardson's methods, but in one study which did do so there was no evidence of the presence of the fungus or the production of gases.[3]

Many of the basic rules of scientific and medical research were not followed in the development of this story. Little is known about the pharmacology and toxicology of stibine in infants and therefore interpretation of blood and tissue concentrations is difficult. Studies to identify the presence of *Scopularioposis brevicaulis* in cot mattresses are inadequate and the production of stibine in this situation remains disputed. More importantly there have been no adequate controlled clinical trials which address the particular problem of the nature of mattress covers.

A recent paper has emphasised the analytical difficulties of accurately determining antimony in urine, blood, and tissues[4] and in the March issue of the journal Cullen and colleagues[5] began to supply some of the important missing data with a study of the blood and urine antimony concentrations in normal infants under one year of age. Further similar studies, together with clinical trials, should finally prove or disprove the contaminated mattress hypothesis.

One lesson to be relearned is that the popular media are not necessarily the best place for scientific disputes to be aired and resolved.

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