Crib Death: Some Promising Leads But No Solution Yet

No one claims to have solved the problem of crib death yet, but, for the first time, investigators have several promising—and testable—leads to follow. This represents a marked change from the situation as recently as 3 years ago. Then, because physicians had no idea what caused these sudden, unexpected deaths of apparently healthy babies, crib death or the sudden infant death syndrome (SIDS) was an almost mystical phenomenon.

Now there is a growing body of evidence that the victims of crib death are not completely normal—and their deaths not as inexplicable—as was once thought, but rather that these infants have subtle physiological defects, probably in the mechanisms that control breathing. Thus, it may eventually be possible to detect potential crib death victims and prevent them from dying. This is important because, in the United States alone, up to 10,000 infants die every year of SIDS; it is the leading cause of death between the ages of 1 and 12 months. Moreover, many "near miss" infants, that is, those who stopped breathing but were found in time and resuscitated, appear to be normal children later in life.

One of the observations that have stimulated the current surge of research on SIDS is that infants who die of crib death may be prone to prolonged periods of not breathing (apnea) during sleep. In 1972, Alfred Steinschneider of the Upstate Medical Center of the State University of New York observed such abnormal breathing during sleep in five hospitalized infants who were either "near-misses" or siblings of SIDS victims. Two of the infants died suddenly in apneic episodes after discharge from the hospital.

Because many infants, and adults too, have periods of apnea during sleep, the question of what constitutes a dangerously long apneic episode is hard to answer. Most investigators, however, consider apneas of more than 15 to 20 seconds to be potentially hazardous. Steinschneider measures those cessations of respiration lasting 2 seconds or longer. He wants to determine whether measurements of the frequency and duration of apneic episodes in general can be used to identify infants at risk for the more prolonged episodes and, theoretically, SIDS. The evidence thus far indicates that it may be possible to identify such infants.

In other studies, some of which are still in progress, Steinschneider has been trying to determine whether there is any correlation between sleep apnea and the characteristics known to be associated with an increased risk of SIDS. Epidemiological studies have shown that crib death reaches a peak incidence in infants about 2 to 4 months old; that low-weight infants, especially those that are premature, are at greater risk than those of normal weight for their age; that evidence of mild, not life-threatening, upper respiratory infections is found in as many as 50 percent of crib death victims; and that the siblings of victims are at greater risk than other members of the population. The risk for siblings is still fairly low, however. For the general population of infants, the crib death incidence is about 1 in 350; the incidence of crib death among siblings of victims is about five times greater than this.

Since some of the studies are still in progress the results are preliminary, but Steinschneider is finding that problems with sleep apnea increase up to about the fourth week of life and then decrease. The low-weight infants studied have more frequent and longer periods of apnea than do those with normal weights. Furthermore, according to Steinschneider, upper respiratory infections are associated with more frequent, prolonged apneas, and may also cause recurrences of apneic episodes in infants who had stopped having them. This result is consistent with the views of a number of investigators that such infections are usually not themselves the cause of sudden death in infants but are instead the trigger that initiates the fatal series of events.

Three Kinds of Apnea

William Dement and Christian Guilleminault of Stanford University School of Medicine have distinguished between three kinds of apnea in premature and "near-miss" infants and also in children and adults. By their definition, central or diaphragmatic apnea involves no movements of the respiratory muscles of the abdomen and chest. In upper airway apnea, the muscles move but there is no air exchange. In mixed apnea, a period of upper airway apnea follows one of central apnea.

The investigators think that these distinctions are important. The heart rate of normal people slows when they hold their breath; this is the "diving reflex." Dement and Guilleminault find that a similar slowing of the heart rate occurs in infants during all three types of apnea but that it is more severe during episodes of the upper airway and mixed types. Moreover, they have measured a greater loss of oxygen from the blood during these two kinds of apnea than during central apnea. Finally, they observe frequent abnormalities in the rhythm of heart beats during upper airway and mixed apneas. The aberrant rhythms include those which can be fatal.

"Near-miss" infants and premature infants with relatively high birth weights have all three kinds of apnea, according to Dement and Guilleminault, whereas premature babies with very low birth weights have predominantly central apneas. These investigators also found that upper respiratory infections may exacerbate the apneic episodes and cause a reappearance of upper airway apneas in infants who had been free of them. They hypothesize that mild upper respiratory infections in infants with defective respiratory control may cause upper airway apnea, consequent abnormalities in heart rhythms, and, in some cases, death.

In the past, autopsies of SIDS victims gave few if any clues about the cause of death. About the only significant finding was the presence of tiny spots of bleeding in the lungs. However, recent observations of pathological changes in the victims support the hypothesis that sleep apnea and consequent oxygen deficiency are critical elements in many cases of sudden infant death. Richard Naeye of the Milton S. Hershey Medical Center of Pennsylvania State University College of Medicine found that the tissues of crib death victims have certain characteristics resembling those seen in infants known to have had chronically low concentrations of oxygen in their blood. The characteristics include the presence of considerably more muscle about the small arteries of the lungs than is seen in infants not subject to oxygen deficiencies; synthesis of red blood cells in the liver and not just in the bone marrow as in normal infants; and prolonged retention of brown fat around the adrenal glands. In normal infants brown fat is gradually replaced by white fat during the first year of life. In crib death victims and also in infants who died from congenital heart conditions and were therefore receiving inadequate oxygen, the loss of brown fat was greatly slowed in comparison to that in infants who had died suddenly in accidents or from acute infections.

Marie Valdes-Dapena of St. Christopher's Hospital for Children in Philadelphia has recently confirmed Naeye's observations on brown fat retention, with one exception. Unlike Naeye, she found no difference in brown fat retention by infants

Nitrogen Fixation in Maize

Scientists have long dreamed of being able to entice nitrogen-fixing bacteria to live in or on the roots of cereals just as they do on the roots of legumes. The idea is that the bacteria would help meet the plants' requirements for nitrogen-containing nutrients by fixing nitrogen—that is, by reducing atmospheric nitrogen, which plants cannot use, to ammonia, which they can. The hope is that this would enable farmers to decrease their dependence on expensive—with regard to both money and energy—synthetic nitrogen fertilizers without decreasing cereal crop yields. Although there is a long way to go before this goal is actually reached, if it ever is, recent research in Brazil is at least pointing in the right direction.

According to Johanna Döbereiner and Joachim von Bülow of the Universidade Federal Rural do Rio de Janeiro, some strains of maize or corn, growing under field conditions, have roots with the capacity to fix nitrogen. There were wide variations in the capacities of the strains tested, but Döbereiner says that the activity of roots from the best strain was almost as good as that of soybean roots. She attributes the nitrogen-fixing capacity of the maize roots to the presence in them of the bacterium *Spirillum lipoferum*. Döbereiner had previously found that this bacterium associates with the roots of a number of tropical grasses and fixes nitrogen almost as actively as do bacteria of the genus *Rhizobium* in legumes (*Science*, 12 July 1974).

There are some problems with potential applications of this discovery to agriculture. Döbereiner has shown, for example, that nitrogen fixation by *Spirillum* is optimal at soil temperatures between 31° and 40°C; little nitrogen fixation occurs below 25°C. She measured soil temperatures of between 26° and 31°C during the tropical summer of Rio de Janeiro, but soils in more temperate climates would be cooler than this.

Spirillum and Corn Grown in Temperate Climates

Preliminary work does indicate, however, that the roots of corn strains grown in a temperate climate can at least be infected with *Spirillum lipoferum*. Robert Burris of the University of Wisconsin has inoculated several strains of corn, including some common commercial varieties, with the bacterium, and is growing them in field plots in Wisconsin. He says that the bacteria will infect the roots, and confirms Döbereiner's observation that the bacteria are actually inside the roots and not just in a loose association around them. The plants are still immature, so it is too early to tell whether inoculation has any effect on yields. Inoculated plants do not look any better than uninoculated ones, according to Burris.

Obviously, a great deal more work will be required before the Brazilian research bears practical fruit. The effect of *Spirillum* infection on the quantity and quality of cereal yields is generally unknown and must be determined. Also needed is an analysis of the plant characteristics that favor infection and nitrogen fixation by the bacterium and a better characterization of the soil or climate conditions that limit these processes. Another unanswered question is whether *Spirillum* or some other bacteria can infect and fix nitrogen in the roots of additional cereals, especially wheat.

But the potential is there, and an international effort to attain that potential is under way. The Brazilian National Research Council is sponsoring the Program for International Cooperation in Training and Basic Research on Nitrogen Fixation in the Tropics to facilitate all aspects of the research at the Universidade Federal Rural do Rio de Janeiro. The program will include bringing qualified scientists from laboratories around the world to Brazil, where they can contribute some kinds of expertise currently lacking there and help train Brazilian students to do research on nitrogen fixation; at the same time, the visitors would benefit from the Brazilians' more extensive experience with *Spirillum lipoferum*.

An advisory committee consisting of members from the United States, Canada, the United Kingdom, and Australia will help the Brazilians coordinate research in laboratories throughout the world with that in Brazil. The National Academy of Sciences of the United States is coordinating this country's participation in the program.—J.L.M.

who died of SIDS between the ages of 2 and 5 months compared to that in controls (accident victims) in the same age group; victims of SIDS between the ages of 5 and 12 months did have a significantly greater brown fat retention than controls. Valdes-Dapena says that she cannot explain this discrepancy.

Although finding diagnostic criteria specific for SIDS is a major goal of investigators, Valdes-Dapena does not think that any one characteristic, such as percentage of brown fat retained, is adequate in this regard. She says that the average percentages for the different groups may differ significantly but that there are wide variations between the values found for members of the same group. There is also considerable overlap between those found in individuals in different groups.

Even if sleep apnea is one of the events culminating in sudden infant death, as the evidence indicates, a full understanding of the etiology of SIDS will still require an explanation of the cause of the apnea. One place to look for abnormalities in respiratory control is the brainstem—the location of respiratory centers that establish the basic rhythm of breathing. Naeye has observed two abnormalities in the brainstems of SIDS victims. One is an unusual proliferation of astroglial fibers. (Glial cells are nonneuronal cells necessary for the maintenance and function of neurons.) The other is a retardation of the formation of the membranous coverings of neurons. This would affect transmission of nerve impulses. Although Naeye cannot rule out the possibility that the alterations are the cause of prolonged sleep apnea, he currently thinks that they are the result of inadequate oxygen supply to the brain resulting from the apnea. A vicious circle could result, however, in which these changes lead to further loss of respiratory control and more apnea.

According to Harold Mars of Case Western Reserve University, there are preliminary indications that the formation of certain neurotransmitters, including dopamine, norepinephrine, and serotonin, is impaired in premature infants with apnea compared to premature infants with no apnea. The same was true for some but not all "near-miss" infants. (Neurotransmitters are chemicals involved in the transmission of nerve impulses.) Mars said that an enzyme required for synthesis of dopamine and serotonin appears to be lacking or very low in concentration in the brainstems of SIDS victims, but more data are required to confirm this.

Other investigators have been looking at respiratory control directly, especially at a reflex of newborn or very young animals that appears capable of counteracting the

normal respiratory drive. Among researchers studying this phenomenon are Geoffrey Dawes of the University of Oxford, England, S. Evans Downing of Yale University School of Medicine, and Barry Sessle of the University of Toronto.

Animals apparently have nerve receptors, located just above the larynx, that are sensitive to different chemicals. Contact of some chemicals with the receptors of very young animals can cause prolonged—even fatal—apnea. Dawes, for example, found that bathing the laryngeal receptors with water, glucose solutions, or cow's milk produced sustained apnea in lambs. A salt solution or sheep colostrum (the milklike material secreted by mothers for a few days immediately after they have given birth) had no effect. Cutting the laryngeal nerves that carry the impulses to the brain prevents the response. Conversely, stimulating the nerves electrically produces the response in the absence of chemical stimulation.

Most animals lose the apnea response to chemicals within a few days after birth. In piglets the reflex remains stronger for longer periods of time, according to Downing.

Investigators think that a similar chemosensitive reflex many cause sudden death in some human infants who aspirate water or formula into their upper respiratory tracts. Downing points out, however, that all babies may do that without harm in the vast majority of cases. He hypothesizes that infants who succumb to SIDS have reduced respiratory drives, that is, that the respiratory control centers of the brain are less effective in maintaining respiration in these infants. He has found that the anesthetic chloralose, which depresses the activities of the respiratory centers, increases the sensitivity of piglets to apnea-provoking chemicals. Less chloralose was required to produce a given inhibition in respiration in young animals than in older ones.

During these investigations, Downing discovered that piglets suffering from anemia, which is a common problem in these animals, were exceptionally sensitive to the anesthetic. He thinks that anemia may play a critical role in reducing the respiratory drive. Crib death is more common in infants from poor socioeconomic environments than in those with more affluent backgrounds. The former would be more likely than the latter to be anemic or to be born of mothers who were anemic during pregnancy. Moreover, the red blood cell concentrations of all infants falls progressively after birth, reaching a minimum at about 3 to 4 months of age—the same age at which SIDS incidence is greatest.

Inadequate respiratory control could be a result of delayed or impaired development, or, alternatively, the resultant oxygen lack could cause abnormalities in the brain. Either way, aberrant behavioral patterns could result in the infants. A number of investigators are interested in this possibility because such patterns might be used to identify infants with increased risk of sudden infant death. Naeye, for example, has noted that SIDS victims may differ somewhat from their siblings in the way they cry and feed and in their reactions to many external stimuli. Not all of the infants showed all of the differences, and they are difficult to measure quantitatively in any event. Nevertheless, Naeye, as well as other investigators, thinks that it will be possible to devise some kind of a test predictive for SIDS.

In addition to anemia, a number of alternative suggestions have been made to account for the abnormalities of SIDS victims. They include magnesium deficiency, according to Joan Caddell of St. Louis University School of Medicine, and lead poisoning. Both of these would be more prevalent in individuals from a poor socioeconomic environment than in those from more affluent ones. Henry Lardy of the University of Wisconsin has another hypothesis. He thinks that impaired glucose synthesis from amino acids and consequent failure of the body to maintain adequate glucose levels could contribute to crib deaths.

Most such deaths occur during the winter months and at night, at an age when infants begin to sleep through the night without a feeding. Inability to synthesize glucose might not be a problem while an infant has frequent feedings, but a long interval after eating, combined with the stress of cold weather, might cause a rapid and fatal drop in the concentration of glucose in the blood, according to Lardy. Glucose is the primary source of energy for all tissues, including the brain. Lardy has found that livers from SIDS victims have much lower concentrations of an enzyme required for glucose synthesis than do livers from infants who have died suddenly in accidents.

It is too early to say whether any of these possible mechanisms actually do contribute to sudden infant death, but they are not mutually exclusive; most investigators think that there is more than one cause. For example, only 50 percent of crib death victims show signs of having an upper respiratory infection. Such an infection may be the trigger of death for them, but for the others, different factors must be involved.

Several lines of investigation appear to be converging toward a better understanding of a problem that has long baffled physicians. They include the observations on sleep apnea and its effects on heart rhythm, on respiratory reflexes, and on pathological changes in SIDS victims. There is also a major effort to apply this new information to devise tests that will predict which infants are at risk of dying suddenly. The hope is that such a test will save lives—and spare parents the anguish of losing a child.—JEAN L. MARX

Energy: ERDA Stresses Multiple Sources and Conservation

Issuing its first national plan, the Energy Research and Development Administration has made major changes in the priorities previously espoused in Washington. Solar electric energy has been elevated to the highest priority, as a potentially "inexhaustible" source along with fusion power and the breeder reactor. The breeder is now being called one of several possible sources of energy in the long term, which should not be expected to produce significant power before the turn of the century. And the reduction of energy demand through conservation now has equal priority, at least on paper, with the creation of new sorts of energy supply.

Whether the dramatic shift in priorities will be reflected in budget dollars remains to be seen, since the legacy of energy programs passed on to ERDA was heavily weighted with nuclear energy expenditures. The fossil fuel programs administered by ERDA have been hastily expanded from $85 million to $391 million in the last 3 years, but even those burgeoning programs are still dwarfed by the $775 million expenditure for nuclear energy in fiscal 1976. The agency has requested a budget supplement of $131 million to restructure its priorities in the current fiscal year.

As required by the legislation that enacted ERDA, director Robert Seamans Jr. presented to the Congress (and to President Ford) a comprehensive national energy plan on 30 June. The early deadline, only 5 months after the creation of the new agency, may have hampered Seamans somewhat, especially since the staffing of ERDA is just being completed. Richard W. Roberts, previously head of the National Bureau of Standards, was confirmed as assistant administrator for nuclear ener-