Botulism in Infants: A Cause of Sudden Death?

A newly discovered infectious form of botulism may cause some cases of sudden death in infants. About 2 years ago, researchers at the California State Department of Health recognized that the bacterium (*Clostridium botulinum*) causing botulism could grow in the intestines of infants and produce enough of its potent toxin to make the babies seriously ill. Babies hospitalized for the condition rarely died, but the investigators hypothesized that if the infection were to develop very rapidly, before the infant's condition was detected and medical attention sought, the bacteria might produce enough toxin to cause sudden death. Recently, this hypothesis gained support when botulinum bacteria were found in fecal specimens taken from ten infants who had died suddenly.

The sudden infant death syndrome (SIDS) has long troubled medical researchers. In the United States alone, as many as 10,000 infants die annually of SIDS; it is the leading cause of death between the ages of 1 and 12 months. But the cause or, perhaps more likely, causes of the syndrome have remained elusive. Most of the infants who succumb are described as "normal" before they die, and, afterward, autopsies have not revealed an obvious cause of the deaths.

A few years ago investigators chipped away some of the mystery surrounding SIDS by presenting findings suggesting that the apparently normal victims might actually have suffered subtle neurological defects and breathing abnormalities making them prone to sudden death (*Science*, 1 August 1975). No one expected these defects to be the sole cause of the syndrome, however. Other factors, including infections, were also thought to be involved, although botulism was low on the list of suspected factors if it was there at all.

The reason for not suspecting botulism was the general belief that infants did not get the condition. In adults, botulism, which is often fatal, is not an infectious disease; rather, it is a type of poisoning caused by eating food contaminated with botulinum toxin. Young infants were thought not to be at risk from the toxin because they rarely eat the kinds of foods that may be contaminated with it. But that view had to be changed when it was found that botulism in infants could be an infectious disease caused by ingestion of the bacterial spores.

The spores, which are everywhere in the environment, are inert themselves and do not produce toxin. They are known to be harmless to children and adults who eat them—on fruits and vegetables, for example—without suffering any ill effects. In contrast to this situation, however, the spores can apparently develop into toxin-producing bacteria in the digestive tract of some infants.

Indications that this could happen first came about 2 years ago when Jackson Pickett, Bruce Berg, and their fellow clinicians at the University of California Medical Center suspected that two infant patients had botulism. Their clinical diagnosis was confirmed when Thaddeus Midura and Stephen Arnon of the California Department of Health at Berkeley found botulinum bacteria and toxin in the feces of the affected infants.

At that time, says Arnon, he and his colleagues expected to identify a toxin-contaminated food as the cause of the infants' condition. Only when they could identify no such food for these and for subsequently diagnosed infants, did they consider the possibility of botulism being an infectious disease in the very young.

A major danger for both infants and adults with botulism is respiratory arrest. The toxin, which is the most potent poison known, acts by irreversibly binding to nerve terminals and preventing the release of the neurotransmitter called acetyl choline. Consequently, muscles, including those needed for breathing, are not stimulated to contract and become paralyzed in the relaxed or flaccid state. The treatment is entirely supportive—the use of respirators to maintain breathing, for example—until the patients recover. Nevertheless, the prognosis of infants hospitalized with botulism is good. Only one of the 48 babies hospitalized in California has died; the rest have recovered, apparently completely.

The symptoms of the babies who are eventually hospitalized for botulism usually develop slowly, allowing the parents time to seek medical help. Constipation, neither an uncommon nor a specific symptom, is often the first abnormality to appear. After this, the neurological symptoms begin, within hours or as long as a week or two later. The first nerves affected by the toxin are those of the head and neck. Thus, the parents may find that the affected infant cries and sucks poorly, has difficulty in swallowing, and becomes unable to hold up his or her head. If the paralysis proceeds, arm and leg movements cease and the respiratory muscles may be affected. By this time, the infant is usually hospitalized, however.

An episode involving one of the first infants to be diagnosed as having infant botulism suggested to the California Health Department team that there might be a connection between infant botulism and SIDS. In this episode, the infant stopped breathing while being held in his mother's arms—and could have died suddenly if resuscitation had not been immediate.

Arnon and his colleagues hypothesized that the severity of infant botulism, like that of other infectious diseases, could range from inapparent to fulminant. If this were true, the milder cases could have a slower progression of paralysis with a correspondingly better chance of recognition and hospitalization. At the most severe extreme, however, paralysis of the respiratory muscles might be so rapid that sudden death could occur at home before anyone noticed that a serious problem was developing, especially since very small amounts of toxin would be sufficient to kill an infant. Based on the results of animal studies, the lethal dose of botulinum toxin for an adult has been estimated as 10^{-9} milligrams per kilogram of body weight. Arnon calculates that as few as 2000 bacteria could release enough toxin to kill a 7-kilogram infant.

In order to determine whether there is a connection between infant botulism and SIDS, the health department investigators asked coroners throughout California to send them specimens from infants who died before 1 year of age, whatever the cause, to be examined for botulinum toxin and bacteria. The researchers, who did not know which specimens came from SIDS victims when they performed the analyses, have now demonstrated the presence of bacteria or toxin in specimens from nine of the 211 SIDS victims and in only one of the 69 infants who died of other causes. The coroner had listed "cardiopulmonary failure" as the cause of death of this latter infant who had died suddenly and unexpectedly at home.

The ten infants represent only about 5 percent of the SIDS victims, but Arnon thinks that the percentage could be high-

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er than that. Many of the specimens had greatly deteriorated during the 2 to 4 days of transit to the health department laboratories. Thus traces of the botulinum organisms and toxin may have been lost.

The bacteria have recently been found in one SIDS victim in Utah by Joel Thompson and Richard Jackson of the Primary Children's Medical Center and Taira Fukashima and Merlin Smith of the Utah Department of Health, and in another in Seattle by J. Bruce Beckwith and Donald Peterson of the University of Washington Medical School and Melvin Eklund of the National Marine Fisheries Service of the U.S. Department of Commerce. The Seattle researchers have examined specimens from 30 SIDS victims and six controls and have found the bacteria, but not the toxin, in only one of the SIDS victims.

Beckwith, who is a leading authority on SIDS, says he does not expect botulism to be a major cause of the deaths, although it may account for those of a small subgroup of the infants. The Seattle data are consistent with the 5 percent figure reported in California. He points out that the development of the paralysis of botulism does not appear consistent either with the observation that most of the SIDS victims he studied were active and apparently normal just before they died or with evidence, such as tumbled bedclothes, that they were capable of strenuous movements.

According to Peterson, there are also uncertainties about the significance of the presence or absence of bacteria and toxin in the specimens. The Seattle samples were at least several hours old and Peterson agrees that deterioration might lead to loss of evidence incriminating botulism. But another possibility is that deterioration might have allowed growth of a botulinum contaminant that was not actually the cause of the infant's death. Thus far, however, the bacteria have not been found, either by the Seattle or California investigators, in specimens from infants who have died of clearly identifiable causes.

As further evidence in favor of the hypothesis that botulism may cause SIDS, Arnon and his colleagues cite epidemiological data on the age distribution of infants afflicted by the two conditions. Both occur most commonly in infants between the ages of 2 and 4 months, and then the incidences decline with age. Few cases occur in infants older than 6 months. The seasonal occurrence of infant botulism cases in California also parallels that of SIDS cases. Both reach peaks in the late fall and early winter.

Although the importance of botulism as a cause of SIDS remains to be established, the condition is a significant disease in its own right. Since 1976, about 80 cases have been diagnosed throughout the United States. Well over half of them have been reported in California, but this seemingly high incidence undoubtedly reflects the greater awareness of the condition on the part of the physicians and public health officials in that state. Arnon estimates that if the incidence in the rest of the country is the same as that in California, at least 250 cases severe enough to require hospitalization occur annually in the United States. (In 1977, 25 infants were hospitalized for botulism in California, which has

Microcomputers: The Great Electronic Mouse Race

Apart from the experimental psychology community, racing mice through a maze has never caught on as a popular pastime. Microelectronics, which makes it possible to pack the essential elements of a computer on one or a few chips of silicon, could turn this situation around. A contest sponsored by the Institute of Electrical and Electronics Engineers (IEEE) by way of its *Spectrum* and *Computer* magazines is under way which offers $1000 to the builder of the self-contained electronic mouse that can negotiate a maze in the shortest time. Although no one knows what will come of it all, *Spectrum*'s Roger Allan noted that some 6000 persons from around the world were interested enough to pay a $3.95 entry fee by the March deadline.

James Hamblen's mouse tries the maze.

The contest consists of a series of trial runs to be held at computer conferences and electronic trade conventions. Entries that successfully negotiate a maze at one or more of the trial runs (a different maze will be used at each trial) are scheduled to compete in a final race-off next June at the National Computer Conference in New York City. The first trial has already been held at a personal computing conference this past June in California. Of six entries, two mice managed to complete the course.

The rules of the contest are designed to emphasize microelectronics. Mice are allowed three passes through the maze. Thus, by using a microcomputer to "remember" where it has been, an electronic mouse can "learn" the vagaries of the maze on its first two trips and select an optimum path on the last pass. Furthermore, the mouse must be completely self-contained, although it need not physically look like a real animal. Live mice are not prohibited, but a rule outlawing the deposition of any material substances on the race course strongly discourages their use. Finally, radio-controlled mice are barred.

Basic elements of the maze include straightaways, U's, T's, L's, and dead ends (mousetraps). These are connected to form a maze of up to 20 feet square. The width of the pathway is $6\frac{1}{2}$ inches, and the height of the walls is 2 inches. There is no ceiling, so that the mice can be tall enough to look over the walls, but they cannot be so tall that they tip over. Neither can they step or fly over the walls.

Winning mice in the first trial run negotiated a 5- by 10-foot maze of this type in 51.4 seconds and 4 minutes 32.5

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a population one-tenth that of the nation as a whole.) And the hospitalization is expensive. The average victim spends 28 days in the hospital at a cost of $10,000.

Moreover, the disease is not limited to this country; at least one case has now been reported in England and another has turned up in Australia. Since botulinum spores are found throughout the world, additional cases will probably be found in other countries as more physicians become aware of the existence of infant botulism.

Arnon stresses, however, that this is not a new disease. It simply was not recognized before. In the past, the condition may have been diagnosed as any of a variety of ailments, such as "failure to thrive," myasthenia gravis (a disease characterized by muscular weakness), meningitis, encephalitis, or acute infantile polyneuropathy (polyneuropathy is a catch-all term meaning a disease affecting several nerves).

A major question investigators would like to answer is why botulinum spores can produce toxin-producing bacteria in the intestinal tracts of only some infants even though all infants are presumably exposed. Daniel Mills and Hiroshi Sugiyama of the University of Wisconsin have recently developed an animal model for infant botulism that they think will help in answering this question. According to these investigators, spores introduced directly into the stomachs of infant mice develop into toxin-producing bacteria in the gastrointestinal tracts of animals between the ages of 7 and 12 days. The toxin is not found in animals younger or older than that.

Mills says, however, that the toxin does not appear to be absorbed from the intestines of the mice. The animals do not get sick, even though there is enough toxin in their intestines to kill other mice injected with extracts of the intestinal contents. Mills speculates that differences in the intestinal conditions, possibly in the composition of the bacterial populations found there, account for the increased susceptibility to botulinum infection of 7- to 12-day-old mice compared with mice of other ages.

Because botulinum spores are so common, there is little anyone can do to protect their children from contact with the spores. One precaution can be taken, however, that is, not giving honey to infants under 1 year of age. The California investigators and others have identified botulinum spores in 10 to 15 percent of the honey samples they tested. Even the Sioux Honey Association, a cooperative of honey producers, has issued a press release advising parents to avoid giving the sweetener to infants less than a year old. Thirty percent of the infants hospitalized in California for botulism had been fed honey before they became ill, but Arnon says that none of the ten SIDS victims whose deaths were linked to *C. botulinum* had eaten any honey. Soils, dust, and most raw agricultural products carry the spores and there are numerous other ways in which an infant can come in contact with them. Thus, although the importance of botulism as a cause of SIDS remains to be established, it now appears that parents and physicians need to be aware that it is possible for infants to contract a disease from which they were once thought to be safe.—JEAN L. MARX

seconds, respectively. The large time difference was primarily due to the different strategies devised by the "trainers" of the mice. Surprisingly enough, the four nonfinishers failed not because of poor learning ability but because they could not make 90-degree turns—the only kind in the maze—when they bumped into the walls of a corner.

The fastest mouse was built by Art Boland, Phil Stover, and Ron Dilbeck of the Battelle Northwest Laboratories in Richland, Washington. According to Boland, they built their entry around a microcomputer with enough memory to store the information needed to make decisions at 99 different positions in the maze. The general strategy adopted was, for the first of the three allowed passes through the maze, to allow the mouse to make random choices at each decision point. For the second pass, the mouse was made to try new paths that it "knew" it had not tried on the first. The information collected was then used to compute the best course to follow on the third run.

The Battelle engineers used a number of infrared emitting light diodes (LED's) coupled with photodetectors as sensors to monitor the white walls of the maze and to locate the holes in the walls at corners or where new paths began. The mouse, measuring 5 inches long by 5 inches wide by 7 inches tall, was powered by alkaline cells.

James Hamblen of Martin Marietta Aerospace, Denver, designed the second place finisher. Hamblen's mouse was not as smart as the Battelle entry; it was programmed simply to follow the left wall of the maze. As long as the entry and exit slots are on the outside perimeter of the maze, such a strategy guarantees a solution, even if it takes a while to find it. Another difference was that Hamblen's mouse was cylindrical; thus, it could always manage a turn, even after running into a wall. The Battelle mouse's sensing system was designed to prevent the square mouse from getting too close to a wall. In other respects the two mice were similar. In particular, the use of separate stepper motors to drive a wheel on each side of the mouse permitted both to make sharp turns—one wheel could be driven forward and the other in reverse, for example.

Both mice took considerable effort to build. Boland estimates his group put in about 500 man-hours, all after hours, while Hamblen guesses he spent approximately 1000 hours on his project.

According to Allan, the reason for the "Amazing Micro-Mouse Maze Contest" is twofold. The first is promotional, to give the society a bridge to the general public. The trial run held this June, for example, appeared on a Los Angeles news telecast. The trial also attracted strong spectator interest; particularly popular was one Italian entry that appeared lifelike but which failed to solve the maze. A second goal was to present a challenge to engineers that might ultimately have an impact elsewhere, although exactly where is not clear. Credit for coming up with the contest idea is given to the editor of *Spectrum*, Donald Christiansen.

It is said that no matter what new idea one comes up with, a thorough search of the literature will reveal that it has already been published. The electronic mouse is no exception. It turns out that in the early 1950's Claude Shannon, now retired from Bell Laboratories, demonstrated a maze-solving mouse. What Shannon did not emphasize, however, was that under the maze, connected to the mouse by a magnet and surrounded by curtains, was a device driven by instructions from a large electromechanical (no solid state electronics in those days) computer. As it happens, Shannon's maze-solving mouse was using a program based on those being developed for the electronic switching machines that route calls through the maze of the telephone network.—ARTHUR L. ROBINSON