Reye's Syndrome: A Medical Mystery

Although it is one of the most intensively treated diseases in medicine, Reye's syndrome has yielded few clues to its cause or cure

Six years ago, recalls John Freudenberger of Bryan, Ohio, his 5-year-old daughter Tiffini was recovering from chicken pox. On a Thursday night, the Bryan, Ohio girl began vomiting. The next morning, Tiffini's mother noticed that the child was not acting right. She was disoriented, her eyes wandered. Becoming alarmed, Terri Freudenberger telephoned her daughter's pediatrician, who prescribed some medicine to stop Tiffini from vomiting. But the medicine did not help and as the day wore on Tiffini became increasingly lethargic and unresponsive.

Finally, the doctor agreed to see her, whereupon he admitted her to a community hospital. The doctors there tentatively diagnosed her as having Reye's syndrome, a potentially deadly disease of children. She was transferred that night to a hospital in Columbus, Ohio, but, says her father, "nothing could reverse what was happening." Tiffini went into a coma and died Sunday morning.

The Freudenbergers had to drive for 3½ hours to return to their home in Bryan. "We were mad," says John Freudenberger, "because Reye's syndrome had killed Tiffini and we didn't know anything about Reye's." There are some tragedies parents know about and can more or less accept, he believes. A child could be hit by a car, for example. But Reye's syndrome?

Their own experience led the Freudenbergers to start the National Reye's Syndrome Foundation in the hope of spurring research on the disease and of educating parents and doctors about it. Unfortunately, the current state of knowledge about Reye's syndrome is all too aptly summarized on the cover of a flier put out by the foundation. It says, "Reye's Syndrome, Medical Mystery. A lethal children's disease. Cause and cure unknown."

What has happened in the years since Tiffini Freudenberger died is that parents and physicians have become increasingly aware of and on the alert for Reye's syndrome. The foundation has sent speakers to schools and distributed information on Reye's, and the disease has received a great deal of publicity in the media. This year, there have been reports of unusual outbreaks of Reye's syndrome in the wake of the flu epidemic, and it has been said that the Midwest, and Ohio in particular, has had a large number of Reye's syndrome patients.

Reye's syndrome specialists say, however, that the data on the disease's incidence are too poor to say whether there are unusual outbreaks and that the harder one looks for Reye's, the more cases one finds. So the publicizing of the disease in certain areas of the country may have led to more frequent reports of it.

With the increasing public attention to Reye's syndrome, more and more doctors at major medical centers have become familiar with the disease and have devised dramatic ways of treating its symptoms. Their treatments have become so sophisticated that they now think doctors not at these major centers cannot properly handle cases of Reye's syndrome.

"The treatment of Reye's is one of the most intensive therapies you can imagine. I'd say it's *the* most intensive in medicine," says Allen Glasgow of Children's Hospital in Washington, D.C. The effectiveness of the treatment, however, is unknown. The mortality rate from the disease is often said to have declined from a high of 80 percent 15 years ago to 40 percent today. But, as Reye's syndrome specialists readily admit, the true extent of the decline in mortality is hard to measure. The patient population may have changed because with the increasing publicity about the disease, more and more cases are being diagnosed. It is not clear how many would have progressed to the serious and deadly form.

Reye's syndrome was first described in 1963 by an Australian pathologist, R. Douglas Reye. Because it was so recently described, there has been some speculation that it may be a new disease—a possibility of considerable etiological significance. Yet Reye's specialists say there really is no way of deciding whether the disease is new or just newly named. John Partin of Children's Hospital Medical Center in Cincinnati says that many cases of Reye's were and still are diagnosed with the catchall term "viral encephalopathy."

The syndrome seems to occur in the aftermath of a viral infection, particularly influenza or chicken pox. Nearly all of the victims are children or teen-agers. The first sign of Reye's is intractable vomiting. Next, the child shows signs of brain dysfunction, including disorientation, lethargy, and personality changes such as unprovoked shouting and use of abusive language. Finally, if the disease progresses, the child may become comatose. At his institution, says William Schubert of Children's Hospital Medical Center in Cincinnati, about one-sixth of the Reye's patients who enter comas die and about one-sixth suffer permanent brain damage. The disease runs its course in a few days.

At autopsy, the liver of a Reye's syndrome patient has a considerable amount of fat that is distributed in small droplets. Schubert says that "the pattern [of fat in the liver] is very unusual. It's almost typical of Reye's."

The liver mitochondria are also abnormal, being large and swollen. Consequently, the liver loses some of its enzymatic activity, particularly the ability to detoxify ammonia. A diagnostic test for Reye's syndrome is the presence of ammonia in the blood. Jacqueline and John Partin recently found that the mitochondria in brain neurons of these patients have the same sort of abnormal appearance as the liver mitochondria.

Brain dysfunction and death in Reye's syndrome patients are usually caused by a swelling of the cells of the brain. If this swelling cannot be controlled, the pressure in the skull can become greater than the blood pressure and the brain can die from lack of blood. Death can also occur when portions of the brain are destroyed by the pressure. Or the patient can die from respiratory failure caused by the brain pushing on the spinal cord and putting pressure on vital brain centers that control breathing. The swelling can also cause irreversible brain damage, including mental retardation, in children who survive the disease.

Because uncontrolled brain swelling seems to be the real danger of Reye's syndrome (the liver damage is usually reversible), the main objective of treatment is to monitor and control this swell-

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ing. Different doctors favor different methods of treatment, but all say that a major advance has been the widespread adoption, within the past few years, of devices to continuously monitor intracranial pressure. With the use of these pressure monitors, doctors can constantly adjust their treatments to keep the pressure down.

To give an idea of the sort of intensive therapy given to Reye's syndrome patients, Glasgow explains the treatment at his hospital. When a patient is not appropriately responsive—does not withdraw a finger when it is pricked, for example—he begins treatment.

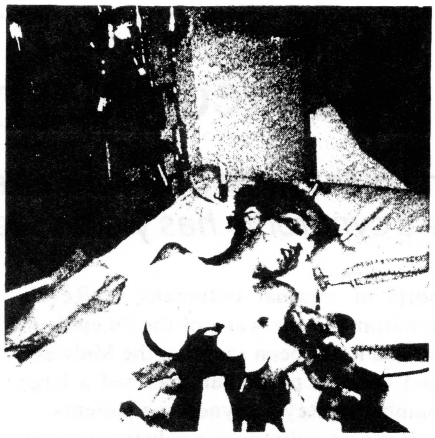
First, Glasgow asks a neurosurgeon to put a monitor in the child's skull to measure pressure. Tubes are put in a vein to monitor the blood fluid balance and in an artery to measure blood pressure and blood gases. A urinary catheter is inserted, as is a tube to the stomach which delivers antacids to prevent ulcers. The child is also given intravenous glucose.

If the child begins to struggle and thrash about and if the pressure in his brain is elevated, the very act of struggling can further increase the brain pressure. In those cases, says Glasgow, he administers a drug to paralyze the child and puts the child on a respirator. If the brain pressure continues to rise, he administers mannitol, a sugar that is not broken down by the body. The mannitol in the blood raises its osmotic pressure with the result that fluid is drawn out of the brain and other tissues. The fluid is excreted in the urine. At the same time, the child is made to breathe more rapidly, since this, too, often decreases brain pressure. If mannitol is not working, the child is given glycerol, which also acts by raising the osmotic pressure of the blood.

In cases where neither mannitol nor glycerol works, Glasgow administers the barbiturate pentobarbital—enough to put the child into a drug-induced coma. This is a controversial treatment, Glasgow explains, because the balance between risk and benefit is unknown. "We give enough pentobarb to arrest almost all neurological functions. The EEG [electroencephalogram] is nearly flat, the pupils don't dilate," says Glasgow. The child's brain is, in effect, nearly dead. A child can take a week to come out of the pentobarbital-induced coma, if he comes out at all.

When all else fails, Glasgow goes to the most extreme treatment in his repertoire. He has a neurosurgeon remove two flaps of skull from the child's head to release the pressure on the brain.

Amazingly, children have been known to go through all of these procedures, including the craniectomy, and recover with no apparent neurological damage. "We've had three patients with nearly flat EEG's on pentobarbital, one of whom also had a craniectomy, and all are back to normal now," Glasgow reports. He also had a patient last year, however, who was given both pentobarbital and a craniectomy; the patient died. "When the pentobarb wore off, there was no neurological function," Glasgow says. Schubert says he has had four patients with craniectomies: One is normal, one has a learning disability, one is mentally retarded, and one is still at the hospital being treated for Reye's.



Child in a barbiturate coma who eventually recovered from Reye's syndrome. The device at the top of the boy's head is a Richmond screw, inserted by a neurosurgeon to measure intracranial pressure. [Courtesy of Allen Glasgow, Children's Hospital, Washington, D.C.]

What is not clear is how effective the various treatments are, when to start treatment, and whom to treat. In Cincinnati, for example, there has been an extensive media campaign this year to make parents aware of Reye's syndrome. Consequently, says Partin, "we saw a lot of mild cases." Since the second week in December, 40 children were admitted to Children's Hospital with Reye's syndrome. Most of them were vomiting and had signs of liver damage, but did not have brain dysfunction. Should these children be vigorously treated? Should they even be classified as Reye's syndrome patients? The Center for Disease Control (CDC) does not count such children as Reye syndrome cases because its definition includes brain dysfunction. If these children are treated and recover, is it due to the treatment, or would they have gotten better anyway?

It is Partin's belief that even the children with mild Reye's syndrome should be treated. He gives them glucose intravenously, reasoning that he is compensating for the deleterious effects on energy metabolism caused by the liver damage. "We never had a death in a child we treated that early," he says, but explains that there are no controlled studies to support his faith in the early treatment regime.

Of the 40 children admitted to the Cincinnati hospital, only four became comatose and only one died. These data have been interpreted as meaning that there has been a substantial decrease in mortality with early detection and that, because so many patients were seen, there is an epidemic of Reye's syndrome in Ohio. Some doctors even say Reye's is mainly a midwestern disease or a Farm Belt disease. Yet Schubert, Glasgow, and other Reye's specialists agree that the number of cases detected depends on how hard you look for them.

The CDC has been trying since 1963 to keep tabs on Reye's syndrome, according to Cornelia Davis of the CDC. The center's best estimate of the disease's annual incidence is 1 to 2 cases per 100,000 persons under the age of 18 years. (The annual incidence of measles in that age group, according to the CDC, is 42 per 100,000.) Since only 16 states have laws making Reye's syndrome a reportable disease and since reporting it is voluntary, it is hard to determine whether there are regional differences in the disease's incidence, Davis says.

The CDC has also been conducting field investigations to see whether the disease is associated with any toxins or medications or whether there are any factors that could predict which children will get it. So far, the center has no promising leads.

One thing that has been learned from Reye's syndrome, says Glasgow, is how to manage intracranial pressure in general. Patients can have brain swelling from episodes of near-drowning, from severe lead poisoning, or from severe meningitis, for example. Doctors have begun inserting pressure monitors in the skulls of these patients and treating the swelling of their brains with methods borrowed from their treatment of Reye's syndrome.

As for Reye's syndrome itself, it remains very much a medical mystery. But doctors are convinced that as they become increasingly adept at treating the symptoms of the disease and as pediatricians become increasingly likely to refer Reye's cases to major medical centers, they can reduce the mortality rate and prevent severe brain damage in many of those who do survive.

—GINA BARI KOLATA