Tale of Triumph on Every Aspirin Bottle

By LAWRENCE K. ALTMAN M.D.

In 1951, pediatricians in Sydney, Australia, were puzzled by the death of a 10-month-old boy. The child had been screaming and vomiting for 30 hours, and doctors believed that he had a systemic infection or meningitis. But it was neither.

Peering into a standard microscope at tissues from the boy's autopsy, Dr. Ralph Douglas Kenneth Reye found no evidence of infection. Instead, he noticed distinct liver and brain damage of a type that he had never seen. Over the next 11 years at the Royal Alexandra Hospital for Children, Dr. Reye identified 20 more cases of what his colleagues nicknamed Reye's syndrome. The doctors suspected the damage had resulted from a toxin they could not identify.

In 1963, Dr. Reye (pronounced like rye) described the cases in The Lancet. Although the report came from the same hospital where in 1942 Dr. Norman Gregg first recognized the damage that rubella virus infection in a pregnant woman could cause in her fetus, Reye's syndrome drew little attention. Still, these reports started a chain of events that led to one of the century's major public health triumphs, while leaving the man the syndrome was named for nearly obscure.

Two decades passed before American epidemiologists linked Reye's syndrome and the use of aspirin to control fevers among children with viral infections, particularly influenza and chickenpox.

Then aspirin manufacturers and the Government fought acrimoniously over the Food and Drug Administration's efforts to issue warning labels on aspirin containers. The drug industry attacked the aspirin studies as methodologically unsound. But news

Courtesy of the Royal Alexandra Hospital for Children, Australia

When Dr. Douglas Reye died in 1977, few realized the importance of his work.

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the 21 children had taken aspirin. "When a kid had a fever, we used to give aspirin as the first line of defense," Dr. Baral said. He said the information on aspirin was not included in The Lancet paper because little thought was given to it as the culprit.

Although most doctors call the disease Reye's syndrome, American doctors often call it Reye-Johnson syndrome. The reason is that shortly after Dr. Reye's report, another group led by Dr. George M. Johnson, now at the University of North Dakota in Fargo, reported the deaths of 16 school-age children in North Carolina from the same type of liver and brain damage. They linked it to an influenza B viral infection.

Reports of new conditions often bring responses from others who claim they discovered it earlier. No less a figure than Britain's leading neurologist, Dr. W. Russell Brain, claimed that the Australian findings were the same his team had made in 1929. But Dr. Reye retorted that there was more difference than similarity in the reports.

Dr. Morgan said that when he worked in Los Angeles in 1967, many American colleagues "dismissed our report as having no significance." But, he said, "To anyone who knew how meticulous Douglas was, the suggestion that he was making a fuss about nothing would have been ridiculous."

Dr. Morgan went on to specialize in pediatric genetics and Dr. Baral moved to Babies Hospital in Manhattan, where he searched the records for cases of Reye's syndrome since 1929 and found none.

Neither the Reye nor Johnson teams pursued further investigations into the syndrome, but a small number of other scientists did. In the early 1970's, health officials became concerned about the increasing number of Reye's syndrome cases being re-

the use of aspirin to control fevers among children with viral infections, particularly influenza and chickenpox.

Then aspirin manufacturers and the Government fought acrimoniously over the Food and Drug Administration's efforts to issue warning labels on aspirin containers. The drug industry attacked the aspirin studies as methodologically unsound. But news reports led to a sharp drop in both the use of aspirin among children and the incidence of Reye's syndrome in the United States.

The 555 cases in 1980 represent the largest number recorded in this country in any year, though that number is believed to be a fraction of those that did occur. Even though it was uncommon, Reye's syndrome became a household word. Parents feared their children might develop the relentless vomiting, fever, convulsions, delirium, screaming, intense irritability and violent movements that characterize the syndrome. The symptoms begin from 1 to 14 days after an illness like flu or chickenpox. If the syndrome is not recognized and treated in time, coma and death come quickly.

In recent years, the Food and Drug Administration and the Centers for Disease Control and Prevention have reported that Reye's syndrome has virtually disappeared from the United States. Seven or fewer cases were reported each year from 1994 through 1998. When cases occur now, doctors are urged to look for a genetic disorder known as an inborn error of metabolism.

Direct proof that aspirin causes Reye's syndrome is still lacking; the evidence is based on the statistical association between the declining use of aspirin in children and the incidence of the syndrome.

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Attaching a doctor's name to a disease or syndrome is one of medicine's highest accolades, and it often thrusts the doctor into the limelight. But not Dr. Reye, the father of pediatric pathology in Australia.

Colleagues interviewed described Dr. Reye as a tall, stately, reserved man who spoke slowly, never wasted words, was courteous to everyone and did meticulous work. He sat at a large desk in a large paneled office with the door closed. Although that reserve was intimidating to some younger doctors, when a physician entered to discuss a case Dr. Reye would devote full attention and would soon turn to a nearby microscope to point out the damage.

Dr. Leslie Hardacre is credited with first naming the syndrome. He said he wrote it in a patient's chart in 1959 as a joke. Dr. Hardacre recalled Dr. Reye as "a pretty aloof guy who you could not get very close to."

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Dr. Reye spent his entire career at the Royal Alexandra Hospital, where he also first described the pathology of a type of tumor in infants that some doctors, in a play on the medical term for tumors called Reyeomas. But he was not of the publish-or-perish mentality, writing only 32 papers.

Although Reye's syndrome bears one name, it took many scientists elsewhere to make it a public health success story. It also took two colleagues, Dr. Graeme Morgan and Dr. Jim Baral, to push Dr. Reye to publish his findings about the syndrome. Dr. Baral said that when he began training at the hospital in 1961, one of his first patients was admitted with the diagnosis of Reye's syndrome. Dr. Baral had never heard of it. So he consulted textbooks and journals.

How a little-known doctor helped vanquish a scourge of childhood.

"I couldn't find any reference because it had not been reported," said Dr. Baral, now a dermatologist in Manhattan. "Dr. Reye sat on this for 10 years."

Dr. Baral then began discussing the syndrome with Dr. Reye. Soon, Dr. Reye invited Dr. Baral to spend a year training with him in pathology. The hospital's chief resident, Dr. Morgan, became interested in the syndrome and also spent a year working with Dr. Reye. Both young doctors prevailed on Dr. Reye to publish the cases.

Dr. Morgan went to Dr. Reye, saying, "Listen, it's about time we reported this, and I am willing to help." Dr. Reye agreed.

"Graeme and I dug up the charts on all the cases and we spent a year reviewing every item in them," Dr. Baral said.

The health department joined in, interviewing the involved families and performing toxicology tests. They found that 11 of bies Hospital in Manhattan, where he searched the records for cases of Reye's syndrome since 1929 and found none.

Neither the Reye nor Johnson teams pursued further investigations into the syndrome, but a small number of other scientists did. In the early 1970's, health officials became concerned about the increasing number of Reye's syndrome cases being reported, and in 1976, the C.D.C. began national surveillance for Reye's syndrome. The emerging pattern was puzzling because the incidence varied from region to region within the United States.

Then about 1980, studies in Arizona, Michigan and Ohio linked aspirin use in children with viral infections to the syndrome. Despite the scientific findings, medical leaders were at first extremely skeptical about them. By then aspirin had been used extensively for half a century and was considered a safe drug. How could it be causing a previously unknown hazard? The answer lay in epidemiologic studies, but the drug industry attacked the methodology as flawed.

A battle developed over the Government's efforts to have manufacturers put warning labels on aspirin bottles and to remove aspirin as an ingredient in most products intended for children. After a delay, warnings were required in 1986 and remain, saying: "Children and teen-agers who have or are recovering from chickenpox, flu symptoms or flu, should NOT use this product. If nausea, vomiting or fever occur, consult a doctor because these symptoms could be an early sign of Reye's syndrome, a rare but serious illness."

In calling attention to the disappearance of Reye's syndrome in the current New England Journal of Medicine, Dr. Arnold S. Monto of the University of Michigan School of Public Health said puzzles remained. Japanese doctors have reported Reye's syndrome during outbreaks of influenza among children who did not receive aspirin.

Dr. Johnson said he believed that Reye's syndrome was due to mutations in the influenza and chickenpox viruses and that aspirin played only a minor role. In Australia, the incidence of the syndrome has sharply declined, Dr. Morgan said, but he is not convinced the link is proven.

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Dr. Reye died suddenly and unexpectedly in 1977, a day after his mandatory retirement at 65. The man whose obituary in The Medical Journal of Australia was less than two lines now has his name prominently mentioned on every bottle of aspirin.