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

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.

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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.

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.