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Is Aspirin a Cause of Reye's Syndrome?
A Case Against

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Abstract

Reye's syndrome was a rare disease which appeared suddenly in the early 1950s and disappeared just as suddenly in the late 1980s. An association between Reye's syndrome and the ingestion of aspirin (acetylsalicylic acid) was claimed, although no proof of causation was ever established. The presence of salicylates in the blood or urine of Reye's syndrome patients has not been demonstrated, and no animal model of Reye's syndrome has been developed where aspirin causes the disease. It is clear from epidemiological data that the incidence of Reye's syndrome was decreasing well before warning labels were placed on aspirin products. Reye's syndrome disappeared from countries where aspirin was not used in children as well as from countries which continued to use aspirin in children. Reye's syndrome was probably either a viral mutation which spontaneously disappeared, or a conglomeration of metabolic disorders that had not been recognized or described at that time.

This article will attempt to convince the reader that aspirin (acetylsalicylic acid) is not a cause of Reye's syndrome. Sufficient objective data will be presented to demonstrate to the open-minded and logical reader that although aspirin may be associated with Reye's syndrome, it is unlikely, illogical and unfounded to state that aspirin causes Reye's syndrome.

1. Historical Aspects

Reye's syndrome was first described in 1963 when Ralph Douglas Kenneth Reye along with Graeme Morgan and Jim Baral, published a report in the *Lancet* of 21 children who had been seen at the Royal Alexandra Hospital for Children, in Sydney, Australia between 1951 and 1962 with a disease they called 'Encephalopathy with fatty degeneration of the viscera'.[1] Multiple investigations of pathological specimens from around the world by subsequent investigators confirmed that Reye's syndrome did not exist before 1950.[2,3] It suddenly appeared in the early 1950s and just as suddenly disappeared in the late 1980s. Such a sudden appearance does not fit with aspirin causation because aspirin had been discovered in 1899, and was in wide use throughout the 20th century. Of interest, paracetamol (acetaminophen) was discovered in 1955. This sudden appearance and disappearance fits best with a precipitous mutation in a virus, with the mutation disappearing just as suddenly about 40 years later.

RDK Reye himself investigated a number of potential causes for Reye's syndrome including aspirin, and came to the conclusion that aspirin was not a cause of Reye's syndrome.[1]

2. Clinical Aspects

Reye's syndrome typically presents with a prodromal viral illness, most often influenza B, influenza A, or varicella (chicken pox) which runs its typical course for 3 to 5 days. There is then a transient period of recovery for 1 to 3 days, followed by the onset of protracted vomiting defined as more than five emeses in an 8-hour period. This is followed by symptoms of encephalopathy with delirium alternating with stupor or lethargy, and at this time the vomiting subsides. The patient may then either recover or progress to coma with decortication or decerebration associated with cerebral oedema. Death is usually due to brainstem dysfunction or compromise, and recovery is usually complete. This pattern of a prodromal viral illness, followed by transient recovery, and then the development of vomiting proceeding to encephalopathy is referred to as the classic, biphasic illness of Reye's syndrome.

The laboratory findings typically include an ALT level of greater than twice normal in 99% of patients, an AST level of greater than three times normal in 95%, an ammonia level greater than three times normal in 90%, a prothrombin time less than 80% of normal in 79%, a bilirubin greater than 2.0 mg/dl in 24%, and hypoglycaemia with a glucose less than 40 mg/dl in 18%.

The pathological findings in Reye's syndrome were extensively described by RDK Reye and include a microvesicular steatosis (fat globules in the cells smaller than the size of the nucleus) on light microscopy, and mitochondrial changes of swollen mitochondria with disrupted cristae on electron microscopy.

Various epidemiological studies showed that Reye's syndrome was predominantly a disease of suburban, school-age, White children under 18 years of age, living in temperate climates. Therefore, Reye's syndrome was associated with (but not caused by) being Caucasian, middle or upper class, in grade school, and living in areas that get snow in the wintertime.

3. Epidemiological Studies and the Aspirin/Reye's Syndrome Association

Individuals who purport a causal role for aspirin in Reye's syndrome, always point to the US Public Health Service (PHS) epidemiological studies that showed an association between aspirin ingestion and the development of Reye's syndrome.[4-8] There are a number of problems with these studies, not the least of which is that association can never be used to prove causation. In fact, the number of epidemiological associations that have not been substantiated by subsequent scientific studies is so great that a list would require more pages than this journal contains. Only a few points will be made about each of these epidemiological studies, since the proponents of the association are likely to focus most of their attention on these studies.

The first study was the Arizona study by Starko et al,[4] conducted over 4 days (21 to 25 December 1978) in which seven children hospitalised with Reye's syndrome were compared with 16 controls. The Reye's syndrome patients all had influenza A (H_1N_1) infection, and all seven had ingested aspirin by history. The 16 controls were all ill during the same period, but not hospitalised, no viral studies were done to confirm the cause of their viral illness, and only 8 of the 16 had ingested aspirin by history. Two points are clear: we do not know if the controls had the same prodromal illness, and 50% of the controls had also taken aspirin.

The next two studies are usually referred to as the Michigan 1 & 2 studies,[5] and involved two sequential years of influenza outbreaks. Study 1 involved an influenza B outbreak in 1979 to 1980, in which 25 of 56 known Reye's syndrome cases were studied, based on whether they lived within easy driving distance of the Michigan Department of Public Health. Interviews were conducted with parents an average of 45.5 days after their child had been diagnosed with Reye's syndrome. Controls had a flu-like illness (no confirmation of influenza B) in the same time period and were interviewed an average of 55.3 days after the onset of their illness. In the Reye's syndrome cases, 24 of 25 had

taken aspirin, whereas in the controls 30 of 46 had taken aspirin. In study 2, attempts were made to improve parental recall ability by conducting interviews much earlier. Study 2 involved an influenza A outbreak in 1980 to 1981. Twelve of 17 known Reye's syndrome cases were interviewed an average of 4.8 days after the onset of Reye's syndrome and all 12 had taken aspirin. Twenty-nine matched controls, but again with no confirmation of the virus involved, were interviewed 12.2 days after the onset of their illness, and 13 of 29 controls had taken aspirin. It is clear that although more cases than controls took aspirin, aspirin ingestion still occurred in patients who did not develop Reye's syndrome, and yet had a similar viral illness. There was no laboratory confirmation of the history of aspirin ingestion, and no confirmation that the viral illnesses were the same in the cases and controls.

The next study, the Ohio Study,[6] was both the largest and most controversial. It was conducted between December 1978 and March 1980, and one of the authors of this paper (JPO) was one of the six investigators submitting cases of Reye's syndrome to the Ohio Department of Health. In the Ohio study there were 97 cases of Reye's syndrome, of which 94 took aspirin, whereas 110 of 156 controls took aspirin. As confirmed in congressional hearings before a subcommittee of the US Congress and an independent audit of the results by the US Food and Drug Administration (FDA),[9] JPO submitted 11 cases of Reye's syndrome to the Ohio Department of Health (ODH), more than half of whom had not ingested aspirin, but only six cases were included in the final results of the study – four of whom had taken aspirin, and two of whom had not. Of interest, whereas 71% of controls and 97% of cases of Reye's syndrome had ingested aspirin, a little known fact is that more than five times as many cases of Reye's syndrome had ingested phenothiazines as controls (22% of cases *vs* 4% of controls). There were a number of design flaws in the Ohio study, not the least of which was retroactive alteration of the research hypothesis. The Ohio study was originally designed to look at the particular viruses associated with Reye's syndrome. The study hypothesis was altered after the first year to assess the role of medications, especially aspirin, based on the Starko et al. study in Arizona.[4] Retroactive alteration of research design is a serious violation of research methodology and statistical analysis requirements. Other problems with the Ohio study included the facts that fever was significantly more prevalent in cases than controls (76% of Reye's syndrome cases *vs* 61% of controls), that decreased liquid intake as an indicator of severity of disease during the antecedent illness was present in 53% of cases but only 17% of controls, and important differences in the antecedent illness between study cases and excluded cases, with only 10% of study cases having varicella, but 25% of excluded cases having varicella. There were 227 cases of Reye's syndrome reported to the ODH during the study period, but only 97 cases were included in the study.

Subsequently, the US Public Health Service (PHS) conducted two studies, a pilot study and a main study.[7,8] These also showed the expected association of aspirin with Reye's syndrome, since all of the previous studies had also been conducted under the auspices of the PHS and its Centers for Disease Control (CDC). In the pilot study[7] there were 30 cases of Reye's syndrome and 145 controls. Ninety-three percent of cases and 46% of controls had ingested aspirin. In the main study[8] 26 of 27 cases (96%) and 53 of 140 controls (38%) had taken aspirin. There were a number of important problems with all of these epidemiological studies, not the least of which is that association does not equal causation, that as G.U. Yule stated in 'The Function of the Scientific Method in Scientific Investigation'[10] that 'You can never prove anything by statistics', and most importantly, statistics are no substitute for judgement.

Some of the problems common to all of these epidemiological studies included the facts that the studies were all retrospective, that the ability of parents to recall events accurately is questionable, especially when the public at that time typically

referred to paracetamol as 'liquid aspirin', that there was no pharmacological or laboratory confirmation of the medicines that were reported to have been ingested (no salicylate levels were performed as part of the studies), that there were no virologic studies or cultures performed to identify the responsible viruses or even to confirm that cases and controls had the same illness, no attempts were made to control for the degree of antecedent illness between cases and controls which might influence the medications that were taken, there was no dose-response relationship found between salicylates and Reye's syndrome, and most importantly, there was no attempt made to confirm that all of the cases were indeed Reye's syndrome. Biopsy confirmation of the diagnosis of Reye's syndrome was obtained in only 19% of the cases in the Ohio study,[6] and in fewer than a third of the PHS study cases.[7,8] The question of whether these studies were actually looking at Reye's syndrome is important because the mortality rate in the Ohio study was only 5%, compared with a national mortality rate for Reye's syndrome at the same time of 20 to 40%. This exceptionally low mortality for Reye's syndrome is especially conspicuous when one realises that the Ohio study specifically excluded the mildest cases of Reye's syndrome, which would be expected to have the lowest mortality. Reye's syndrome is typically a biphasic illness with a period of recovery between the prodromal illness and the encephalopathy. When the FDA analysed the Ohio study results in terms of a classic biphasic illness, there was no statistically significant difference in the use of aspirin between the classic cases and controls.

One of the problems facing these epidemiological studies, was when to define Reye's syndrome as beginning, in order to separate medicines that were given before the start of Reye's syndrome and therefore might be associated with the development of Reye's syndrome, from medicines given after the start of the Reye's syndrome, which probably did not play a role. The onset of Reye's syndrome was arbitrarily designated as occurring when the protracted vomiting began. As Maria Casteels-Van Daele and her colleagues[11] have pointed out, if the epidemiological studies are reanalysed with the onset of Reye's syndrome occurring with the onset of altered mental status, then phenothiazines also play a statistically significant role in Reye's syndrome, and 'weaken the validity of the epidemiological surveys suggesting a link with acetylsalicylic acid'.

In addition to the above epidemiological studies, two other epidemiological studies, the Yale study[12] and the British Paediatric Surveillance study of Dr Susan Hall,[13] also showed an association between aspirin ingestion with Reye's syndrome. However, one should not get the impression that all epidemiological studies showed an association between aspirin with Reye's syndrome. An even larger number of epidemiological studies conducted in the US and around the world, failed to show any association of aspirin with Reye's syndrome. Orlowski et al.[14] published two studies from Australia, one in 1987 involving 20 patients with Reye's syndrome where only one (5%) ingested aspirin, and one in 1990[15] describing 49 cases of Reye's syndrome where only four (8%) took aspirin. Hofman and Rosen[16] from South Africa described a series of 21 cases of Reye's syndrome in 1982 where only five patients took aspirin; Glasgow[17] reported 23 cases of Reye's syndrome from Ireland in 1984 where 14 took aspirin; Yamashita et al.[18] published two series in 1985, one from Japan where 7 of 30 Reye's syndrome cases had taken aspirin, and one from Thailand where 52 of 73 cases had ingested aspirin. Palomaque et al.[19] from the Spanish Pediatric Intensive Care Society reported that only 23 of 57 cases of Reye's syndrome in 1986 had taken aspirin. Gladtke and Schousell-Zipf[20] found aspirin ingestion in only 3 of 15 cases of Reye's syndrome from West Germany and Yu[21] from Hong Kong in 1988 reported that only 3 of 27 Reye's syndrome cases had taken aspirin. In the US, Nicolosi et al.[22] in 1985 published their results from the Mayo Clinic in Olmstead County, Minnesota and only

one of five cases of Reye's syndrome had taken aspirin, and Lichtentein et al.[23] from Cincinnati, Ohio in 1983 found that less than half (15 of 31) of their patients with Reye's syndrome had taken aspirin.

4. How Does One Prove that a Suspected Agent is the Cause of a Disease?

If epidemiological studies cannot prove that an agent causes a disease, but can only suggest an association, what is necessary to prove causation? Robert Koch, the discoverer of the cause of tuberculosis, and the father of the scientific method, elaborated four principles to prove that a specific aetiological agent is the cause of a given disease. The first principle was that the agent occurs or is found in association with the disease. This is clearly the case with aspirin and Reye's syndrome, as well as other agents including various viruses and other drugs. The second principle is that the agent can be recovered from patients with the disease. This is the first major stumbling block for the proponents of aspirin causing Reye's syndrome. No study has shown consistent presence of aspirin in the blood or urine of patients with Reye's syndrome, and in fact most studies have found negative aspirin levels in patients with Reye's syndrome when tested. The third principle is that the disease can be reproduced in an animal model by the agent. This is the major hurdle in theorising that aspirin plays a role in Reye's syndrome. No animal model of Reye's syndrome has been developed where aspirin will produce the disease. Animal models have been created where viruses will produce the disease, but aspirin plays no role. The final principle is that the agent can then be recovered from the animal model, and again this has not been successful.

5. What About the Disappearance of Reye's syndrome?

Many epidemiologists would like to point to the disappearance of Reye's syndrome in the late 1980s as an experiment in nature that proves that aspirin causes Reye's syndrome. They claim that once warning labels were placed on aspirin, and its use was severely curtailed in children, that Reye's syndrome disappeared. There are a number of problems with this hypothesis. A careful examination of the incidence of Reye's syndrome over the 1970s and 1980s, shows that Reye's syndrome was clearly disappearing before warning labels were instituted in 1986. In fact, the incidence of Reye's syndrome was steadily falling from 1979 on, despite its mortality remaining relatively unchanged at 25 to 50% (figure 1).

Three other authors have examined the disappearance of Reye's syndrome from a diagnostic standpoint, with results that differ greatly from the epidemiologists. Gauthier et al.[24,25] published an article in 1988 in which they reassessed the diagnosis of Reye's syndrome in 49 children diagnosed with Reye's syndrome between 1970 and 1986. Using more accurate diagnostic criteria, they found that the diagnosis of Reye's syndrome was confirmed as certain in only one of the cases, was probable in 11 (22%), was unlikely in 21 cases (43%), and was completely excluded in 15 cases (31%). DeVillemeur et al.[26] in 1993 reported on their personal experience of 30 patients referred to their metabolic unit with a diagnosis of Reye's syndrome. After a comprehensive metabolic evaluation, an inborn error of metabolism was demonstrable in 15 patients, and was highly suspect in an additional six others. Orlowski[27] reported in 1999, the results of the reassessment of the diagnosis in 26 patients from Australia who had survived their Reye's syndrome in the 1980s and were re-examined approximately ten years later. Of the original 26 patients with Reye's syndrome, 18 or 69% had been diagnosed with other diseases, most commonly inborn errors of metabolism, as the cause of their alleged Reye's syndrome. The most commonly diagnosed metabolic disorder was medium-chain acyl-coenzyme-A dehydrogenase deficiency.

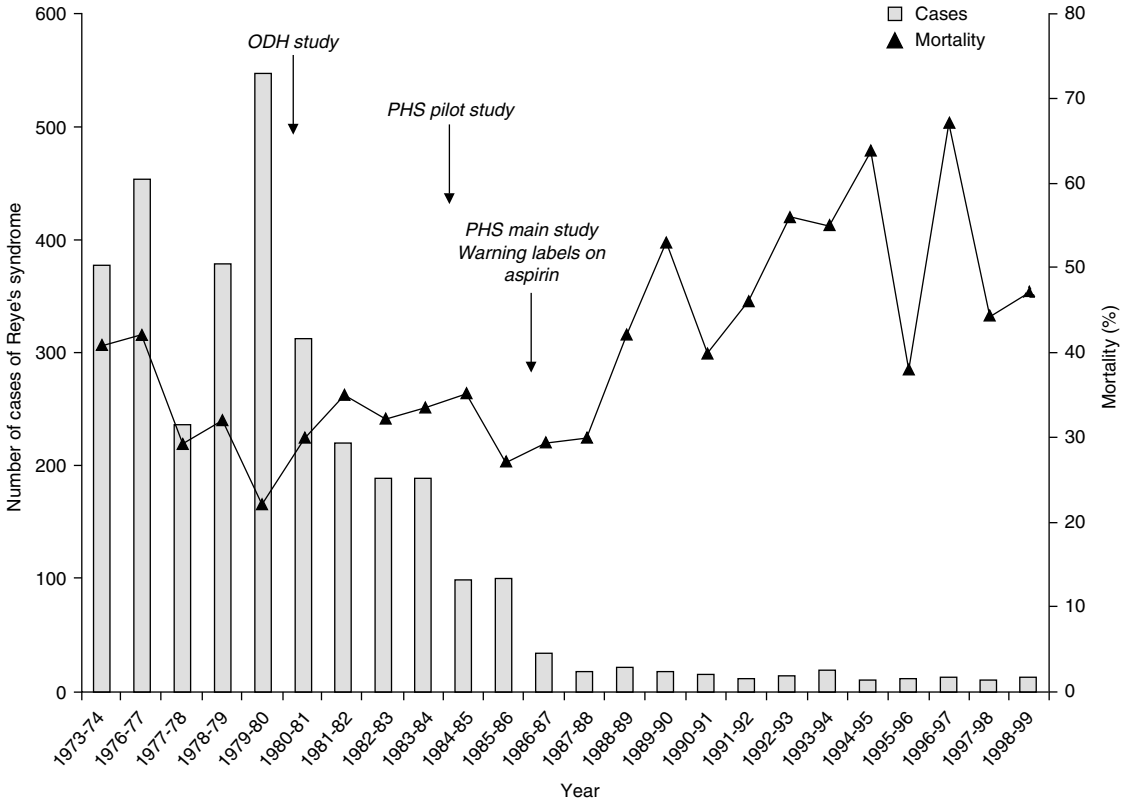

Fig. 1. The incidence and mortality of Reye's syndrome in the US from 1973 to 1999 showing that Reye's syndrome was disappearing well before warning labels were placed on aspirin (acetylsalicylic acid)-containing products. **ODH** = Ohio Department of Health; **PHS** = US Public Health Service.

6. Conclusions

Is aspirin a cause of Reye's syndrome? Definitely not. How salicylates, which have been used for over 100 years, could be associated with a syndrome which did not appear until the 1950s was never explained. What was equally mysterious was that Reye's syndrome disappeared from countries like Australia which had not used aspirin in children since the 1950s, as well as from countries like France and Belgium which continued to use aspirin in children without change throughout the 1970s, 1980s, and 1990s. With better diagnostic techniques and criteria for diagnosing Reye's syndrome, most cases originally diagnosed as Reye's syndrome are now known to be metabolic disorders. The disappearance of Reye's syndrome was probably related to the discovery and ability to diagnose inborn errors of metabolism which mimicked Reye's syndrome clinically, biochemically, and pathologically.

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