# Early Studies of Reye’s Syndrome After Aspirin Use for Fever

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**Reye's syndrome and salicylate use.**

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**Abstract**

During an outbreak of influenza A, seven patients with Reye's syndrome and 16 ill classmate control subjects were evaluated for characteristics of the patients' prodromal illness and the control subjects illness and for medication usage. Patients during the prodrome and control subjects had similar rates of sore throat, coryza, cough, headache, and gastrointestinal complaints except for documented fever which occurred significantly more often in patients than in control subjects (P = .05). While medications which did not contain salicylate were taken as frequently by patients as control subjects, patients took more salicylate-containing medications than did control children (P < .01). All seven patients took salicylate whereas only eight of 16 control subjects did so (P < .05). Patients took larger doses of salicylate than did the entire control group (P < .01). When the eight control subjects who took salicylate were compared with the patients, the patients still tended to take larger doses (P = .08). Patients with fever took salicylate more frequently than control subjects with fever (P < .01). In addition, salicylate consumption was correlated with severity of Reye's syndrome (P < .05). It is postulated that salicylate, operating in a dose-dependent manner, possibly potentiated by fever, represents a primary causative agent of Reye's syndrome.

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# Reye Syndrome -- Ohio, Michigan

### [Reye Syndrome -- Ohio, Michigan](http://www.cdc.gov/mmwr/preview/mmwrhtml/00049023.htm)

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In addition to a previously reported study from Arizona (1), CDC has received reports of studies conducted in Ohio and Michigan which suggest a relationship between Reye syndrome and salicylates (i.e., aspirin) taken during an associated antecedent illness.

Between December 1978 and March 1980, a prospective case-control study of Reye syndrome was conducted by the Ohio State Department of Health. This study involved 6 pediatric centers in the state and examined the possible relationship between Reye syndrome and medications taken during the antecedent illness. One hundred fifty-nine cases were identified in this study; slightly more than half were relatively mild, developing only stage I encephalopathy (difficult to arouse, lethargic, sleepy). A large percentage of these patients were identified during an outbreak of influenza A (H1N1) that occurred in December 1978-March 1979 and an outbreak of influenza B that occurred in December 1979-March 1980, or had varicella as an antecedent illness.

Reye syndrome patients and controls, selected from the same school classroom or neighborhood and matched for age, sex, race, and the occurrence of a similar antecedent illness (respiratory, varicella, or gastrointestinal) within 1 week of that which occurred in the case, were interviewed concerning medications taken between the time of onset of the antecedent illness and either admission to the hospital for Reye syndrome (for cases) or recovery from the illness (for controls). For each Reye syndrome case, the date of onset of vomiting, which is usually associated with the onset of Reye syndrome, was recorded. The frequency of usage of only 2 medications was found to be significantly different statistically in cases and controls. Salicylates, including those contained in various compounds, were the only medications which were taken significantly more frequently in cases (95/98, 97%) than controls (114/160, 71%) (p less than .001). All of the Reye syndrome cases with a history of salicylate ingestion took salicylates during their antecedent illness and prior to the onset of the pre-encephalopathic vomiting associated with this syndrome. Multiple logistic analysis using a model that included histories of salicylate ingestion, fever, headache, and sore throat has demonstrated that although a history of fever was significantly greater in cases than controls, this difference did not account for the even stronger association of cases with a history of salicylate ingestion. Using this model, the estimated relative risk of Reye syndrome for patients taking salicylates was 11.3 (95% confidence limits 2.7-47.5). Histories of headache and sore throats were not significantly different in cases and controls. Medications containing acetaminophen were taken by only 16% (16/98) of cases compared to 32% (51/160) of controls (p less than 0.01). Although analysis has not yet been completed concerning the dose of salicylates ingested by the patients with Reye syndrome, the majority had a history of taking no more than normally recommended. The medication history was usually obtained from parents within 7-10 days (for cases) and 10-20 days (for controls) after the onset of antecedent illness.

The recently reported study from Michigan involved 25 patients with Reye syndrome and 44 controls selected in a manner similar to that of the Ohio study, matched for the same criteria, and interviewed 4 to 83 days (mean 6.5 weeks) after their acute illness. When cases and controls were retrospectively matched for fever ( plus or minus 1o F), aspirin was taken significantly more often in cases (14/14, 100%) than controls (14/21, 67%, p less than 0.02), and acetaminophen-containing compounds were taken significantly less often in cases (0/14), than in controls (6/21, 29%, p less than .05).

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editorial note: Although the epidemiologic association between Reye syndrome and antecedent viral illnesses is well established, the etiology of this rare disease remains unclear. Several previous reports have suggested the possibility that medications taken during the antecedent illness of patients with Reye syndrome may play a role in the development of this disease, and aspirin is 1 medication which has been mentioned frequently (2-4).

The Ohio and Michigan studies reported here and the previously reported smaller study from Arizona (involving 7 cases and 16 controls) are the only controlled studies of the relationship between Reye syndrome and medications taken during the antecedent illness reported since this disease was first described. All 3 of these studies involved in-home interviews focusing specifically on medication histories of Reye syndrome patients and controls.

A number of potential problems are encountered when conducting and analyzing such studies. These include 1) difficulties in obtaining comparable and accurate medication histories in patients following a significant event (Reye syndrome) when compared to controls who have had a relatively minor illness, and the difficulty of accurate recall of events several weeks later, 2) the possibility that cases had a more severe antecedent illness and/or a pre-encephalopathic illness that included severe vomiting and headaches -- both of which may have predisposed them to take more medications than controls -- and 3) the presumed need to select cases and controls with the same viral infections, including influenza B, influenza A (H1N1), and varicella, since Reye syndrome is thought to be more strongly associated with these infections.

It is possible that parents of patients with Reye syndrome were more likely than parents of controls to recall events immediately preceding their child's major illness and hospitalization, including medications taken by their child during this period. Recall of medication histories for Reye syndrome patients may also have been more accurate and complete than the recall for controls because parents of cases were frequently interviewed earlier after their child's acute illness than were parents of controls. However, the fact that only aspirin or salicylate-containing compounds were found to have been taken significantly more frequently during the antecedent illness in cases than controls in these studies suggests that the association between Reye syndrome and salicylates may indeed be real. Furthermore, the fact that acetaminophen-containing compounds were taken by significantly fewer cases than controls in both studies, which might be expected if Reye syndrome patients were more likely to use salicylates than acetaminophen for fever or other symptoms, suggests that the recall of parents of cases was not greater than the recall of parents of controls for these medications.

Another possible reason for differences in medication histories in cases and controls is that Reye syndrome patients may have a more severe or prolonged antecedent illness and/or may subsequently develop a pre-encephalopathic illness, associated with severe vomiting, for which they might receive additional medications. Because elevated temperatures are 1 major reason for taking salicylates, both of these studies have attempted to compare the effects of differing histories of fever among cases and controls. In the Michigan study, even when cases and controls were matched for degree of fever, the difference in salicylate usage remained significant. Analyses completed in the Ohio study have demonstrated that a history of fever, as well as headaches and sore throats -- symptoms which might also cause cases to take more salicylates than controls -- did not account for the observed differences in salicylate ingestion. Additional analyses in Ohio of aspirin ingestion histories of Reye syndrome patients for the specific period between onset of prodromal illness and onset of vomiting demonstrated that all of 95 patients who received salicylates received some during their antecedent illness -- before the onset of pre-encephalopathic vomiting. The possible confounding effects of other symptoms and combinations of symptoms are being further examined in the Ohio study.

Reye syndrome is rare and associated frequently with certain viruses. Thus, comparison of medication histories in cases and controls who had the same viral infection may be important. In both of these studies, controls were selected from the same school and had a prodromal illness within 1 week of that of the cases. It is probable that many cases and controls were matched for infection because a large percentage of the cases occurred during outbreaks of influenza, and varicella patients were matched with other children who had varicella. Further analysis of the salicylate association by specific type of infection should be possible in the Ohio study.

In 1976 the Food and Drug Administration advised that, when treating children who develop vomiting associated with a viral illness, caution should be exercised in using acetaminophen, salicylates, and antiemetics because of the suspicion that these drugs, in combination with a viral illness (a possible cause of vomiting in children) might contribute to the development of Reye syndrome (5). The results of these studies suggest that during certain viral illnesses the use of salicylates -- even before the onset of vomiting -- may be a factor in the pathogenesis of Reye syndrome. In view of these data, parents should be advised to use caution when administering salicylates to treat children with viral illnesses, particularly chickenpox and influenza-like illnesses. references

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### Editorial Note

Editorial Note 1997: Reye syndrome (RS) was first described in Australia (1) and in the United States in 1963 (2). During the 1960s and 1970s, RS outbreaks in the United States became increasingly recognized in association with outbreaks of influenza and following chickenpox. National surveillance for RS, first conducted during the 1973-74 nationwide epidemic of influenza B, resulted in the recognition of regional as well as nationwide outbreaks of RS. Although children of all ages were affected, incidence peaked among children aged 5-15 years. During the initial years of national surveillance, 236-555 cases were reported each year; the largest number occurred in association with outbreaks of influenza B and influenza A(H1N1). Population-based studies suggested that the average annual incidence among children aged less than 18 years was approximately one case per 100,000 persons. Case-fatality rates reported through national surveillance were initially as high as 40% and between 20% and 35% during the late 1970s to mid-1980s.

Although anecdotal reports during the 1970s had suggested the possibility of an association between RS and aspirin, the series of studies reported in 1980 -- the first from Arizona (involving seven cases and 16 controls) followed by larger studies conducted in Michigan and Ohio -- were the first case-control studies to examine this issue. However, the possibility that a commonly used medication such as aspirin, which had been prescribed for several decades for febrile illnesses by those taking care of pediatric patients, might be associated with a severe and frequently fatal illness was not readily accepted by many in the medical community. As a reflection of the controversial nature of this matter, the initial Editorial Note published in the November 7, 1980, issue of MMWR outlined several of the most important potential limitations of these studies and the considerations that had led CDC to conclude that the studies were strongly suggestive of an association between aspirin use and increased risk for RS. In an effort to fulfill CDC's public health responsibility, the Editorial Note advised parents to "use caution when administering salicylates to treat children with viral illnesses, particularly chickenpox and influenza-like illnesses."

In October 1982, after CDC received a report of a fourth case-control study conducted in Michigan during the 1980-81 influenza season demonstrating a similar association, CDC convened a working group of expert consultants to review all four studies. The working group, which included pediatricians and epidemiologists as well as representatives of the Food and Drug Administration (FDA) and the American Academy of Pediatrics (AAP), reviewed the studies that had been completed and the many concerns expressed by those in the medical community, including consultants and representatives of the pharmaceutical industry. The working group supported CDC's original recommendation and stated that "until the nature of the association between salicylates and RS is clarified, the use of salicylates should be avoided, when possible, for children with varicella infections and during presumed influenza outbreaks" (3).

Soon after CDC made these recommendations, FDA conducted an independent audit and analysis of the data from the Ohio and Michigan studies. FDA then convened a scientific workshop to review the data, including analyses completed by FDA. Experts from the academic community, the pharmaceutical industry, and consumer organizations attended the meeting and had opportunities to present their independent analyses and concerns and to express their opinions regarding the studies. After an intensive review of all the concerns, the scientific working group concluded that the new analysis supported earlier evidence of the association between use of aspirin and increased risk for RS. As a result of this review process, in June 1982, the Surgeon General issued a recommendation advising "against the use of salicylate and salicylate-containing medications for children with influenza and chickenpox" (4).

Despite the numerous reviews by expert panels and intense scrutiny of the first four studies, many continued to express concerns about these studies, including industry representatives, the Office of Management and Budget (5), and the executive committee of the AAP, which issued a statement calling for further investigation. These concerns focused on the nature of the case-control studies and the many potential epidemiologic issues in such studies, including potential biases of selection and reporting as well as possible confounding (5). As a result of the concerns expressed by many groups, in December 1982, the Assistant Secretary of Health appointed a Public Health Service Task Force, comprised of representatives from CDC, FDA, and the National Institutes of Health, to assist in planning and conducting additional research on this issue. A decision about warning labels on packages of certain medications for children was deferred pending the results of this research (5).

The Public Health Service Task Force designed a new epidemiologic study to address the concerns that had been raised about the first four studies. A committee was convened by the Institute of Medicine to serve as an advisory board to review the protocol, monitor the study's progress, and review the analysis and results. Between February and May 1984, a pilot study, designed to test the methods for the main study of the relation between medication use and risk for RS, was undertaken. The pilot study, which involved 14 states and 33 pediatric tertiary-care centers, demonstrated a high odds ratio (16.1; lower 95% confidence limit=4.6) associated with the ingestion of aspirin during an antecedent respiratory or chickenpox illness and the development of Reye syndrome, consistent with the risks observed in previous studies. Evaluation of the epidemiologic issues raised concerning previous studies did not indicate that any of these issues could explain the observed association. Although in 1983 there had been no agreed-upon plans to publish the pilot study, the study was subsequently published in October 1985 (6) at the recommendation of the Institute of Medicine committee. In March 1986, FDA ruled that all over-the-counter aspirin and aspirin-containing products were required to be labeled with a warning about RS. \*

Following completion of the pilot study, the main study of RS and medications was conducted during January 1985-May 1986. Although 70 pediatric tertiary-care centers throughout the United States participated in this study, including many that had previously reported the largest number of cases through CDC's national surveillance, only 33 cases of RS that met the study criteria were identified during the 17-month study period, which included two influenza seasons. However, the number of cases enrolled was fewer than had been expected based on prior experience and than had been specified by the original protocol (at least 100 cases), and the decision was made to discontinue the study because of the small number of cases identified, which reflected the declining incidence of RS that had been observed nationally during the preceding several years. In addition, in this study, as in the earlier studies, a high odds ratio was observed that could not be explained by any of the epidemiologic issues that the study had sought to address (7).

Although several years were required to address all the concerns about the initial studies, assessment of temporal trends in RS in the United States indicate that a dramatic decline in the incidence of this disease began to occur in the early 1980s soon after the initial and subsequent MMWR reports of these studies. This decline appeared to coincide with a decline in aspirin use among children that occurred as a result of the publicity surrounding these studies (8-10). The initial studies conducted during the early 1980s suggested that aspirin was administered to up to 70% of children with febrile respiratory illnesses. The national intervention involving the removal of a risk factor, aspirin use among children, was associated with a marked reduction in the incidence of this disease, providing the most convincing corroborating evidence for the association first reported in the case-control studies.

1997 Editorial Note by Eugene S Hurwitz, MD, Day Care Activities Coordinator, and Lawrence B Schonberger, MD, MPH, Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, CDC.

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