# Public Health Service Study of Reye's Syndrome and Medications

## Report of the Main Study

Eugene S. Hurwitz, MD; Michael J. Barrett, MD; Dennis Bregman, MS; Walter J. Gunn, PhD; Paul Pinsky, MPH; Lawrence B. Schonberger, MD; Joseph S. Drage, MD; Richard A. Kaslow, MD; D. Bruce Burlington, MD; Gerald V. Quinnan, MD; John R. LaMontagne, PhD; William R. Fairweather, PhD; Delbert Dayton, MD; Walter R. Dowdle, PhD

Between January 1985 and May 1986, following completion of a pilot study, a main study concerning the possible association between Reye's syndrome and salicylates was conducted. Twenty-seven patients with stage II or deeper Reye's syndrome whose diagnoses were confirmed by an expert panel and who had appropriate antecedent illnesses (chickenpox, respiratory illness, or gastrointestinal illness) prior to the onset of Reye's syndrome were compared with 140 controls matched for age, race (black or not black), and type and timing of onset of antecedent illness. Controls were selected from the same hospital, emergency room, or school as case-patients or were identified by random-digit telephone dialing. As in the pilot study, a strong statistical association with ingestion of salicylates during the antecedent illness and prior to the onset of Reye's syndrome was observed (odds ratio, 40; lower 95% confidence limit, 5.8). Analysis of the independent risk of aspirin and nonaspirin salicylates revealed a significant association with aspirin (odds ratio, 26; lower 95% confidence limit, 6.4); the independent risk of nonaspirin salicylates could not be assessed because only two cases were not exposed to aspirin. Assessment of epidemiologic issues of concern, including case-control differences in the severity of the antecedent illness, did not explain the high odds ratios that were observed. The high percentage of patients with Reye's syndrome exposed to salicylates (≥90%) in this and prior studies suggests that, though the reported incidence of Reye's syndrome has declined in recent years, concomitant with a decline in salicylate use among children, a majority of Reye's syndrome cases may be attributable to salicylate use.

(*JAMA* 1987;257:1905-1911)

BETWEEN 1980 and 1982, four case-control studies reported an association between Reye's syndrome and ingestion of salicylates during antecedent chickenpox and respiratory illnesses.[1-3] These reports resulted in the recommendation by several expert groups that children avoid salicylates for such illnesses,[4,5] but, as with many epidemiologic studies, some concerns were expressed regarding methodological issues and limitations of the studies. To address these concerns, the Public Health Service task force on Reye's syndrome was formed to design and implement a new epidemiologic study concerning the possible relationship between Reye's syndrome and medications. A committee of the Institute of Medicine of the National Academy of Sciences served as an advisory board to evaluate the study protocol, monitor the study's progress, and review the analyses and results.

**For editorial comment see p 1941.**

A pilot study,[6] undertaken prior to the initiation of the full study, was completed in 1984. The pilot study demonstrated the feasibility of the study methods and the usefulness of the data to address epidemiologic issues of concern. It also showed a strong epidemiologic association with ingestion of salicylates (almost entirely aspirin) during antecedent illnesses and prior to the onset of Reye's syndrome. The Institute of Medicine recommended that the pilot study be published and that the main study of Reye's syndrome and medications be conducted to further address public health questions, determine the reliability of the pilot study findings, and expand the number and geographic distribution of cases and controls.

Data collection for the main study was conducted between January 1985 and May 1986 and involved the participation of 50 pediatric tertiary-care centers throughout the United States during the first 11 months. Twenty additional tertiary-care centers participated in the final six months of the study, December 1985 to May 1986, the 1985-1986 influenza season. Despite the facts that, nationally, the largest number of Reye's syndrome cases occur in association with influenza B and that in 1985-1986 an influenza B epidemic occurred that was the largest in the United States since the 1968-1969 influenza season,[7] only 33 patients with Reye's syndrome, confirmed by a physician review panel, were identified for this study. This number was well below the desired 100 to 200 cases specified in the protocol but consistent with the declining incidence of Reye's syndrome in the United States.[8-10]

The Public Health Service Reye Syndrome Task Force conducted a planned midpoint analysis, which was reviewed by the Institute of Medicine Committee on the Reye Syndrome. Following this review, the task force recommended and the Institute of Medicine committee concurred that, in view of the strong association between salicylates (and specifically aspirin) and Reye's syndrome observed in the midpoint analysis, which was consistent with the findings of the pilot study, as well as the increasing rarity of this disease and the consequent expense and difficulty of enrolling additional cases in a reasonable period of time, the study should be ended. This report describes the major findings of this study.

### METHODS

Methods for this study were similar to those used in the pilot study,[6] which have been detailed previously.

From the Public Health Service Reye Syndrome Task Force, consisting of members from the Centers for Disease Control, Food and Drug Administration, and National Institutes of Health, US Department of Health and Human Services, Atlanta.

Reprint requests to Bldg 6, Room 117, Centers for Disease Control, 1600 Clifton Rd NE, Atlanta, GA 30333 (Dr Hurwitz).

### Criteria for Eligibility

To be enrolled in the study, all patients had to have (1) received a diagnosis of Reye's syndrome from a physician, (2) reported an antecedent respiratory or gastrointestinal illness or chickenpox within three weeks before hospitalization (for the purposes of this study, chickenpox was defined as characteristic blisters with fluid; respiratory illness as any two of the following manifestations—fever, runny nose or congestion, cough, and sore throat—lasting two or more consecutive days in the absence of chickenpox; and gastrointestinal illness as three or more loose watery stools for two or more consecutive days in the absence of either chickenpox or respiratory illness), and (3) stage II or deeper encephalopathy as defined in a previously reported National Institutes of Health consensus conference.[11] Guidelines for diagnosing Reye's syndrome were based on previously published criteria of the Centers for Disease Control.[12] At the conclusion of the study, an independent expert panel of physicians (the physician review panel) reviewed the hospital records of the enrolled patients using a two-step procedure: first, with all historical medication information as well as results of drug and toxicology screens deleted from the records, and second, with all information available.

### Study Sites and Case Enrollment

Eligible patients were identified through the cooperation of initially 50 (January to November 1985) and subsequently 70 (December 1985 to May 1986) participating pediatric tertiary-care centers (defined as hospitals with 50 or more pediatric beds or a pediatric intensive care unit, or both) located in 26 states.

At each pediatric center, a hospital surveillance officer (usually a nurse or physician who was involved in the care of patients with Reye's syndrome) notified a central coordinator of all hospitalized patients with confirmed or possible Reye's syndrome (including those identified with possible stage 0 or I) within 24 hours of hospitalization or diagnosis. Patients hospitalized with stage 0 or I Reye's syndrome were followed up daily by telephone (for five days or until the day of discharge) to determine whether they met the study's criteria for eligibility. Seventeen patients with stage 0 or I Reye's syndrome were reported; none of these patients progressed to stage II or deeper encephalopathy.

The attending physician completed a two-month follow-up questionnaire for each case-patient initially enrolled to determine whether the patient's diagnosis was still considered to be Reye's syndrome or whether an alternative diagnosis (for example, an inborn error of metabolism) had been established.

### Controls: Source and Matching Criteria

Four types of controls were sought: children visiting the emergency room where the case-child was hospitalized (emergency room controls), children hospitalized at the same center as the matched case-patient (inpatient controls), those attending the same school or day-care center (school controls), and those identified by random-digit telephone dialing (community controls).

The controls were randomly selected from children matched to case-patients on the basis of age group, race (black or not black), and the occurrence of an antecedent illness meeting the definition (whether chickenpox or respiratory or gastrointestinal illness) within a preestablished period. Ninety-seven percent of the parents of control subjects selected agreed to participate.

In contrast to the pilot study, the main study protocol specified that two analyses would be conducted comparing case-patients and hospital and emergency room controls, one analysis including and one excluding subjects with chronic illnesses. This was planned because of concern about possible overrepresentation of patients with certain chronic illnesses among hospital and emergency room controls when compared with case-patients. The chronic illnesses of concern were those requiring frequent physician visits (including cancer, hematologic disorders, and cardiac defects), during which advice about medications might be given, or for which antipyretics were indicated or contraindicated. Similar percentages of case-patients (23% [six]) and emergency room controls (20% [six]) had such illnesses. Although a larger percentage of inpatients (43% [nine]) had such chronic illnesses, this difference did not substantively alter the results of the medication analyses; thus, analyses reported herein are based on inclusion of case-patients and controls with chronic illnesses.

### Interviews, Questionnaires, and Visual Aids

Parents or guardians of case-patients and controls were screened by telephone to identify the main care provider, that is, the person who provided the most care for the child during the antecedent illness (usually a parent). During the screening interview, the date of onset, type, and specific symptoms of the antecedent illness were obtained to determine if subjects met the antecedent-illness definition. In-depth interviews were conducted with the main care provider and included questions concerning the child's illness as well as medications administered.

The parent or guardian was also asked to identify other care providers, defined as persons who had taken care of the child for four or more consecutive hours on any day during the illness or had been present when the child might have taken medication. Other care providers were contacted by telephone and those who reported that they were present when medications were administered or themselves administered medications were interviewed in person concerning medication histories.

Whenever possible, older children (between 10 and 12 years old) and teenagers (≥13 years old) were interviewed concerning medications self-administered or administered by others.

Interviewees were asked to show the bottles or containers of medications to the interviewer for documentation; when medication containers were not available for verification, interviewees were asked to identify medications from a set of pictures, developed from the *Physicians' Desk Reference*,[13] of the most commonly used nonprescription medicines.

### Onset of Reye's Syndrome

To compare the antecedent illness of case-patients with the matched antecedent illness of controls, the onset of Reye's syndrome among case-patients was defined, as in the pilot study, as the first day when any of a series of classically described symptoms (alone or in combination) occurred for one or more consecutive days and resulted in hospitalization, including nausea, vomiting, dry heaves, hyperactivity, excitability, disorientation or confusion, delirium, combativeness, and coma. The onset was designated as one calendar day earlier if headache, dizziness, lethargy, or severe loss of appetite first occurred on that day. This definition was applicable to all but two case-patients, both of whom had had only one day of classic symptoms of Reye's syndrome just before hospitalization; for these two patients, the onset was defined as the day of onset of the classic symptoms.

### Study Analyses

Medication analyses were based on information obtained from interviews with (1) main care providers only, (2) main and other care providers combined, and (3) main and other care providers as well as study subjects (that is, children) who were interviewed.

Odds ratios comparing case vs control medication exposures were estimated with the use of univariate and multivariate conditional logistic regression mod-

els. The potential confounding role of variables indicating severity of antecedent illness was assessed using this method in a model similar to that described for the pilot study.

Analyses were conducted comparing medication exposure for cases with each control group and all control groups combined. These analyses revealed similar results unless otherwise specified. For the sake of brevity, only the results of comparisons of case-patients and all control groups are provided for many of the results reported here.

One-tailed (95%) confidence limits provided here were based on the group sequential design of the study. The midpoint and final analyses were each allocated a type I error rate of 0.0294. Together, these error rates would have produced an overall nominal type I error rate of 0.05 if the study had not terminated at the midpoint.

## RESULTS

### Case Review

Fifty-three patients were initially identified by attending physicians for possible enrollment in the study. Seven of these, for whom the diagnosis of Reye's syndrome was considered at the time of hospitalization, were subsequently reported by the attending physician to have received another diagnosis. The physician review panel independently concurred with the non–Reye's syndrome diagnoses for six of these patients (one record was not available) and recommended that these cases be excluded from analyses. (The ages and reasons for exclusion and/or other diagnoses reported by attending physicians and/or the physician review panel for the six patients with medical records were as follows: 13-month-old patient, carnitine deficiency; 1-year-old, citrullinemia; 3-month-old, miliary tuberculosis; 4-year-old, ornithine transcarbamoylase deficiency; 6-year-old, possible viral hepatitis, hepatic failure, and cerebral hemorrhage; and 5-month-old, systemic infection and possible metabolic disorder, cerebrospinal fluid containing 67/mm$^3$ [67 × 10$^6$/L] white blood cells.)

The physician review panel also recommended that an additional 13 patients who had been enrolled by attending physicians be excluded from analyses because another diagnosis appeared more likely (ten patients) or there was insufficient information in the medical records to determine whether the patient had Reye's syndrome (three patients). (The patients recommended for exclusion included the following: 10-month-old, probable viral hepatopathy with elevated bilirubin level; 9-month-old, acute encephalopathy [insufficient information]; 10-year-old, head injury/shock/cerebral edema, results of electron microscopy of liver not consistent with Reye's syndrome; 16-year-old, electron microscopy demonstrating cholestasis; 8-year-old, possible hepatitis, bilirubin level = 8.8 mg/dL [150 μmol/L]; 18-month-old, diarrhea and dehydration [insufficient information]; 6-month-old, acute encephalopathy [insufficient information]; 3-year-old, multisystem disease, persistent elevated liver enzyme levels; 4-year-old, viral myocarditis; 2-year-old, persistent hyperammonemia; 2-year-old, bacterial infection and elevated bilirubin level [mental status improved with rehydration]; 4-month-old, undiagnosed metabolic disorder; and 4-month-old, hypoxic encephalopathy.) Ten (77%) of these patients were less than 5 years old.

Of the remaining 33 patients, six with cases of Reye's syndrome confirmed by the expert panel were not included in the analyses because an antecedent illness that met the definition specified in the protocol (and could be used for matching purposes) was not identified in the screening or the main care provider interview. These patients included one patient whose only reported symptom was three days of headaches, one with five days of headache and two days of earache, and three patients who had symptoms of a respiratory illness that were insufficient either in number, duration, or both to meet the definition of an antecedent respiratory illness. (The symptoms reported for these patients all occurred within three weeks prior to hospitalization.) One additional patient was not included in the analyses because the onset of Reye's syndrome according to the study definition was on the first day of the antecedent respiratory illness. Thus, 27 Reye's syndrome cases with appropriate antecedent illnesses and their matched controls were available for analyses.

With the exception of three patients, all decisions of the physician review panel concerning the exclusion of patients were the same whether medication histories and drug and toxicology screens were deleted or provided. Three patients recommended for inclusion in the study in the first step were excluded by the panel during the second step because information in the medical records was considered inadequate to confirm the diagnoses and no drug or toxicology screen was available.

The demographic characteristics and types of antecedent illnesses for the 27 Reye's syndrome case-patients and 140 controls are shown in Table 1. As in the pilot study, the majority of study subjects (67% of case-patients and 68% of controls) were more than 10 years old. These 27 case-patients were hospitalized in 19 states and included seven cases during the first 11 months of the study (January to November 1985, which included 50 participating tertiary-care centers and an influenza season characterized by influenza A[H3N2] activity) and 20 during the following six months (December 1985 to May 1986, which included 70 participating centers and a period of major influenza B activity).

Table 1.—Characteristics of 27 Reye's Syndrome Case-Patients and 140 Controls

| | Case-Patients | Controls |
|---|---|---|
| Age, y | | |
| Range | 3-16 | 2-17 |
| Median | 12 | 12 |
| Mean | 11.0 | 10.6 |
| No. (%) of subjects by age group, y | | |
| <5 | 3 (11) | 18 (13) |
| 5-9 | 6 (22) | 27 (19) |
| 10-18 | 18 (67) | 95 (68) |
| Race, No. (%) | | |
| White | 23 (85) | 125 (89) |
| Black | 1 (4) | 8 (6) |
| Asian/American Indian | 2 (7) | 4 (3) |
| Other | 1 (4) | 3 (2) |
| Sex, No. (%) | | |
| Male | 14 (52) | 72 (51) |
| Female | 13 (48) | 68 (49) |
| Antecedent illness, No. (%) | | |
| Respiratory | 25 (93)* | 135 (96)* |
| Chickenpox | 1 (4)* | 2 (1)* |
| Diarrhea | 1 (4)* | 3 (2)* |

*Percentages do not add up to 100 because of rounding.

The mean highest levels of serum aspartate aminotransferase, alanine aminotransferase, and ammonia in the case-patients were 1491 U/L, 1570 U/L, and 273 μg/dL (160 μmol/L), respectively. Biopsy or autopsy evidence of Reye's syndrome was reported for eight patients. Sixteen patients did not progress beyond stage II encephalopathy; 11 progressed to stage III or deeper encephalopathy. Three patients died—a case-fatality rate of 11%.

Among the 140 controls were 30 emergency room, 22 inpatient, 45 school, and 43 community controls. The largest percentage of both emergency room and inpatient controls were admitted or seen in the emergency room because of an acute infectious process (60% of emergency room and 45% of inpatient controls); other reasons for hospitalization or emergency room visits included trauma, asthma, seizure disorder, and abdominal pain.

In addition to the main care provider, a mean of 1.3 care providers for case-patients vs 0.83 care providers for controls was reported. Ninety-four percent (34/36) of these additional care providers reported for case-patients and 87% (101/116) reported for controls were successfully contacted and interviewed by telephone to determine if they had been present when medications were administered or themselves administered medications. Of those contacted, 59% (20/34) for case-patients and 60% (61/101) for controls reported that they

Table 2.—Generic Components of Medications Administered to 20% or More of Study Subjects During Antecedent Respiratory or Chickenpox Illnesses

| Generic Component | Case-Patients Exposed, % (n=27) | Controls Exposed, % | | | | |
|---|---|---|---|---|---|---|
| | | Emergency Room (n=30) | Inpatient (n=22) | School (n=45) | Community (n=43) | Total (N=140) |
| Acetaminophen | 29.6 | 90.0 | 77.3 | 91.1 | 81.4 | 85.7 |
| Alcohol | 44.4 | 53.3 | 50.0 | 46.7 | 72.1 | 56.4 |
| Amoxicillin | 7.4 | 20.0 | 0.0 | 4.4 | 11.6 | 9.3 |
| Caffeine | 22.2 | 6.7 | 4.5 | 2.2 | 14.0 | 7.1 |
| Camphor | 14.8 | 10.0 | 9.1 | 13.3 | 20.9 | 14.3 |
| Chlorpheniramine maleate | 22.2 | 23.3 | 22.7 | 20.0 | 37.2 | 26.4 |
| Dextromethorphan hydrobromide | 29.6 | 36.7 | 22.7 | 33.3 | 60.5 | 40.7 |
| Eucalyptus oil | 29.6 | 13.3 | 13.6 | 28.9 | 27.9 | 22.9 |
| Guaifenesin | 22.2 | 43.3 | 36.4 | 31.1 | 34.9 | 35.7 |
| Menthol | 40.7 | 26.7 | 13.6 | 33.3 | 39.5 | 30.7 |
| Phenol | 11.1 | 16.7 | 4.5 | 8.9 | 20.9 | 13.6 |
| Phenylephrine hydrochloride | 14.8 | 6.7 | 22.7 | 20.0 | 20.9 | 17.9 |
| Phenylpropanolamine hydrochloride | 18.5 | 40.0 | 36.4 | 33.3 | 44.2 | 38.6 |
| Pseudoephedrine hydrochloride | 29.6 | 16.7 | 31.8 | 26.7 | 48.8 | 32.1 |
| Salicylates* | 96.3 | 40.0 | 27.3 | 44.4 | 34.9 | 37.9 |

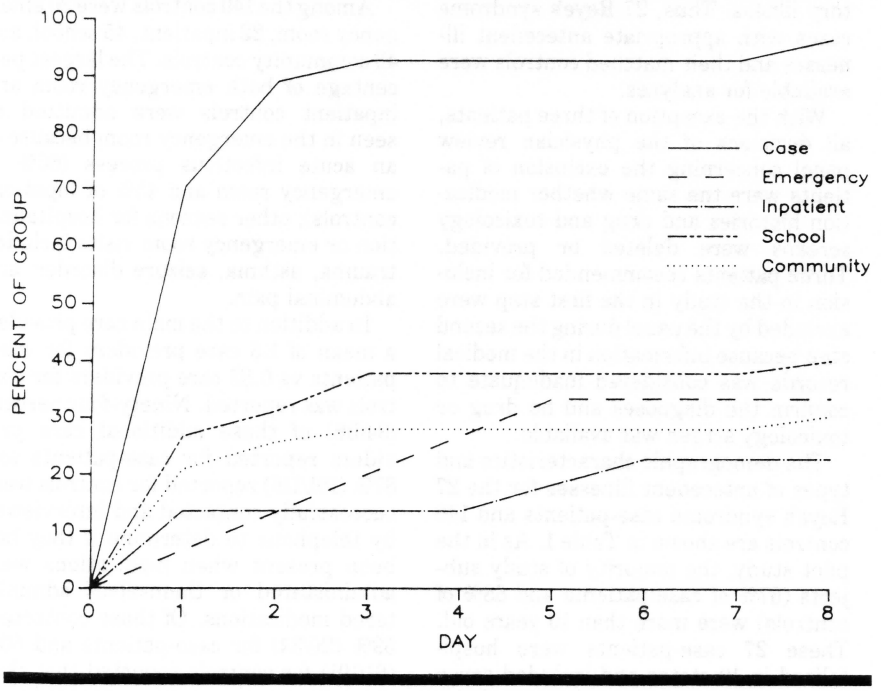
*Salicylates include bismuth subsalicylate, magnesium salicylate, and acetylsalicylates; the only salicylate exposure for one case and 11 controls was to bismuth subsalicylate, and for two additional controls the only exposure was to magnesium salicylate.

Table 3.—Odds Ratios for Exposure to Salicylates and Acetaminophen of 27 Case-Patients vs 140 Controls*

| | Controls | | | | |
|---|---|---|---|---|---|
| | Emergency Room | Inpatient | School | Community | Total |
| Salicylates | (4.9)† 39 | (7.8) 66 | (4.4) 33 | (5.9) 44 | (5.8) 40 |
| Acetaminophen | 0.04 (0.18)‡ | 0.13 (0.51) | 0.04 (0.16) | 0.08 (0.30) | 0.06 (0.18) |

*Odds ratios are based on matched set analyses and are not adjusted for differences in the severity of the antecedent illness.
†Lower 95% confidence limit.
‡Upper 95% confidence limit.

Fig 1.—Cumulative percentages of subjects exposed to salicylates by day of antecedent illness.




had been present or had directly administered medications during the antecedent illness (or before hospitalization for case-patients and hospital controls). Among the individuals who met this additional care provider definition (as a second main or other care provider), 100% (20/20) were successfully interviewed for case-patients vs 95% (58/61) for controls.

None of the case-patients and five (19%) of the control children 13 years old or older were interviewed as their own main care provider. In addition, eight (44%) case-patients and 62 (65%) control children 10 years old or older were interviewed concerning medications they self-administered or that were administered by others.

The interviews for 18 (67%) of the case-patients took place in the hospital, compared with nine (41%) of hospital-based controls. Interviews of main care providers were completed a mean of 12.3 days (range, six to 21) after the onset of antecedent illness for case-patients vs 13.2 days (range, six to 28) for all controls. Seventy-seven percent of case-patients were interviewed within two weeks and 100% within three weeks after onset of antecedent illness, vs 66% of controls within two weeks and 94% within three weeks.

## Generic Components of Medication

Analysis of the generic components of medications reported by the main care providers and/or other care providers to have been administered before the clinically defined onset of Reye's syndrome in case-patients and at any time during the matched antecedent illness in controls revealed 15 compounds given to at least 20% of case-patients or controls (Table 2). As in the pilot study, only two compounds, salicylates and acetaminophen, were used with a significantly different frequency among case-patients and all four control groups. Case-patients had significantly higher odds of receiving salicylates and significantly lower odds of receiving acetaminophen during the antecedent illness than did controls (Table 3).

Main care providers reported salicylates were administered to 96% of case-patients and 32% of controls and that they themselves directly administered salicylates to 93% of case-patients and 26% of controls.

Almost all case-patients (26 [96%]) and controls (126 [90%], including 90% of emergency room, 77% of inpatient, 96% of school, and 91% of community controls) ingested either salicylates or acetaminophen during the antecedent illness. The majority of these (96% of case-patients vs 89% of all controls) first took these medications on or before the third day of illness. As in the pilot study,

differences in the percentages of case-patients and controls who took salicylates were apparent in the data on the first day of illness (Fig 1).

Analyses were conducted to assess the possible independent risk of aspirin and nonaspirin salicylates (which included bismuth subsalicylate and magnesium salicylate). Ninety-three percent of cases and 29% of controls were exposed to aspirin (odds ratio, 26; lower 95% confidence limit, 6.4). No differences were apparent among case-patients and controls taking nonaspirin salicylates (19% of case-patients vs 14% of controls). Assessment of the risk of nonaspirin salicylates, independent of aspirin, would be best accomplished by comparisons of nonaspirin salicylate exposure among case and control subjects not exposed to aspirin. However, there were too few case-patients not exposed to aspirin (two) to allow such analyses.

## Brands of Medication

Interviewers were able to verify medications by seeing the bottles for 67% of the case-patients vs 68% of all controls. Pictures of medications were used to verify medications for an additional 14% of case-patients and 19% of controls. Specific brand names for salicylates were reported for almost all case-patients and controls; brand names were reported for 26 of 26 (100%) of case-patients and 11 of 12 (92%) emergency room, six of six (100%) inpatient, 20 of 20 (100%) school, and 14 of 15 (93%) community controls.

## Dose of Salicylates

Analyses of salicylate doses were based on doses reported only by the main care provider to reduce the possibility that the same doses would be reported twice. The median total reported dose of salicylates administered during the antecedent illness among those exposed to salicylates was 74.3 mg/kg for case-patients (range, 4.1 to 534.1) compared with 24.5 mg/kg for controls (range, 2.4 to 357.1). Case-patients received a median dosage of 26.4 mg/kg/d (range, 4.1 to 89.0) compared with 11.1 mg/kg/d for controls (range, 2.4 to 51.0). Wilcoxon rank-sum analyses indicated that case-patients were administered significantly higher total and average daily doses of salicylates than were controls ($P = .0052$ and $P = .0015$, respectively). Sixty-seven percent of case-patients received 20 mg/kg/d or more of salicylates compared with only 22% of controls (Fig 2). Weights of two case-patients and seven controls exposed to salicylates were unknown; these persons were excluded from the analyses related to dose of salicylates.

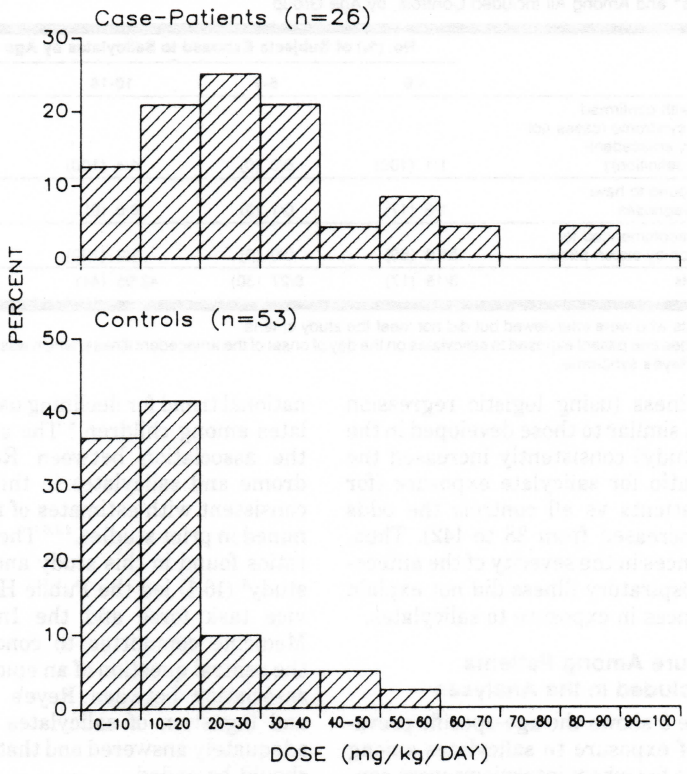



Fig 2.—Doses of salicylates administered to case-patients (n = 26) and controls (n = 53) (doses grouped by 10-mg/kg/d intervals).

Table 4.—Symptoms and Associated Actions Reported During Antecedent Respiratory Illnesses for 25 Case-Patients and 135 Matched Controls

| Symptom or Action | Case-Patients (n = 25) | Controls | | | | |
|---|---|---|---|---|---|---|
| | | Emergency Room (n = 29) | Inpatient (n = 22) | School (n = 41) | Community (n = 43) | Total (n = 135) |
| Duration (mean days) | 4.9 | 10.2 | 10.7 | 8.9 | 9.4 | 9.6 |
| Overall severity score (mean)* | 1.5 | 1.6 | 1.8 | 1.7 | 1.6 | 1.7 |
| Fever score (mean)* | 1.8 | 1.9 | 2.1 | 1.9 | 1.9 | 1.9 |
| Mean peak temperature, °C† | 38.2 | 38.4 | 38.7 | 38.4 | 38.4 | 38.4 |
| Fever‡ | 64 (2.8) | 79 (3.70) | 68 (3.20) | 88 (3.97) | 72 (3.29) | 78 (3.59) |
| Cough‡ | 76 (4.16) | 97 (6.71) | 82 (6.72) | 93 (6.66) | 91 (6.92) | 91 (6.77) |
| Headache‡ | 56 (2.79) | 48 (3.36) | 55 (3.08) | 83 (3.62) | 74 (3.31) | 68 (3.41) |
| Muscle aches‡ | 24 (3.17) | 31 (4.00) | 41 (4.89) | 37 (3.20) | 42 (3.67) | 38 (3.79) |
| Sore throat‡ | 64 (2.88) | 62 (6.39) | 59 (3.54) | 76 (4.55) | 72 (3.74) | 69 (4.49) |
| Absent from school/in bed‡ | 80 (3.35) | 93 (3.69) | 82 (3.50) | 95 (3.97) | 77 (4.18) | 87 (3.94) |
| Consulted/saw health care provider‡ | 44 | 66 | 55 | 49 | 40 | 50 |

*Based on main care provider's report of none (= 0), mild (= 1), moderate (= 2), or severe (= 3).

†Included only if fever was indicated and measured (13 case-patients, 18 emergency room controls, 13 inpatient controls, 29 school controls, and 22 community controls).

‡Values are percentages of patients; mean number of days of duration among patients reported to have these symptoms or actions are shown in parentheses.

## Antecedent Illnesses of Case-Patients and Controls

Twenty-five of the 27 case-patients had an antecedent respiratory illness. As in the pilot study, these case-patients tended to have a somewhat less severe respiratory illness than did controls as measured by the prevalence and reported severity of various symptoms, as well as by the mean peak temperature (Table 4). The mean duration of the antecedent illness was shorter for cases than controls because it was truncated at the day of onset of Reye's syndrome. Because of this less severe illness among case-patients, controlling for these differences in the severity of the antece-

Table 5.—Exposure to Salicylates During Antecedent Illnesses Among Patients Not Included in Study Analyses* and Among All Included Controls, by Age Group

| | No. (%) of Subjects Exposed to Salicylates by Age Group, y | | | |
|---|---|---|---|---|
| | <5 | 5-9 | 10-18 | Total |
| Patients with confirmed Reye's syndrome (cases not meeting antecedent-illness definition)† | 1/1 (100) | 0/0 (0) | 4/4 (100) | **5/5** (100) |
| Patients found to have other diagnoses | 1/6 (17) | 0/1 (0) | 0/0 (0) | **1/7** (14) |
| Patients recommended for exclusion by expert panel | 5/10 (50) | 0/0 (0) | 3/3 (100) | **8/13** (62) |
| All controls | 3/18 (17) | 8/27 (30) | 42/95 (44) | **53/140** (38) |

*Patients who were interviewed but did not meet the study criteria.
†Excludes one patient exposed to salicylates on the day of onset of the antecedent illness, which was also the day of onset of Reye's syndrome.

dent illness (using logistic regression models similar to those developed in the pilot study) consistently increased the odds ratio for salicylate exposure (for case-patients vs all controls the odds ratio increased from 38 to 142). Thus, differences in the severity of the antecedent respiratory illness did not explain differences in exposure to salicylates.

### Exposure Among Patients Not Included in the Analyses

Table 5 shows the age-specific prevalence of exposure to salicylates among patients for whom interviews were conducted but who were not included in the analyses because they did not meet study criteria. All of the six case-patients who were not eligible because they did not meet the antecedent-illness definition took salicylates during their illness; five of the six were exposed before the clinically defined onset of Reye's syndrome. The sixth patient, in whom the antecedent illness and Reye's syndrome appeared on the same day, took salicylates on that day. In contrast, only one of the seven case-patients (14%) (all but one of whom were <5 years old) given definitive alternative diagnoses by the attending physicians took salicylates; this proportion was similar to that observed among controls in this age group (<5 years). Among the 13 additional case-patients recommended for exclusion by the physician review panel, eight (62%), including the three recommended for exclusion with inadequate medical information and no drug or toxicology screens, had taken salicylates.

## COMMENT

This study demonstrates a strong association (matched odds ratio, 40; lower 95% confidence limit, 5.8) between Reye's syndrome and ingestion of salicylates during antecedent illnesses. In this study, as in all prior studies, more than 90% of patients with Reye's syndrome enrolled took salicylates. However, fewer controls in the current study (38%) than in prior studies (range of 71% to 46% in the most recently conducted pilot study) took salicylates, reflecting a national trend for declining use of salicylates among children.[8] The strength of the association between Reye's syndrome and salicylates in this study is consistent with estimates of risk determined in prior studies.[2,3,6] The high odds ratios found in this study and the pilot study[6] (16.1) led the Public Health Service task force and the Institute of Medicine committee to conclude that the central question of an epidemiologic association between Reye's syndrome and ingestion of salicylates had been adequately answered and that the study should be ended.

The relatively small number of cases identified for this study illustrates the difficulties in conducting studies of this increasingly rare syndrome. The declining incidence of Reye's syndrome in the United States, even during outbreaks of influenza B, when the largest number of cases occur, has been documented through national surveillance as well as through surveillance conducted in several states.[8-10] Despite the fact that 50 major pediatric tertiary-care centers in the first 11 months and 70 in the second six months (which included the 1985-1986 influenza season) participated in the study, only 33 cases of stage II or deeper Reye's syndrome (confirmed by the physician review panel) were identified during the 17-month study period. This period included an influenza season characterized by a level of influenza B activity among the highest reported nationally within the past 18 years. Although the number of subjects enrolled in this study was fewer than the protocol specified (at least 100 cases), the study's midpoint analysis revealed odds ratios that were of a sufficient magnitude to address the central issue of the study. Despite the fact that there are some additional questions that remain unanswered, both the Institute of Medicine committee and the Public Health Service task force concluded that, in view of the declining incidence of Reye's syndrome, it would be extremely difficult to address these questions in a reasonable period of time. Furthermore, both groups concluded that the expense incurred in extending the study would not be compensated by additional gains in scientific or public health information.

One question that this study could not adequately address is whether an increased risk of Reye's syndrome is associated with aspirin (acetylsalicylic acid) or with all salicylates. Results reported here are based on case-control comparisons of ingestion of salicylate compounds as a generic group sharing many common pharmacologic properties and mechanisms of action. Some have argued, however, that the pharmacologic properties of aspirin that are not found with nonaspirin salicylates may be responsible for the risk of Reye's syndrome. In this study, as in earlier studies, almost all case-patients (25/26 [96%]) and the majority of controls (40/53 [75%]) who took salicylates took aspirin; only a small percentage of case-patients and controls took nonaspirin salicylates either alone or with aspirin. Thus, when assessing the independent risk of aspirin and nonaspirin salicylates, only aspirin was found to be significant (odds ratio for exposure to aspirin, 26; lower 95% confidence limit, 6.4). While there were no significant differences in exposure to nonaspirin salicylates among cases and controls overall, the number of case-patients unexposed to aspirin (two) was too small to allow adequate separate statistical assessment of the potential independent risk of nonaspirin salicylates and Reye's syndrome.

In addition to observing a significant association between ingestion of salicylates and development of Reye's syndrome, analyses suggested that case-patients were significantly more likely to receive larger doses of salicylates than were controls on each day of their antecedent illness. This higher total dose of salicylates administered to case-patients suggests that the risk of Reye's syndrome is related not only to exposure but also to the quantity of salicylates ingested. In a study conducted in Michigan,[2] a similar trend was observed. (In the Michigan study, case-patients were reported to have received 121.6 mg/kg of aspirin during the antecedent illness compared with 64.0 mg/kg for controls, and the mean daily dose of aspirin for case-patients was 24.6 mg/kg vs 16.8 mg/kg for controls.) In another study,[3] in Ohio, the mean dose for controls was not determined, but the mean daily dose during the antecedent illness for case-patients (47 mg/kg) was even higher than those in this or the Michigan study.

Neither this nor the pilot study provides evidence that other epidemiologic issues could explain the observed high odds ratios. These issues included possible differential recall of illness and

medication among case-patients' and controls' parents, exposure to salicylates for symptoms of Reye's syndrome rather than for the antecedent illness among case-patients, misclassification of drugs, differences in the severity of the antecedent illness among case-patients and controls, or misdiagnosis of Reye's syndrome. Features incorporated into the study design to diminish or address concerns about these limitations have been previously described.[6]

As in the pilot[6] and at least one earlier study,[3] there was no evidence of differential recall of medications between case-patients' and controls' parents, based on the fact that similar numbers of medications and generic components were administered to both groups (Table 2), with the exception of salicylates—administered to significantly more case-patients—and acetaminophen—administered to significantly more controls. The greater use of acetaminophen by controls has been consistently observed in studies associating Reye's syndrome and salicylates[2,3,6] and is explained by the fact that controls tended to use acetaminophen as an alternative antipyretic/analgesic to aspirin. Analyses also demonstrated, as in the pilot study, that even by the first day of illness there were differences among case-patients and controls with respect to exposure to aspirin as well as acetaminophen; thus, the differences did not appear to be explained by exposure to aspirin for the symptoms of Reye's syndrome rather than the antecedent illness. Nor was there any evidence that differences in the antecedent illnesses among case-patients and controls would explain the greater use of salicylates among case-patients; in fact, analyses suggested that antecedent illnesses of case-patients were not as severe as those reported for controls.

This study attempted to obtain information about use of medications from all possible persons who may have provided care. These persons included those who provided the majority of care to the child (the main care provider), all others who were present when medications were administered or may have administered medications themselves (other care providers), children 10 to 12 years old who potentially self-medicated, and, where possible, all children 13 years old or older. Although there were some differences in the numbers of care providers of various types interviewed for case-patients and controls—more other care providers were reported and interviewed for case-patients and more children who potentially self-medicated were interviewed for controls—these differences did not account for observed differences in use of medications. Analyses comparing medication use reported by the main care providers only, who were uniformly interviewed for case-patients and controls, revealed that almost all exposures to salicylates and acetaminophen were reported in these main care provider interviews. Furthermore, as in the pilot study, when restricting the definition of exposure to those medications administered directly to subjects by the main care provider, significant differences in exposure to these two medications continued to be observed.

To ensure the prompt recognition and enrollment of all potentially eligible patients in this study, all patients were required to have stage II or deeper encephalopathy. It seems unlikely that attending physicians at participating pediatric tertiary-care centers would fail to consider the diagnosis of Reye's syndrome for any patient who was combative, stuporous, and verbalizing inappropriately (stage II Reye's syndrome) or in a coma. However, not all patients who develop encephalopathy are subsequently found to have Reye's syndrome, as illustrated by the seven patients originally reported as possible cases of Reye's syndrome and subsequently determined, by the attending physicians, to have other diagnoses. Six of the seven patients excluded by these physicians were less than 5 years old and most were found to have metabolic defects. This illustrates the difficulty of distinguishing Reye's syndrome from other entities, particularly among young children.

In addition to the seven patients determined to have alternative diagnoses by attending physicians, 13 of the remaining 46 patients initially enrolled in the study were recommended for exclusion from the analysis by the expert physician panel. The majority of these patients (10 [77%]) were less than 5 years old, again illustrating the difficulty of diagnosing Reye's syndrome in this age group. To ensure that panelists were not influenced by knowledge of medication exposure, the panel made an initial recommendation without knowledge of medication histories or drug or toxicology screens. Although the panel recommended that 13 patients be excluded, the members were not able to establish definitive alternative diagnoses for these patients. Thus, it is possible that some excluded patients did indeed have Reye's syndrome.

To further address this concern, as was completed for the pilot study, a panel from the Institute of Medicine advisory committee also reviewed the hospital records for the eligible patients. The second panel concurred with the review of the first panel for 47 of 52 (90%) of the patients. However, the Institute of Medicine committee recommended that five cases, which had been recommended for exclusion by the first panel, be included as Reye's syndrome cases in the analyses. While these differences again illustrate the difficulty of diagnosing Reye's syndrome among certain groups of patients (three of the five were <5 years old), the odds ratios would remain high and the major conclusion of the study would not be altered by including these patients, four of whom were exposed to salicylates.

Though several studies have demonstrated that the prevalence of salicylate use has declined in the United States since 1980, when publicity about Reye's syndrome and salicylates first began,[8] data from control children from throughout the United States identified in this study suggest that a substantial proportion of children (38%) were exposed to salicylates (including 29% exposed to aspirin). From a public health standpoint, the substantial exposure rate in controls and the high odds ratios observed in this study suggest not only a strong association between Reye's syndrome and salicylates (and specifically aspirin), but also that a large proportion (>90%, assuming an odds ratio of 40) of Reye's syndrome cases may be attributable to salicylates. Thus, this study reinforces the importance of reducing the use of aspirin (and possibly all salicylates) for the treatment of children with chickenpox and influenza-like illness to further reduce the incidence of Reye's syndrome in the United States.

#### References


1. Starko KM, Ray CG, Dominquez LB, et al: Reye's syndrome and salicylate use. *Pediatrics* 1980;66:859-864.
2. Waldman RJ, Hall WN, McGee H, et al: Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982; 247:3089-3094.
3. Halpin TJ, Holtzhauer FJ, Campbell RJ, et al: Reye's syndrome and medication use. *JAMA* 1982; 248:687-691.
4. Committee on Infectious Diseases: Aspirin and Reye syndrome. *Pediatrics* 1982;69:810-812.
5. Surgeon General's advisory on the use of salicylates and Reye syndrome. *MMWR* 1982;31:289-290.
6. Hurwitz ES, Barrett MJ, Bregman D, et al: Public health service study on Reye's syndrome and medications: Report of the pilot phase. *N Engl J Med* 1985;313:849-857.
7. Influenza—United States, 1985-1986 season. *MMWR* 1986;35:470, 475-479.
8. Barrett MJ, Hurwitz ES, Schonberger LB, et al: Changing epidemiology of Reye syndrome in the United States. *Pediatrics* 1986;77:598-602.
9. Remington PL, Rowley D, McGee H, et al: Decreasing trends in Reye syndrome and aspirin use in Michigan, 1979 to 1984. *Pediatrics* 1986;77: 93-98.
10. Virginia Health Department: Reye syndrome in Virginia, 1976-1985. *Epidemiol Bull* 1986;86 (February):1, 9.
11. Diagnosis and treatment of Reye's syndrome, CONSENSUS CONFERENCE. *JAMA* 1981;246:2441-2444.
12. Hurwitz ES, Nelson DB, Davis C, et al: National surveillance for Reye syndrome: A five-year review. *Pediatrics* 1982;70:895-900.
13. *Physicians' Desk Reference for Nonprescription Drugs*, eds 5 and 6. Oradell, NJ, Medical Economics Books, 1984 and 1985.