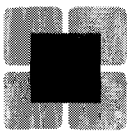

A catch in the Reye is awry

A BODY OF EVIDENCE linking aspirin with Reye's syndrome (RS), a devastating encephalopathy of childhood, has accumulated in the United States in the past decade. The data include epidemiologic studies of increasing sophistication and comprehensiveness.[1-6] The most recent of these confirmed the association.[6]

The findings of all the studies were strikingly consistent: 95% of patients with RS had received salicylates during the illness which typically precedes the onset of encephalopathy, compared to between 48% and 70% of control children with similar antecedent illnesses in whom RS did not develop. Odds ratios for the association of aspirin with RS ranged up to 40.[5]

As a result of these studies and the associated publicity, a dramatic change in antipyretic use among children has occurred in the United States. In the early 1980s, as many as 70% of children younger than 18 were given aspirin to treat common febrile illnesses, but aspirin use has declined markedly in recent years, and acetaminophen is the primary antipyretic of choice for the common febrile illnesses of childhood.[7]

■ *See Orlowski and associates (pp 323-329)*

This changing pattern of antipyretic use in the United States resulted in a natural experiment that has provided further important evidence for the association between aspirin and RS. The decline in aspirin use for children in the United States has paralleled a similar dramatic decline in the incidence of RS. The decline has been evident even in years with major influenza B activity, when outbreaks of RS would have been expected.[7,8] The declining incidence of RS in the United States prior to concern about aspirin is not evidence of a lack of a relation to aspirin; instead it reflects cyclical patterns of influenza A and B.[8,9]

In this issue of the *Cleveland Clinic Journal of Medicine*, Orlowski and colleagues report the findings of a case-control study of medication use among children diagnosed with RS in Australia. They claim that this study negates the overwhelming evidence of an association between RS and aspirin that has accrued in the United States in the past 10 years. The methods used in this and other studies cited as refuting the RS-aspirin association were far less rigorous than those employed in the six US case-control studies.[10] In particular, the authors relied upon medical records for all information regarding medication use. This method has repeatedly been demonstrated to be far less precise than face-to-face interviews conducted shortly (within days to weeks) after the onset of disease—the method used in the US studies. Nonetheless, we agree that the syndrome displayed by most of the patients studied in Australia by Orlowski and coworkers is usually unrelated to aspirin, if only because aspirin is indeed infrequently used in that country.

DIFFERING EPIDEMIOLOGY

The evidence suggests that the Australian children described by the authors had a disorder that differs from RS in this country. For example, the present report demonstrates the epidemiology of RS in Australia to be strikingly different from that in the United States. We believe that this differing epidemiology *supports* the RS-aspirin association, rather than refutes it.

In the United States, RS until recently occurred predominantly in children between ages 5 and 14 (71% reported through national surveillance in the period Dec. 1979–Apr. 1980),[11] with a peak incidence during the winter months of influenza activity (particularly influenza B), and following chickenpox. The syndrome characteristically occurred in outbreaks and in association with these viruses. As a result, most children included in aspirin-RS studies in the United States were older than 5 years, and most had experienced the onset

of their disease during the winter months of influenza activity.

In contrast to the US studies, almost all the children included in the Australian study (85%) were 5 years old or younger, and most (65%) were younger than 3 years. These cases occurred in association with a wide variety of viruses and with no distinct seasonality. Although identified in a single hospital, the cases were apparently typical of all cases in Australia. Thus the epidemiology of the syndrome in Australia, including the age distribution, differs from that in the United States.

The epidemiologic differences between the two countries were apparent from the first reports of the syndrome in 1963: Reye first described a syndrome in Australia with no distinct seasonality that occurred primarily in infants and children younger than 2 years[12]; Johnson described cases of encephalopathy primarily among older children—between 6 and 13 years of age—in the United States during an outbreak of influenza B.[13] Although Orlowski and associates contend that the incidence of the disease is the same in both countries, age-specific comparisons of the incidence of RS in New South Wales, Australia between 1973 and 1983,[14] and in Ohio between 1973 and 1977[15] show that, while the incidence among children younger than 1 year is similar, among older children the incidence is substantially higher in the United States (Centers for Disease Control, unpublished data).

It appears that RS in Australia occurs primarily in infants and young children and with no seasonal pattern; in the United States, at least until recently, the disease affected mostly older children and occurred most commonly during the winter months of influenza activity. There is a growing body of evidence that, in contrast to RS in older children, many or most cases of RS in younger children represent a wide variety of metabolic disorders which share similar clinical, laboratory, and even pathologic features.[16]

A DIFFICULT DIAGNOSIS

A recent US study demonstrates the difficulties in establishing the diagnosis of RS in infants and young children.[5] After reviewing the medical records of 53 patients with possible RS from 70 pediatric referral centers, a panel was able to confirm the diagnosis of RS in 88% (23 of 32) of patients 5 years and older, but in only 20% (4 of 20) of those younger than 5. For many patients younger than 5 years, another diagnosis—such as metabolic disorder—appeared more likely.

It appears that RS among older children, which has been strongly linked to aspirin, is a relatively homogeneous disorder with which few other conditions may be confused. In contrast, infants and young children with the clinical, laboratory, and pathologic features of RS, are frequently found to have one of a number of metabolic disorders, many of which have only recently been described. We believe that many of the patients in the Australian study who were diagnosed with RS between 1973 and 1982 actually had such metabolic disorders, many of which had not yet been identified.

The Australian study also suggests that typical RS, occurring among children 5 to 15 years of age in the United States, is extremely rare in that country. This observation *supports* the association of aspirin with RS. Orlowski and colleagues observe that paracetamol rather than aspirin has dominated the analgesic/antipyretic market in that country for 25 years. This lack of aspirin use would explain the rarity of RS in Australia. As the incidence of RS has declined in the United States, it has become apparent that many of the few cases that still occur actually represent a variety of metabolic disorders that mimic RS and are unrelated to aspirin.[17]

Epidemiologic comparisons of diseases in differing geographic regions and populations can provide valuable clues regarding risk factors. Such comparisons include examination of the basic epidemiologic characteristics of a disease: time (seasonality), person (age distribution), and place (geographic distribution), as well as more focused cohort or case-control studies such as the one here. The study by Orlowski and colleagues supports the role of aspirin in the United States and suggests that aspirin plays no role in many of the metabolic diseases that resemble RS in younger children. This lack of association will need to be confirmed in more rigorous case-control studies such as those completed in the United States among older children.

To conclude that the current admonition against the administration of aspirin to children with influenza and varicella is unwarranted on the basis of a lack of association with a different disease that occurs in infants would be dangerous indeed.

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REFERENCES

1. Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF. Reye's syndrome and salicylate use. Pediatrics 1980; **66:**859–864.
2. Waldman RJ, Hall WN, McGee H, Van Amberg G. 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. 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.
5. Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study of Reye's syndrome and medications: report of the main study. JAMA 1987; **257:**1905–1911.
6. Forsyth BW, Horwitz RI, Acampora D, et al. New epidemiologic evidence confirming that bias does not explain the aspirin/Reye's syndrome association. JAMA 1989; **261:**2517–2524.
7. Arrowsmith JB, Kennedy DL, Kuritsky JN, Faich GA. National patterns of aspirin use and Reye syndrome reporting, United States, 1980 to 1985. Pediatrics 1987; **79:**858–863.
8. Centers for Disease Control. Reye syndrome surveillance—United States, 1987 and 1988. MMWR 1989; **38:**325–327.
9. Barrett MJ, Hurwitz ES, Schonberger LB, Rogers MF. Changing epidemiology of Reye syndrome in the United States. Pediatrics 1986; **77:**598–602.
10. Hall SM, Plaster PA, Glasgow JFT, Hancock P. Preadmission antipyretics in Reye's syndrome. Arch Dis Child 1988; **63:**857–866.
11. Centers for Disease Control. Follow-up on Reye syndrome—United States. MMWR 1980; **29:**321–322.
12. Reye RD, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. Lancet 1963; **2:**749–752.
13. Johnson GM, Scurletis TD, Carroll NB. A study of sixteen fatal cases of encephalitis-like disease in North Carolina children. NC Med J 1963; **24:**464–473.
14. Orlowski JP, Gillis J, Kilham HA. A catch in the Reye. Pediatrics 1987; **80:**638–642.
15. Sullivan-Bolyai JZ, Marks JS, Johnson D, et al. Reye syndrome in Ohio, 1973-77. Am J Epidmoil 1980; **112:**629–638.
16. Reye's syndrome and aspirin: Epidemiological associations and inborn errors of metabolism. Lancet 1987; **2:**429–31.
17. Rowe PC, Valle D, Brusilow SW. Inborn errors of metabolism in children referred with Reye's syndrome. A changing pattern. JAMA 1988; **260:**3167–3170.