Study of Reye's-Aspirin Link Raises Concerns

A pilot study has produced unexpectedly strong results, prompting a quandary over whether action should be taken on the basis of limited data

13 December 1984, says Floyd Denny, Jr., was one of the most fascinating days of his life. Denny, a professor of pediatrics at the University of North Carolina at Chapel Hill, is chairman of an Institute of Medicine committee that is overseeing a study by the Centers for Disease Control (CDC) on the relationship between risk of Reye's syndrome and aspirin use in children. The CDC, at the committee's request, had begun its investigations with a small pilot study; 13 December was the day the CDC announced its results to Denny's committee.

Since it was a pilot study and so small in scale and less than rigorous in its methodology, no one expected its results to have public health significance and the Institute of Medicine had anticipated keeping them confidential. "We thought that all the study would do was let us hone up on our techniques," Denny says. But, to everyone's amazement, the study had striking results. Denny explains: "In planning the final study, we had talked of a final odds ratio [which is a statistical measure of risk] of 4. Lo and behold, the odds ratio in the pilot study was as high as 25." That indicated that children with chicken pox or flu who take aspirin may be 25 times more likely to get Reye's syndrome than those who do not.

The study included 29 children with Reye's syndrome and 143 controls, some of whom were selected because they had been admitted to the same hospital or emergency room or because they attended the same school as the children with Reye's, and others of whom were selected by telephoning people at random. Ninety-seven percent of the Reye's syndrome children received aspirin during the chicken pox or influenza that typically precedes this disease, whereas only 28 percent of the emergency room controls, 23 percent of the same hospital controls, 59 percent of the same school controls, and 55 percent of the random digit dialing controls received aspirin during equivalent cases of chicken pox or influenza.

But the pilot study's results were decidedly a mixed blessing. After all, Denny notes, "it is a limited study." The number of children with Reye's syndrome was small and they were selected from a geographically limited area. So, the committee asked, should the results be released and, if they are released, should the larger study go ahead as planned? If the pilot study did show an indisputable association between risk of Reye's syndrome and aspirin use, why do the larger study? If it did not, why publicize the results?

The committee, enormously impressed by the strength of the pilot study's results, decided to publicize them and to go ahead with the larger study anyway. With that decision, they entered into the bitter Reye's syndrome fray.

Aspirin manufacturers and the industry-funded Committee for the Care of Children are disturbed by what they see as the premature release of possibly misleading data. Boston lawyer Neil Chayet, who is spokesman for the Committee for the Care of Children, asks, "What does this mean in the minds of the public? We just want to know what the truth is." On the other side of the argument is Sidney Wolfe, director of the Health Research Group. Wolfe immediately fired off a letter to Frank Young, commissioner of the Food and Drug Administration, demanding warning labels on all aspirin products.

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Then, on 9 January, Margaret Heckler, Secretary of the Department of Health and Human Services, took action. She asked aspirin manufacturers to voluntarily put warning labels on their products saying that aspirin use in children with chicken pox or flu is associated with an increased risk of Reye's syndrome.

On 11 January, the Aspirin Foundation of America, which represents aspirin manufacturers, announced that it is attempting to develop a program to meet with Heckler's request. The foundation is also seeking a full review of the data, says its president Joseph White of Miles Laboratories, and it is discussing the pilot study's results with the FDA "in a spirit of cooperation."

Reye's syndrome is a frequently deadly disease of children and teenagers—98 percent of cases occur in people aged 20 and below. It usually occurs in the aftermath of a viral infection, particularly influenza or chicken pox. The children begin vomiting continuously, then they may become disoriented or lethargic or may undergo personality changes, shouting and using abusive language. As the disease progresses, the child may become comatose. About one-sixth of the children who enter comas die. Another sixth suffer permanent brain damage. The overall mortality for the disease is about 26 percent.

The syndrome is, as it has always been since its first description in 1963, a medical mystery. It is extremely rare—only 190 cases were reported to the CDC in 1984. The CDC estimates that about one-fourth to one-half of all cases are reported. Looking at pre-1980 data, the CDC estimated that the risk of Reye's in children and teenagers is 1 to 2 per 100,000 per year. The cause of the disease is unknown and its treatment is mostly palliative. But for several years, epidemiologists have been tantalized by hints that Reye's syndrome might somehow be linked to aspirin use, although no one has ever said that aspirin actually causes the disease.

The first hints of an aspirin connection were reported in 1980 when the state health departments of Arizona, Ohio, and Michigan completed case-control studies of Reye's syndrome. The studies basically involved questioning the parents of children with Reye's syndrome and parents of other children of the same ages who also had flu or chicken pox but who did not get the syndrome. The goal was to determine whether any medications or other factors might predispose children to develop Reye's. In all three studies, the children who got Reye's syndrome were more likely than the controls to have taken aspirin.

This sort of case-control study is frequently used to get at the causes of rare diseases, and it has been extremely successful. Case-control studies established the link between diethylstilbestrol and vaginal cancer, for example, and between tampon use and toxic shock. The state studies of Reye's syndrome, how-

ever, were subjected to methodological criticisms because it was not always clear, for example, that the diagnoses of Reye's syndrome were firmly established nor that there were no biases in the recollection of what medications were used.

Based on these admittedly limited studies, the CDC recommended in November of 1980 that parents exercise caution in administering aspirin to children with influenza or chicken pox. Four months later, a consensus development conference at the National Institutes of Health issued the same advice. Shortly afterward, a fourth study, this time from the state of Michigan, also found an association between aspirin use and Reye's syndrome risk. But none of these studies was convincing enough to stem the debate.

The Food and Drug Administration, under conflicting pressure from aspirin manufacturers and the Committee on the Care of Children and from the Health Research Group at first proposed warning labels for aspirin and then called for more data before reaching a decision.

In the meantime, by all accounts, sales of children's aspirin fell and, coincidentally, the incidence of Reye's syndrome dropped in children aged 10 and younger "rather dramatically, by about 50 percent" according to Walter Dowdle of the CDC. The proportion of older children and teenagers with Reye's syndrome increased. Teenagers presumably choose their own medication and do not see pediatricians when they get influenza and so, says Dowdle, they are less likely to cease using aspirin because of a Reye's syndrome warning.

This was the background for the CDC study, which was undertaken at the request of the Public Health Service. "There was no question that we needed a more definitive study," Denny says. But it was not expected to be easy. Like the state studies, the CDC's was to be a case-control one, but it was to have a larger number of cases and to have a more stringent experimental design. "This is one of the most complicated epidemiological studies," Denny remarks. "There are so many variables and the disease is so fantastically rare. And the study is done in a milieu where most pediatricians are telling parents not to use aspirin. It becomes very touchy."

The CDC wanted to go right ahead and do a full-scale study, but the Institute of Medicine committee requested that it begin with a pilot study to see if its methodology was even feasible. "We anticipated that that's precisely what it would do," says Denny. "We would see the results, adjust the protocol, and get on with the larger study. We certainly didn't expect to see what we saw."

So why do the larger study? The Institute of Medicine committee notes that a full-scale study would not expose anyone to excess risk of Reye's syndrome because it is to be a case-control study. Therefore, no ethical dilemmas arise. And there still is much to be learned about Reye's syndrome. A larger study may point to additional risk factors for the disease and may help determine whether there are particular doses of aspirin that are safe and others that are high enough to cause excess risk. In addition, everyone would feel a bit more comfortable if the pilot study's results were confirmed.

But, says Dowdle, none of this is meant to detract from the merits of the pilot. The results are sufficiently strong that they cannot be ignored and the study was done rigorously and carefully. "We stand behind the pilot study," Dowdle says. "We think it is a superb study and we think its results are better than those of any other study of Reye's syndrome that went before it."

—GINA KOLATA

Agency Scraps Plan to Limit Ethylene Oxide

A new scientific argument prompts OSHA to reverse itself and drop a controversial proposal

In a major policy reversal, the federal agency in charge of establishing regulations governing hazards in the workplace has decided not to limit short-term exposure to ethylene oxide, a colorless gas widely used to sterilize medical supplies and equipment. Although such a restriction had been supported by the agency's own staff, two other federal health agencies and labor groups, it had been opposed by manufacturers and others and attacked by the Office of Management and Budget. The decision, announced on 2 January by the Occupational Safety and Health Administration (OSHA), illustrates the difficulties faced by regulators when confronted by an obvious and acknowledged health problem but have somewhat incomplete research data.

OSHA's decision not to limit short-term exposure to ethylene oxide left intact a standard issued in June that restricts long-term exposure to the chemical. The long-term limit was supported by industry, which had already instituted controls in anticipation of the regulation. Data collected during the past several years have shown that ethylene oxide is a mutagen and a carcinogen in animals. As for humans, there is evidence, although limited, that at low levels of exposure, it is associated with leukemia, spontaneous abortions, and chromosomal changes. About 75,000 persons are potentially exposed to the gas in bursts of high concentration. Ethylene oxide frequently is released when the chamber door of a sterilizing machine is opened and from the protective wrappings of freshly sterilized material.

OSHA has asserted in the past that a long-term standard should be supplemented by a short-term limit to keep exposure to a minimum. The long-term standard restricts exposure to 1 part per million (ppm) averaged over 8 hours. That means a worker could be exposed to brief, but high, concentrations of ethylene oxide during the day without exceeding the long-term limit. For instance, a person could be exposed to 480 ppm for 1 minute but not exceed the long-term limit if no additional exposure occurred. According to information gathered by OSHA staff, two or more peak exposures per day "are common" and employees could be exposed "to several hundred ppm over very short periods of time." With this in mind, OSHA reasoned that a short-term standard was prudent to further reduce the cancer risk.

Industry, however, resisted the idea, and on 14 June, the day before the agency was to announce the final rule on the short-term limit, the Office of Manage-