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STATEMENT BY SIDNEY M. WOLFE, M.D.
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According to an internal government memo[1] and interviews with other sources, the Reagan Administration, yielding to pressure from drug companies, has delayed for more than two months a major public health warning that could have prevented the injuries and deaths of many children. The preventable disease is Reye's Syndrome, which, according to the memo, afflicts between 600 and 1200 people a year--mainly children--and results in between 120 and 360 deaths.

For several years there has been a suspicion that the use of aspirin to treat either chicken pox or influenza-like illnesses, which usually precede the evolution of Reye's Syndrome, may be a factor in causing this serious disease. The January 21 memo says that in late November 1981, after careful review of studies in Michigan, Ohio and Arizona linking Reye's syndrome to prior use of aspirin, an advisory group to the Centers for Disease Control (C.D.C., part of the Department of Health and Human Services) recommended that:

> "until the nature of the association between salicylates (aspirin) and Reye's syndrome is clarified, the use of salicylates should be avoided, when possible, for children with varicella (chicken pox) infections and during presumed influenza outbreaks."

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1 The memo is entitled "Association of Aspirin with Reye's Syndrome," is dated January 21, 1982 and is from Gene W. Matthews, of the Center for Disease Control Office of General Counsel to H.H.S. to Acting Assistant General Counsel, Joel M. Mangel.

The January 21 memo states that, "since it is very difficult to identify presumed influenza outbreaks, this recommendation would mean that children should avoid using aspirin during the winter flu season."

Although, according to other sources, C.D.C. wanted a Warning issued in December, aspirin manufacturers succeeded in stopping C.D.C. from issuing such a health warning against against use of aspirin by arguing, amongst other things, that C.D.C. should not take action until FDA had decided what to do. According to the memo, "two of the aspirin manufacturers have urged that C.D.C. make no premature statements until FDA takes action...."

It is of interest that even now, when C.D.C. has finally decided it must go public with this important warning (on Friday, February 12, the C.D.C.'s weekly bulletin "M.M.W.R." will contain the warning), FDA, which had originally proposed that the warning be jointly issued by CDC and FDA, is now backing out of co-authorship. According to FDA sources, FDA officials will meet with executives from Sterling Drug Company (Bayer Aspirin) and Schering-Plough (St. Joseph's Children's Aspirin) before taking any action.

The memo concludes:

Present Situation

It is my understanding that Dr. Foege is keeping Dr. Brandt and the Secretary informed of the status of this matter.

In view of the fact that this controversy may become critical at any time, CDC has to consider a number of possible options:

(1) CDC can continue to stand by the statement in the MMWR of November 1980, saying that caution should be used in administering aspirin for influenza and chicken pox.

(2) CDC can adopt the recommendation of its outside review committee that aspirin should be avoided during the flu season.

(3) CDC can simply publish the fact that the outside committee has made such recommendations to CDC.

WHAT IS REYE'S SYNDROME

Reye's Syndrome, according to the memo, "is a childhood illness of unknown cause which can appear following a viral infection such as influenza or varicella (chicken pox). Reyes is characterized by a sudden onset of severe vomiting and fever, progressing rapidly to convulsions and coma." Although the memo states that death occurs in "20 to 30 percent"of the "600-1200 cases" per year, other studies (Am. J. Medicine 61, 615, 1976) have shown death rates of 41%.

HOW MANY CASES OF REYE'S SYNDROME HAVE OCCURRED SINCE LATE NOVEMBER WHEN THE C.D.C. ADVISORY COMMITTEE RECOMMENDED A WARNING AGAINST ASPIRIN USE?

In 1980, (winter 1979-80) the last year for which data are available (C.D.C. Annual Summary, 1980, published September 1981), there were 548 cases of Reye's Syndrome reported to health officials. (Many experts agree that no more than one-half of actually-occurring cases of diseases such as Reye's syndrome are reported to health officials.) Of the 548 reported cases, approximately 225 occurred between the beginning of December 1979, and February 11, 1980. Even if, because of less flu this year, only half as many cases of Reye's Syndrome occurred between December 1, 1981 and February 11, 1982, this means over 100 cases, including 20 to 30 deaths. Many, if not all, of these serious illnesses and deaths could have been prevented if parents and doctors had been warned against the use of aspirin during the winter flu season or in children with chicken pox.

CONCLUSION: RECOMMENDATIONS

According to Drug Topics (July 3, 1981, p. 30), 1980 sales of aspirin and aspirin compounds were 671 million dollars for adult dosage forms and 49.9 million dollars for child dosage forms. It appears that once again, the Reagan Administration is more interested in the health of industries such as drug manufacturers than in saving the lives and health of Americans, largely children in this instance. There will be a sharp decrease in the number of cases and deaths from Reye's Syndrome as soon as this irresponsibly-delayed warning from the C.D.C. gets out. In addition to publishing the warning in the C.D.C's Morbidity and Mortality Report, the situation is serious enough to merit a warning from Surgeon-General Koop who has repeatedly stressed his desire to save the lives of children.

In addition, the FDA should promptly change the labelling for all aspirin-containing products to include this warning.

January 21, 1982

MEMORANDUM

TO: Joel M. Mangel
Acting Assistant General Counsel

FROM: Gene W. Matthews
Legal Advisor, CDC

SUBJECT: Association of Aspirin with Reyes Syndrome

During this week I have been informed of some significant developments concerning the possible association between the use of aspirin and Reyes Syndrome. The following is a summary of my understanding of the situation.

Background

Reyes Syndrome is a childhood illness of unknown cause which can appear following a viral infection such as influenza or varicella (chicken pox). Reyes is characterized by a sudden onset of severe vomiting and fever, progressing rapidly to convulsions and coma. Approximately 600 to 1200 cases of Reyes Syndrome occur each year in the United States, with death resulting in 20 to 30 percent of these cases.

Antipyretics (drugs used to reduce fever) are normally prescribed to control temperature both for the viral illnesses and for Reyes. The most frequently used antipyretics are either salicylates (i.e., aspirin) or acetaminophen (commercially marketed as Tylenol). In general, there is no real evidence to show any significant superiority between aspirin or Tylenol in reducing fever, and both seem to be equally effective.

Research Concerning the Association of Aspirin with Reyes Syndrome

Within the past two years CDC has been aware of or supported 4 studies by state health departments concerning Reyes Syndrome--one in Arizona, one in Ohio, and two in Michigan. These studies have demonstrated a relationship between the development of Reyes Syndrome and the ingestion of aspirin during the preceeding viral illness.

After reviewing the preliminary data from the first three studies, CDC reported the results in its Morbidity and Mortality Weekly Report (MMWR) of November 7, 1980. At that time CDC recommended that, in view of this statistically significant association, parents "should use caution when administering salicylates to children with viral diseases, particularly influenza and chickenpox."

During the past year the fourth study was completed by Michigan and found the same association of aspirin with Reyes. Interestingly, none of the studies showed any association between acetaminophen (Tylenol) and Reyes. Some caution is necessary in interpreting the meaning of the aspirin association due to the fact that there are certain difficulties in each study, such as problems in design, recall bias, and other confounding variables.

CDC Outside Review Group

Because of the concern about the public health importance of this issue, in October 1980 CDC convened a group of outside consultants to review all 4 studies. In their November report to CDC the group recognized the various study limitations, but the members deemed it to be highly unlikely that these limitations could totally explain the strength of the association or the consistency of the observations in all 4 studies. In its recommendations the group took a stronger stand by flatly stating that "until the nature of the association between salicylates and Reyes Syndrome is clarified, the use of salicylates should be avoided, when possible, for children with varicella infections and during presumed influenza outbreaks."

Since it is very difficult to identify presumed influenza outbreaks, this recommendation would mean that children should avoid using aspirin during the winter flu season.

The outside review group also recommended that the presence of salicylates should be clearly identified on the label of all combination drug products.

Recent Developments

By letter of December 10, 1981, the Director of CDC forwarded these recommendations and background materials to the Commissioner of FDA for review.

Naturally the aspirin manufacturers have been keenly interested in this possible disease association and in the public statements made concerning this entire issue. Also the manufacturer of Tylenol has closely monitored these developments.

A continuing problem in the review of these findings has been a lack of access to the raw data--specifically, the individual questionnaires used in the four case-control studies. Because the last three studies are awaiting publication, the state researchers have been reluctant to release sanitized copies of the questionnaires, instead releasing summary data or selected computer print-outs. CDC's policy has been to share all data it obtains with the interested parties; however, neither CDC, FDA, the independent researchers, nor the manufacturers have been able to obtain the actual questionnaires. The Ohio State Department of Health has not provided such information to CDC even though CDC funded part of the study under a contract with Ohio, and even though CDC apparently has the right to obtain these data under the standard "Rights in Data" clause.

Following the report of the outside consultants, CDC needs to determine what, if anything, should be stated concerning this matter in the MMWR. During the early part of this month two of the aspirin manufacturers have urged that CDC make no premature statements until FDA takes action, until the raw data are released by the states, or until "more reliable" studies can be performed.

During December 1981 the Reyes/aspirin issue was separately analyzed by the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP). This committee, which is more commonly known as the "Redbook Committee", periodically makes updates on vaccine and other infectious disease

practices that are found in the AAP Manual on Infectious Diseases (Redbook). In January 1982 the Redbook Committee drafted a recommendation that was even stronger than that of the CDC consultants, indicating that physicians should encourage their patients to refrain from salicylate use during the winter season, and that acetaminophen should be considered as an alternative.

The aspirin manufacturers are currently asking the AAP to not issue this recommendation at this time because the aspirin association has not been sufficiently substantiated. On the other hand, concerned professionals, as well as the manufacturer of Tylenol, are wanting someone to issue a stronger statement immediately.

Present Situation

It is my understanding that Dr. Foege is keeping Dr. Brandt and the Secretary informed of the status of this matter.

In view of the fact that this controversy may become critical at any time, CDC has to consider a number of possible options:

(1) CDC can continue to stand by the statement in the MMWR of November 1980, saying that caution should be used in administering aspirin for influenza and chicken pox.

(2) CDC can adopt the recommendation of its outside review committee that aspirin should be avoided during the flu season.

(3) CDC can simply publish the fact that the outside committee has made such recommendations to CDC.

I will continue to keep you advised as this matter develops. Please let me know if you need any of the background documentation discussed above.

cc: Mr. Riseberg