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BEFORE

FDA WORKSHOP ON
THE ROLE OF ASPIRIN IN REYE'S SYNDROME

MAY 24, 1982

INTRODUCTION

It is now 20 years since Mortimer and Lepow[1] described metabolic abnormalities in 4 children with what is now called Reye's Syndrome who had taken salicylates prior to the onset of this disease. Since then--especially through the work of the Centers for Disease Control and state health departments in Ohio, Michigan and Arizona--these early case reports have been followed by case series, speculation about biological mechanisms involving the role of aspirin in Reye's Syndrome and exploratory epidemiologic studies. In the most recent of these studies(the last of which was completed a year ago), there have been more focussed epidemiologic studies designed to address concerns not addressed adequately in the initial surveys.

All of this is a classic example of how we make progress in identifying preventable causes of disease. At present, indeed since at least 7 months ago when C.D.C. convened a workshop in Atlanta to consider these issues, there is a well-established relationship between the use of salicylates in the treatment of various viral illnesses in children and the subsequent development of Reye's Syndrome. This association does not appear to be due to chance, confounding or bias. As we will discuss later, the time is long overdue for FDA regulatory action to protect children by acting on the basis of this scientific information.

The following are our answers to the questions posed by the Working Group:

1) DO THE DESIGNS OF THE CASE CONTROL STUDIES PERMIT THE DETECTION OF A VALID ASSOCIATION BETWEEN SALICYLATE USE AND REYE'S SYNDROME? IF SO, DOES THE ASSOCIATION APPEAR INCIDENTAL OR REFLECTIVE OF FACTORS RELATED TO CAUSALITY?

There is no flawless study in the biological sciences and, in the present circumstance, as is always the case long after other regulatory decisions are made, there are a variety of other issues which could provide the basis for further case-control studies. The studies to date, however, provide a more than adequate epidemiologic basis for decisions.

As far as whether the association is incidental or related to factors reflective of causality, there are a number of factors used in evaluating causality:

a) Is there a statistical association between the exposure and the disease, with exposure being more common in those developing the disease than those who do not? In the Arizona, Michigan and Ohio studies and the more recent analysis of the Ohio data, there was a statistically significantly greater frequency of aspirin use in children with Reye's Syndrome than in matched control children who also had viral illnesses but did not develop Reye's.

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1 Mortimer EA Jr, Lepow ML: Varicella with hypoglycemia possibly due to salicylates. American Journal of Diseases in Children 103: 91, 1962.

b) Does the putative cause (aspirin ingestion) precede the effect (Reye's Syndrome)? It is obvious that the risk associated with salicylate administration precedes the overt clinical manifestations and diagnosis of Reye's Syndrome as evidenced, for example, by the four-fold excess risk of Reye's Syndrome with salicylate exposure on the first day of a prodromal illness in those patients who will not develop Reye's Syndrome until five or more days later. Whether salicylates act to push a preexisting viral syndrome into Reye's Syndrome or whether Reye's Syndrome, present in a subclinical form early in the prodrome, is pushed by salicylates to its overt clinical manifestations cannot be addressed by the data or methodology currently available. Fortunately, from the perspective of regulatory action, distinguishing between these mechanisms has no practical benefit or significance at this time.

c) The association should not be due to chance, confounding or bias. The likelihood that the association is real and not due to some artifact is enhanced by a relatively strong association with a large difference in risk between those exposed and those not. Much of the FDA report is concerned with examining the possibilities of confounding or bias. To the extent that these can be evaluated in existing data, they do not appear to explain the association. The three to fourfold excess risk observed is a fairly strong association in epidemiology.

d) The presence of dose-response relationships enhances a causal interpretation. Although accurate recordings of milligrams of salicylate or acetaminophen use are not available, using the data on antipyretic exposure from Table 5, pages 62 and 63 of the FDA Reye's Syndrome Working Group Report, it is possible to examine the relationship between the length of latency before onset of Reye's Syndrome and the intensity of salicylate exposure prior to the onset of Reye's Syndrome. As can be seen in Figure 1, the 63 children with Reye's Syndrome are divided into 3 groups: the first group includes the 23 children who started salicylates on day one or two of their prodromal illness and used them continuously until the onset of vomiting the second group are 32 children who also started salicylates on day one or two of their prodromal illness but who discontinued use of salicylates at some time before the onset of Reye's Syndrome; the third group are 8 children who did not get salicylates on day one or two. As can be seen in Figure 1, children who started salicylates on day one or two and who continued using them continuously until the onset of vomiting developed Reye's Syndrome an average of 5.2 days after the onset of the prodrome, with an average salicylate use of .94 doses per day. This can be compared with a latency of 7.1 days and an average of .51 doses per day in the group who started salicylates on the first or second day but discontinued use before the onset of Reye's Syndrome, and a latency of 8.3 days and an average of .22 doses per day in the group who did not get any salicylates during the first 2 days of the prodromal illness. Thus it appears that a continuous bombardment by salicylates of the viral-infected child, especially starting from day one or two of the prodromal illness, is associated with a shorter latency period than the more intermittent use of salicylates, especially if salicylates are not used on either day one or day two of the prodromal illness.

e) Internal consistency of an association within a study among various groups looked at in various ways supports causality. The studies appear to be internally consistent.

f) The replicability of a finding in different studies done with different methodologies by different investigators supports causality. Such is clearly the case for aspirin and Reye's Syndrome wherein a variety of different investigators in different locales have come to remarkably similar findings.

g) The consistency of an association with plausible biologic mechanisms supports causality. There is certainly a biologic rationale for the association, a rationale which seems to have been the stimulus to conduct most of these studies in the first place.

In summary, the association appears highly reflective of factors related to causality.

2) ARE DIFFERENCES IN SYMPTOMATOLOGY IN THE GROUPS OF CASES AND CONTROLS SUFFICIENT TO ACCOUNT FOR THE REPORTED ASSOCIATION (RATHER THAN BEING ACCOUNTED FOR BY A DIRECT EFFECT OF SALICYLATES)?

It is difficult to believe that parents manipulate the type of antipyretic medication based on subtle differences in symptomatology. While symptom differences may affect the decision to treat or not to treat, once a decision is made to treat with drugs, the choice of drugs is more likely to be based on socio-demographic determinants than it is on these subtle differences in symptoms. Moreover, the issue of symptoms has been addressed specifically by the analyses of the second year Ohio data. Control for fever, and for specific level of temperature does not alter the conclusions.

In Figure 2, based on the data in the report from Table 2, page 59, the per cent of the total new symptoms appearing each day is shown with apparent differences on days one, four and five between cases and controls. As can be seen in Figure 3, based on the same data, these differences are substantially reduced when stomach ache, nausea, and vomiting, symptoms especially related to Reye's Syndrome, are omitted. Thus, there is a remarkable similarity over time in the onset of new symptoms in the case and control groups which further supports the analysis done in the working group report.

3) IS THE APPARENT ASSOCIATION OF SALICYLATE USE AND REYE'S SYNDROME ACCOUNTED FOR BY TREATMENT OF THE SYNDROME RATHER THAN THE ANTECENDENT ILLNESS?

In order to see if parents were treating the apparently similar symptoms (save nausea, vomiting and stomach ache) shown in Figure 3 with similar amounts of antipyretics, in Figure 4 we examine the total units of antipyretic therapy per patient (acetaminophen plus salicylates) for each day. Based on data in Tables 5 and 6, pages 62 - 65 of the report, it is clear that remarkably similar total levels of antipyretics were administered for days one through ten. As mentioned above, it is difficult to believe that parents would fine-tune therapeutic decisions (to treat or not to treat, whether to use salicylates or other drugs) on the basis of fairly minor differences in symptom complexes at the early phases of the prodromal illnesses. In section IX, it is concluded that the aspirin exposure rate in those with a putatively earlier onset of Reye's Syndrome is higher in those with later onset and that this may reflect salicylate use for the symptoms of Reye's Syndrome, not for the

prodromal illness. A much more likely explanation (beyond the explanation that the decrease from an 88% exposure rate in the total of 64 cases to a rate of 83% in the 48 cases with late onset is compatible with chance) is that there is a dose effect. As shown in Figure 1, it appears that those patients with prodromal illnesses who are treated with salicylates agressively early may tend to develop Reye's Syndrome earlier.

Therefore the Summary of Section IX on page 57 is misleading. It states that "most or all of the excess frequency of salicylate use in cases might be the result of use of salicylates for treatment of symptoms of Reye's Syndrome." Although the analysis in Section IX "did not demonstrate whether excess salicylate use in Reye's Syndrome cases was explained by this hypothesis," it fails to mention that the analysis in the previous section shows that the excess salicylate use is explained by a causal relationship to Reye's Syndrome.

CONCLUSION

With these new analyses of the data, especially the 64 cases from Ohio, there continues to be enough evidence of a strong association between using aspirin and developing Reye's Syndrome to warrant immediate action by FDA to order warning labels on all aspirin-containing products. The failure of FDA to do so, aside from violating the drug laws which require such labelling in the face of the evidence of the dangers of aspirin, will guarantee the continued deaths and injuries to children. Most if not all of these deaths and injuries appear to be preventable. Action is long overdue.

FIGURE 1

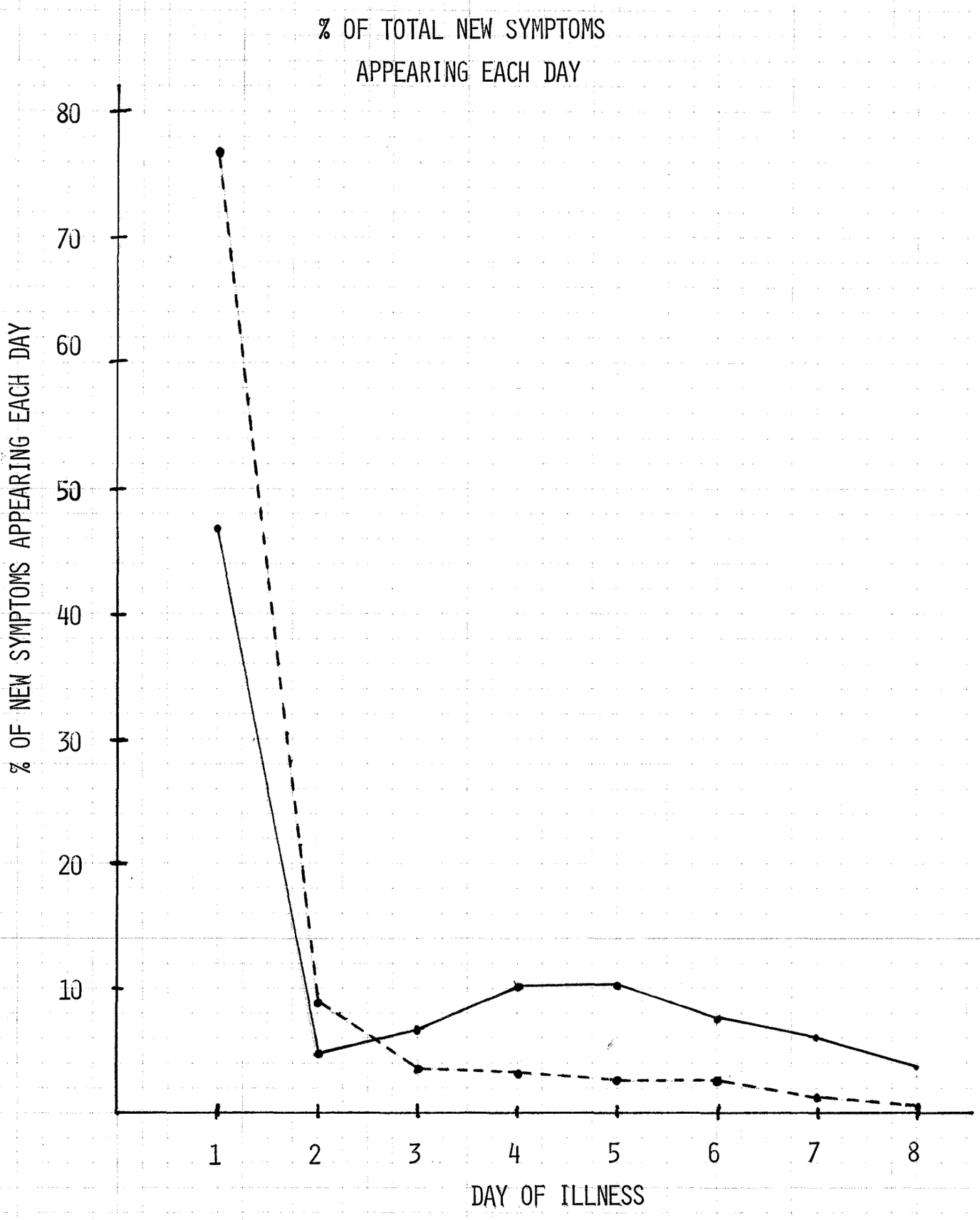
RELATIONSHIP OF LENGTH OF LATENCY BEFORE ONSET OF REYE'S SYNDROME TO INTENSITY OF SALICYLATE EXPOSURE PRIOR TO ONSET

	SALICYLATES STARTED DAY 1 OR 2: CONTINUOUSLY UNTIL VOMIT ONSET (23 CHILDREN)	SALICYLATES STARTED DAY 1 OR 2: DISCONTINUED AT SOME TIME BEFORE REYE'S ONSET (32 CHILDREN)	SALICYLATES NOT STARTED ON DAY 1 OR 2 (8 CHILDREN
AVERAGE DAY OF ONSET OF REYE'S	5.2 DAYS	7.1 DAYS	8.3 DAYS
AVERAGE NUMBER OF DOSES OF SALICYLATE PER DAY UNTIL DAY BEFORE ONSET OF REYE'S	.94 DOSES PER DAY	.51 DOSES PER DAY	.22 DOSES PER DAY

DATA FROM TABLE 5, PAGES 62 AND 63

FDA REYE'S SYNDROME WORKING GROUP REPORT
MAY 18, 1982

FIGURE 2

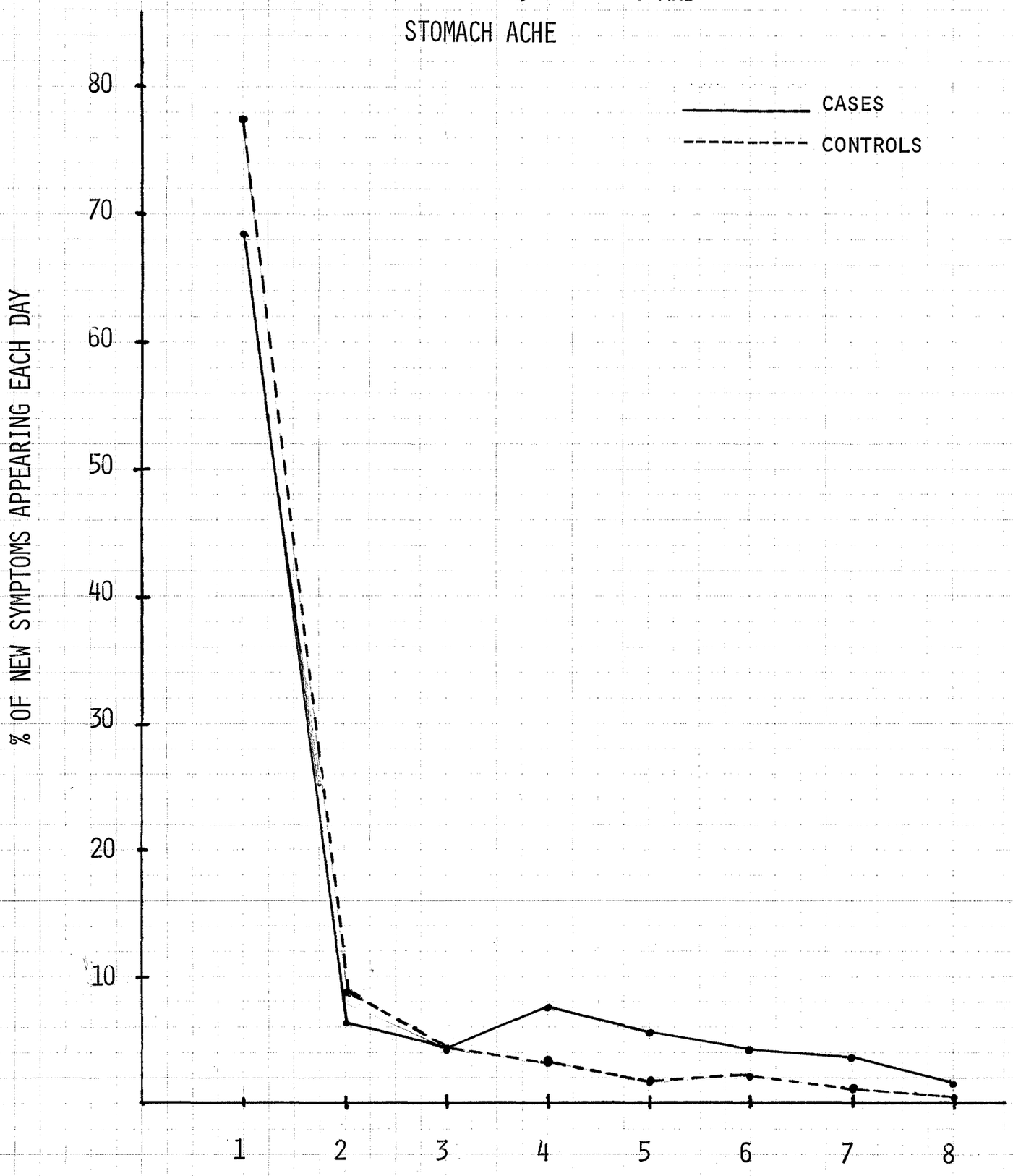


% of New Symptoms	Day of Illness							
	1	2	3	4	5	6	7	8
Cases (New Symptoms=216)	46.7	4.6	6.4	10.1	10.1	7.4	6.0	3.7
Controls (New Symptoms=280)	76.4	8.9	3.5	3.2	2.5	2.5	1.0	.7

Source: FDA Reye's Syndrome Working Group Report, May 18, 1982, p. 59.

FIGURE 3

% OF NEW SYMPTOMS APPEARING EACH DAY--
NOT INCLUDING NAUSEA, VOMITING AND
STOMACH ACHE

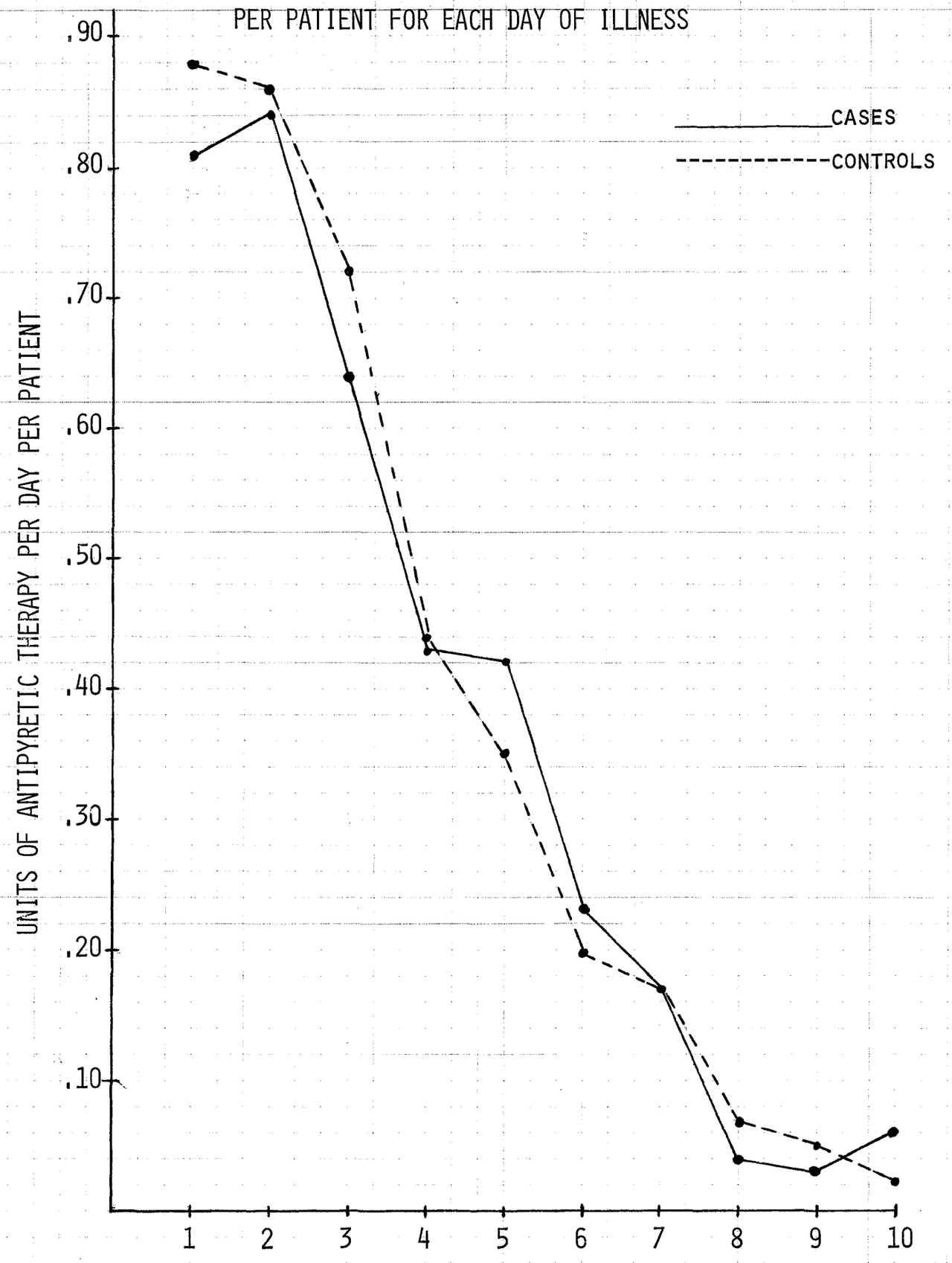


% OF NEW SYMPTOMS	DAY OF ILLNESS							
	1	2	3	4	5	6	7	8
CASES (NEW SYMPTOMS=144)	68.3	6.2	4.1	7.6	5.5	4.1	3.4	1.3
CONTROLS (NEW SYMPTOMS=244)	77.8	8.6	4.0	3.2	1.6	2.0	.8	.4

SOURCE: FDA REYE'S SYNDROME WORKING GROUP REPORT, MAY 18, 1982, P. 59.

FIGURE 4

UNITS OF ANTIPYRETIC THERAPY
(SALICYLATES PLUS ACETAMINOPHEN)
PER PATIENT FOR EACH DAY OF ILLNESS



Units of Antipyretic Therapy Per Patient Per Day	Day of Illness 1	2	3	4	5	6	7	8	9	10
Cases (N=64)	.81	.84	.64	.43	.42	.23	.17	.04	.03	.06
Controls (N=100)	.88	.86	.72	.44	.35	.20	.17	.07	.05	.02

Source: FDA Reye's Syndrome Working Group Report, May 18, 1982, Tables 5 and 6, Pages 62 - 65