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# The Authors' Reply

We appreciate Drs Waller and Suvarna's letter.

First of all, it is important to realise that our article[1] was invited by *Drug Safety* as a pro/con presentation, but the journal was unable to obtain a manuscript for the 'case for' aspirin (acetylsalicylic acid) as a cause of Reye's syndrome, and therefore our 'case against' article was published alone.

Since both Dr Waller and Dr Suvarna are or have been employed by the UK Medicines and Healthcare products Regulatory Agency, we would ask whether it makes sense to have placed warning labels against the use of aspirin for all children and adolescents, when Reye's syndrome at its peak in 1980 affected only eight out of a million children, and throughout its 'heyday' in the 1970s and 1980s affected only three per million children. The association of teenagers driving with fatal traffic accidents is much stronger epidemiologically, but no effort is made to prevent teenagers driving. There is also a very strong association of paracetamol (acetaminophen) ingestion with teenage and young adult suicides and liver failure, but warnings are not placed on paracetamol.

Sir Austin Bradford Hill's criteria[2] were developed for environmental and occupational exposures as causes of disease, just as Koch's postulates were developed for infectious diseases. Both have their strengths and weaknesses for assessing causation of a disease, but if, as Waller and Suvarna state, "There is undoubtedly an infectious component to the aetiology" of Reye's syndrome, then Koch's postulates seem to be a reasonable approach.

We obviously disagree about Austin Bradford Hill's criteria in relation to aspirin and Reye's syndrome. As concerns strength and consistency, our article clearly showed a larger number of studies that have failed to find an association between aspirin and Reye's syndrome. Concerning specificity, Maria Casteels-Van Daele[3] has shown that phenothiazines play a statistically significant role in the development of Reye's syndrome by simply defining the onset of Reye's syndrome as the occurrence of altered mental status. Likewise, inborn errors of metabolism have been shown to be the cause of many cases of what we used to call Reye's syndrome.[4,5]

More importantly are the other Bradford Hill criteria of temporality, biological gradient, plausibility, coherence, and experimental evidence. Temporality is in question because most cases of Reye's syndrome do not have measurable salicylate levels. We would all agree that the association of Reye's syndrome with aspirin lacks both a biological gradient (no dose-response curve) and experimental evidence (no animal model of Reye's syndrome and aspirin use). These deficiencies raise serious questions about the plausibility and coherence of a cause-and-effect relationship. Finally, the association of Reye's syndrome with aspirin fails the analogy test of Hill.

Waller and Suvarna would have to agree that the association of aspirin with Reye's syndrome fails more of Sir Austin Bradford Hill's criteria than it passes, and therefore a cause-and-effect relationship is questionable or unlikely. As Sir Austin Bradford Hill stated, "Here then are nine different viewpoints from all of which we should study association before we cry causation.",[2] and "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*.".[2] Most importantly, Sir Austin Bradford Hill cautioned that one should consider "is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?".[2] We could not have said it better.

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