Epidemiological evidence for the association of aspirin and acute gastrointestinal bleeding

Although Hurst\(^1\) claimed that the intake of aspirin was the likely cause of upper gastrointestinal haemorrhage in half of all those patients remaining, once those with known causes, such as chronic ulceration, had been excluded from consideration, little interest was shown in this suggested association until more recently when Muir and Cossar\(^2\) found a higher aspirin consumption in a group of individuals suffering from haematemesis or melena compared with that of a control group. The effects of aspirin on the gastrointestinal tract have also been explored in animals by various experimental procedures and in man by clinical physiological studies, usually designed to compare the degree of occult or microbleeding inducible by aspirin and other drugs, in groups of individuals with or without a history of upper gastrointestinal haemorrhage, but the critical evidence in establishing an association between aspirin consumption and acute haemorrhage must come from epidemiological studies. That experimental studies may even be misleading is illustrated by the evidence that salicylate compounds can cause hypoprothrombinaemia, a prolonged bleeding time\(^3\), and platelet aggregation\(^4\). Animal studies have also shown that administering systemic salicylates, usually in large doses, can cause gastric erosions and bleeding \(^5,6,7\). However, when acetylsalicylate was given intravenously in man, there was no evidence of any tendency to bleeding when the dose was kept within the usual therapeutic range\(^8\).

No method of study has yet been devised which would allow prospective investigation of the role of aspirin in inducing haemorrhage and therefore retrospective comparisons remain the only available techniques. This is not a disadvantage, at least initially, for in situations where a single factor is an important cause of disease (for instance, the association of smoking and lung cancer) retrospective investigations comparing cases and controls have pointed to that cause.

Epidemiological Evidence Obtained from Controlled Investigations

The available evidence suggesting an association between aspirin consumption and acute gastrointestinal haemorrhage can be divided into three broad categories: (1) uncontrolled studies showing the frequency with which a history of recent aspirin consumption can be obtained from individuals admitted to hospital because of upper gastrointestinal haemorrhage; (2) controlled comparisons of the aspirin intake of individuals admitted with various complaints including gastrointestinal bleeding; and (3) attempts to identify a specific bleeding lesion due to aspirin consumption by retrospective
comparisons of the recent drug-taking habits of patients admitted with bleeding due to different causes, such as acute and chronic gastric ulcer and duodenal ulcer.

The first type of enquiry does little more than suggest an association which may be worthy of investigation. The second variety of study demands a careful comparison between a test or haemorrhage group and a suitable control group, but such an analysis poses difficulties. It is virtually impossible to question the patients without knowledge of the causes of their admission, for even if control and test groups are selected by one individual, and questioned by another, it is almost inevitable that the reason for admission will become obvious during the interview. Bias, conscious or unconscious, during the questioning is therefore hard to avoid.

Aspirin and compounds containing aspirin are common household remedies taken for minor ailments and the initial symptoms of gastrointestinal bleeding, such as a feeling of faintness, could well be mistaken for the onset of a ‘flu-like’ illness. The patient might then take aspirin because of symptoms of haemorrhage and the investigators could interpret this drug consumption as a precipitating factor.

Many of the aspirin compounds which are freely available are not labelled in such a way as to make the acetylsalicylate content obvious; consequently neither patients nor controls may know whether they have taken aspirin. It is also very easy for an individual who has been admitted to hospital as an emergency case to forget the, to him, insignificant event of taking a tablet containing aspirin.

When there are such difficulties it becomes especially important to find a group of individuals who can act as a satisfactory control for comparison with the group under examination, a problem which has been commented upon by other workers 8, 10, 11.

The types of controls which have been selected by eight groups of investigators 8, 12, 18, 14, 15, 16, 17, 18 have reflected these difficulties. They have included dyspeptic patients referred to an outpatient clinic; unselected medical, surgical, and gynaecological admissions; and surgical emergency patients. The selections which have been made can be criticized on various grounds. The arbitrary choice of the individual in the next bed 17 could include, for instance, patients admitted with strokes, whose memory of antecedent events would be likely to be extremely poor. It could also include those who had been admitted some considerable time before, and again, therefore, might not remember their previous drug-taking habits. By contrast with these instances where aspirin intake could be forgotten, it would be a surprise if no history of aspirin intake were obtained from the patient with rheumatoid arthritis.

Unselected control groups, consisting of patients admitted for a wide variety of reasons, can be criticized on similar grounds to those advanced in considering the patient in the next bed. That large variations do exist within such groups has been confirmed by Parry and Wood 18 who found that only one quarter of their control group of patients admitted with gastrointestinal, cardiovascular, haematological, and neurological disorders gave a history of recently taking aspirin as compared with one half of the remaining controls. Salicylate compounds are also commonly stigmatized as liable to exacerbate ulcer symptoms, and the selection of dyspeptic outpatient controls 14 could, therefore, include groups whose salicylate intake had already been limited by the referring physician.

It thus seems possible that the wide variation in proportions of aspirin takers in the eight control series, from 4% 18 to 44% 18, could be due—at least in part—to the difficulty inherent in selecting suitable control populations.

The proportion of patients taking aspirin who were found amongst the patients with acute gastrointestinal bleeding have also varied from one series
to another, though the fluctuation was less than in the control groups, there being just less than a threefold difference for the test groups from 25%\textsuperscript{13} to 72%\textsuperscript{12}, as compared with the elevenfold variation in the control groups. In spite of the wide fluctuation in proportion of aspirin takers between one series and another, all workers consistently found a higher proportion of aspirin takers in the haemorrhage groups than in the control series. Part of the variability between the results obtained by individual groups of investigators could be due to the selection of differing time periods for which patients were asked about their aspirin consumption, for these have ranged from six hours\textsuperscript{9} to two weeks\textsuperscript{10} before admission. In four studies, figures are given for a 48-hour period\textsuperscript{14,16,17,18}, and, with this standardization, the variation between individual groups of patients with haemorrhage has been virtually abolished, the range being 51%\textsuperscript{15} to 58%\textsuperscript{16}. By contrast, there is still a difference more than twofold in the range for the control series, from 11%\textsuperscript{16} to 26%\textsuperscript{12}, all figures being well below those for their comparable test groups.

The overall comparisons, therefore, provide evidence in favour of a real association between aspirin ingestion and acute gastrointestinal bleeding, but the lack of satisfactory control groups and the difficulty of knowing whether in all test groups aspirin was taken before the bleeding started, or afterwards because of symptoms of haemorrhage, prevents any firm conclusions.

Specific Lesions Associated with Gastrointestinal Haemorrhage and their Possible Relation to Aspirin Intake

The uncertainty of general investigations could be clarified if an individual lesion specifically due to aspirin intake were identifiable.

Acute upper gastrointestinal haemorrhage is usually due either to chronic or acute peptic ulceration. The former can be identified radiologically and assumed to be causal in all except a few patients who have either acute gastric ulceration in association with duodenal ulcer or combined chronic gastric and duodenal ulceration. These subgroups are so small, however, that they are not serious causes of error. The remaining patients, leaving aside those with lesions such as gastric cancer and oesophageal cancer, have no abnormality on examinations by barium meal. This radiologically negative group contains a high proportion of individuals with acute gastric erosions and a few who later prove to have chronic ulceration.

The proportions of aspirin takers amongst those with different types of ulceration have been compared in several investigations and in all of these the subgroup with radiologically negative results contained a higher proportion of aspirin takers than did the subgroups of patients with chronic gastric ulcers or with duodenal ulcers. In addition, the subgroup with duodenal ulcers contained a slightly higher proportion of aspirin takers than the subgroup with chronic gastric ulcers in four of five studies in which this comparison was made.

On the evidence, the group in whom bleeding was not shown radiologically would seem to be especially associated with aspirin consumption, although this does not imply that a possible association with chronic ulceration can be dismissed.

It has been repeatedly shown that salicylate compounds will cause acute erosive lesions in experimental animals. Similarly, when ordinary aspirin preparations were given orally to human patients shortly before partial gastrectomy, lesions typical of acute erosions were found in the resected stomach\textsuperscript{5,19}. Though these abnormalities appear histologically like acute
erosions they differ from those found clinically, in that they are not associated with haematemesis and melaena. Gastroscopic evidence has been produced to show that following aspirin consumption in man, aspirin particles can be seen to be surrounded by haemorrhagic areas of gastric mucosa. These latter observations have been contested but are sufficient to make it worthwhile considering separately the recent aspirin consumption of patients admitted to hospital with haematemesis or melaena due to acute gastric ulceration or erosion.

Individuals who are found gastroscopically to have acute gastric ulcers must form a purer group than the total radiologically negative group; only two groups of investigators seem, however, to have attempted to make the separation. Whereas Alvarez and Summerskill detected a lower proportion of individuals who had taken aspirin in those with gastroscopically confirmed erosions than in the radiologically negative remainder, Valman, Parry, and Coghill found the reverse to be true, a conflict which could well be due to chance variations in the small numbers of individuals studied, and is unhelpful in delineating any special risk of acute gastric ulceration.

Some additional but slightly unhelpful information has been obtained from the nocturnal sampling of gastric secretory activity carried out shortly after admission by Valman, Parry, and Coghill. When these patterns were considered in relation to the anatomical lesion and the history of aspirin consumption they were unable to detect a correlation in any diagnostic category. In particular, within the radiologically negative group the proportion of patients with relative achlorhydria, characteristic of acute gastric erosion, was if anything higher in those who had not taken aspirin than in those who had taken the drug (47% and 43% respectively). The reverse might have been expected if there were a real association between aspirin consumption and bleeding from acute gastric erosions. Histological examination of gastric mucosal biopsy specimens obtained from radiologically negative patients with acute haemorrhage has also failed to show any differences between the proportion with chronic superficial and atrophic gastritis who had taken aspirin and those who had not.

There is therefore no clear evidence that acute gastric erosions are associated with aspirin consumption, although there has consistently been found to be a higher proportion of aspirin takers than in those with chronic gastric or duodenal ulcers.

**Epidemiological Studies of the Interrelationships between Aspirin and Other Factors in Inducing Haemorrhage**

'The gun must be loaded in order for an explosion to occur when salicylates pull the trigger.' Salicylate compounds are well known to cause occult bleeding from the gastrointestinal tract, but when a radiochromium method was used to compare the susceptibility to occult bleeding of control individuals and that of patients who had recently suffered from overt haemorrhage associated with aspirin intake no differences were found between the groups. One might, however, have expected that if those developing acute haemorrhage after taking aspirin were unduly susceptible to the gastrointestinal effects of the drug, then they might have had a greater tendency to occult bleeding when rechallenged with it than would control individuals.

It has therefore been suggested that it is the coincidence of aspirin intake with other factors which leads to overt haemorrhage. Jennings considered a number of extrinsic factors and concluded that excessive emotion, fatigue, anxiety, irregular meals, infection, alcohol consumption, and heavy smoking
could all increase liability to gross haemorrhage associated with aspirin consumption. Some of these characteristics are difficult or impossible to quantify and therefore, in assessing them, it would be very important for the investigator to avoid bias by administering a questionnaire about the factors without knowledge of the patient's aspirin consumption. It is not clear whether this problem was taken into account, but even so the data do not seem to support all the postulates quoted.

Analysis of the results reported shows that nervous strain was evident in 88 (43%) of the 205 who had taken aspirin compared with 51 (47%) of the 109 who had not. Whereas, if the nervous strain and aspirin were in fact important combined precipitants one might have expected there to be more patients with strain in the group taking aspirin than in the group not taking aspirin. Similar comparisons show the same tendencies for physical strain (23% and 29% respectively), smoking (37% and 39%), and alcohol consumption (17% and 21%). By contrast, there were slightly higher proportions of aspirin takers amongst those with chronic infections (9.3% and 8.2%) and hypotension (26% and 21%). The only substantial difference between those taking aspirin and those not taking aspirin would seem to be in relation to acute respiratory infection (23% and 6% respectively). Here an association might well be expected, for aspirin is the drug of choice for many acute respiratory infections if they involve the upper part of the tract.

Clear evidence that alcohol intake may accentuate microbleeding following aspirin consumption has been brought forward by Goulston and Cooke. The mean daily loss of faecal occult blood in 13 subjects given aspirin alone was 3.2 ml, but with aspirin and alcohol (undiluted Australian whisky) together the figure rose to 5.3 ml.

The possibility of an interaction between aspirin and other factors, especially alcohol, in inducing gastrointestinal haemorrhage has been considered in detail in three other studies. Allbone and Flint found no obvious association between aspirin intake and alcohol consumption or infections of the upper respiratory tract but this evidence is difficult to weigh, for they did not distinguish between ulcers which caused symptoms due to haemorrhage and to free perforation. By contrast, Astley and Brown and Mitchell claimed that there was an association between aspirin and alcohol consumption in inducing gastrointestinal haemorrhage. Astley analysed the histories of 31 male patients admitted to hospital with haematemesis or melena: 23 had taken aspirin and 16 had taken alcohol within 24 hours of the onset of bleeding, 10 having both aspirin and alcohol. However, further consideration of these figures reveals that in any group of 31 individuals, of whom 23 had taken one substance and 16 a second substance, then one would expect, by chance, that 12 would have taken both together (23/31 × 16/31). Brown and Mitchell found that 32 of 46 patients with duodenal ulcer had taken salicylate compounds, 11 had taken alcohol, and of these four had taken both aspirin and alcohol. As with the previous data, it can be shown that a chance association could well explain an intake of both aspirin and alcohol in the four individuals where this occurred.

A further suggestion has recently been made that subclinical vitamin-C deficiency predisposes to haemorrhage induced by aspirin. Comparison of the white-cell ascorbic-acid concentrations in patients with recent acute haemorrhage showed that a higher proportion of recent aspirin takers could be found in those with relatively low ascorbic acid concentrations than in those with normal concentrations. In an extension of this work scorbutic guinea pigs were found to be unduly prone to aspirin-induced bleeding. If confirmed, this work would give strong support to the claim that aspirin can induce acute haemorrhage under certain limited conditions. It could also help to explain the tendency for acute gastric and duodenal haemorrhage to be more frequent in the winter than in the summer months.
Effects of Different Varieties of Aspirin in Inducing Haemorrhage from the Gastrointestinal Tract

The inconclusive nature of the evidence associating salicylate consumption with acute gastrointestinal bleeding is possibly due mainly to the problem inherent in trying to test epidemiologically for the relationship. However, it might also be due to variations in the potentiality of different aspirin preparations to cause bleeding. Since so many preparations are available it would hardly be surprising if they had unequal effects upon the gut.

Aspirin is well known to cause occult bleeding in most people whether suffering from gastrointestinal disease or not28,29,34,35,36,37 and the amount of occult bleeding induced by a specific preparation could indicate the propensity of that preparation to induce acute haemorrhage.

Jennings13 found that enteric-coated aspirin protected against occult bleeding whilst calcium and glycine aspirin differed little in their effects from ordinary preparations. By contrast, Pierson and his colleagues38 noted a protective effect with calcium aspirin but none with enteric-coated tablets. In a limited series of experiments on nine subjects a fine-mesh aspirin preparation, mesh size 16, was found to induce less occult bleeding than a coarse-mesh preparation, mesh size 12039, both given in gelatine capsules, although previous comparisons of aspirin tablets composed of powder of mesh sizes 20 and 80 had shown no significant differences40.

Buffered aspirin preparations have been found to cause less gastric micro-bleeding than other aspirin compounds27,41,42,43,44 and Stubbe and his colleagues44 also found a protective effect with enteric-coated tablets. Assuming a correlation between micro- and macro-bleeding, one might expect a high proportion of individuals who took ordinary aspirin and a low proportion of those who took enteric-coated and buffered varieties amongst those with haematemesis or melaena.

Alvarez and Summerskill14 enquired about soluble and insoluble varieties taken, but failed to establish any clear differences between their test and control groups. Brown and Mitchell15 found that of the 32 patients in their series who took aspirin, three took at least one preparation. Of the remaining 29, 24 (83%) took insoluble varieties, four (14%) a buffered effervescent preparation, and the remaining individual took salicylate. The habits of their control population are not clearly described but at least 40% took buffered effervescent aspirin preparations from time to time, though not to the exclusion of other compounds. These two sets of figures suggest that insoluble and perhaps unbuffered varieties of aspirin are particularly liable to cause acute haemorrhage. Some support for this view can be obtained from Jennings' study48 in which detailed enquiries were made about the preparation recently taken by patients admitted with haematemesis or melaena. No control group was included in the investigation and therefore the only possible comparison is between the aspirin-taking habits of those who, because radiologically negative, were thought to have acute ulcers and those with chronic ulcers. Since the radiologically negative group is most strongly associated with aspirin consumption one would expect any preparation which was especially liable to induce bleeding to be taken most frequently in this group and less so in the chronic ulcer group. Fifty-nine (42%) of the 139 patients with acute ulceration took ordinary aspirin preparations, 25 (18%) took soluble varieties, and 10 (7%) took a buffered effervescent preparation. By contrast, 24 (29%) of the 84 with chronic ulcers took ordinary preparations, 12 (14%) took soluble varieties, and 18 (21%) took buffered aspirin.
Conclusions

It has been repeatedly demonstrated by epidemiological control studies that patients admitted to hospital with acute upper gastrointestinal haemorrhage, particularly those with no detectable radiological abnormality, contain an unduly high proportion of individuals who have taken aspirin-containing analgesics. However, there are difficulties inherent in such investigations, especially the problems of selecting suitable controls and of separating aspirin consumption before the onset of bleeding from aspirin taken because of the symptoms. The evidence is therefore inadequate to allow firm conclusions about the precise causal role for salicylate compounds. There has also been insufficient attention paid to the possibility that even if some aspirin-containing analgesics, particularly insoluble and unbuffered preparations, cause acute bleeding, others may not. Studies of occult bleeding associated with aspirin consumption are difficult to interpret, for though aspirin can be shown to induce occult bleeding as a regular occurrence in most individuals, no relationship has been found between the severity of occult bleeding and liability to overt haemorrhage. This lack of correlation has been explained by the hypothesis that aspirin only causes overt haemorrhage in association with other factors. Investigation has so far failed to produce any conclusive evidence of what these factors might be, except perhaps subclinical vitamin-C deficiency.

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