Progress report

Aspirin in chronic gastric ulcer: an Australian experience

Since the original report in 1938¹ there has been increasing evidence to suggest an association between aspirin use and the development of acute gastric mucosal lesions, although even after nearly 40 years there is not unanimity on the subject^{2,3}. Related to this is the question of an association of chronic gastric ulcer and aspirin usage which has received more prominence in the Australian literature than elsewhere. It is proposed to review this association of chronic gastric ulcer and aspirin usage. The evidence so far available does not suggest that aspirin plays any significant role in the production or perpetuation of duodenal ulcer.

In an examination of the role of aspirin in gastric ulcer disease there are a number of caveats to be observed. Firstly, it is not widely recognised that there are quite significant regional differences in aspirin consumption. Although precise data on aspirin consumption are to some extent obscure, there is good evidence that the mean daily *per capita* consumption in the United States at 0.27 doses of 300 mg⁴ is less than that in Britain at 0.33 doses⁵, which is less than the Australian consumption of 0.63 doses⁶. Furthermore, unpublished data from market surveys indicate fivefold differences between different regions in Australia, with the largest consumption taking place in the north-eastern part of Australia, embracing the states of Queensland, and New South Wales where the favoured preparations contain at least aspirin and caffeine. Moreover, evidence from Canada⁷ and from Australia⁸ suggests that many patients taking large quantities of aspirin-containing analgesic preparations conceal the fact. In addition, much of the data concerning the consumption of aspirin before gastric bleeding is invalidated by a failure to recognise that aspirin taking before bleeding is often part of a habit of regular aspirin consumption⁹.

In a series of papers that began in 1960 Billington in Sydney drew attention to a curious phenomenon¹⁰⁻¹³. An analysis of mortality data including cohort analysis, radiological records, and hospital admission data showed that in about 1943 there appeared an epidemic of gastric ulcers in young women in eastern Australia. These women developed gastric ulcer in early adult life and the data led him to conclude that the cause was an environmental one the nature of which was unknown and that this environmental factor, one which operated to produce a gastric ulcer in the late teens, continued to operate perhaps for years in that patient. The epidemic was such as to produce a bimodal frequency distribution curve when the data for women were examined by age; no such evidence appeared in males or in duodenal ulcer. The magnitude of this epidemic was such as to produce quite significant changes in the pattern of hospital admissions for gastric ulcer, so that the male to female ratio from uncomplicated gastric ulcer over three decades showed a complete reversal with females now outnumbering males (Table 1).

City	Author	Period	M:F ratio
Sydney (N.S.W.)	Billington (1960a) ¹⁰	1930-39	2.5:1
Sydney (N.S.W.)	Billington (1963) ¹²	1945-55	1.3:1
Townsville (Qld.)	Douglas and Johnstone (1961) ¹⁴	1956-59	1:1
Newcastle (N.S.W.)	Chapman and Duggan (1969) ¹⁶	1960-66	0.7:1

Table 1 Changes in M:F ratio in uncomplicated gastric ulcer in North-Eastern Australia

In 1961 Douglas and Johnstone in northern Queensland reported a series of 77 patients with chronic gastric ulcer of whom 57 were aspirin takers¹⁴. They noted a high frequency of chronic headache in these patients and speculated on whether the large consumption of aspirin by these patients for headaches would be of aetiological significance and related to the epidemic of gastric ulcer then recently described by Billington. In north-eastern Australia, the consumption of analgesic powders in the form of compound preparations containing aspirin, phenacetin, and caffeine is widespread; the powders have some reputation as a stimulant, probably related to the 150 mg caffeine they contain. In recent years, phenacetin has been replaced by salicylamide or acetaminophen, now that the high prevalence of analgesic nephropathy has been recognized.

A prospective study, begun in 1962, of 118 patients admitted to a large general hospital with acute perforated peptic ulcer showed excessive numbers of females with gastric ulcer, compared with British experience¹⁵. These patients were accustomed to taking large quantities of compound analgesic powders containing aspirin. In fact, of these female patients with gastric ulcer only one did not take aspirin regularly; on the other hand, no such association was seen in males with duodenal ulcer. The study also demonstrated that aspirin taking was fairly common among men with gastric ulcer. These correlations were highly significant statistically (Table 2).

Aspirin dose	Site of ulcer	
	Pyloro-duodenal	Gastric
Nil and occasional	28	9
≥ 2/week	6	6
≥ 2/day	12	23

Table 2 Aspirin use in patients with acute perforated peptic ulcer 1962-66

$\chi^2 = 10.8$, $n = 2$, $P < .005$ (Duggan, 1972)¹⁵.

Studies from this unit have also shown that the association of aspirin with bleeding is not as simple as had been believed. In a study of 1634 admissions with acute upper gastrointestinal haemorrhage⁹, there was again noted the bimodal age distribution curve reminiscent of that described by Billington. This study showed that, in considering duodenal ulcer, gastric ulcer, and the 'acute lesion group', there was in all groups a preponderance of patients admitting to two or more doses of an aspirin-containing preparation each week over those who took aspirin within 48 hours of bleeding, not being accustomed to taking it regularly. The study also showed that the regular aspirin takers were predominantly middle-aged women and the association of regular aspirin intake and gastric ulcer was highly significant (Table 3).

Aspirin dose (weekly)	Site of ulcer	
	Duodenal	Gastric
≥ 2	105	91
< 2	139	59
Including before bleeding only		

Table 3 Aspirin use in 394 patients with acute gastrointestinal haemorrhage and ulcer

$\chi^2 = 11.0$, $P < 0.0005$ (Duggan, 1970).

In uncomplicated gastric ulcer the position is less obscure. The original paper by Douglas and Johnstone reported a syndrome of chronic relapsing headache, aspirin ingestion, and chronic gastric ulcer affecting 57 of a consecutive 77 admissions for gastric ulcer¹⁴. Those affected were mainly younger middle-aged women with an average annual consumption of 1460 doses of analgesic or between three and seven times the average consumption in that community. However, this study has the defect of being quite uncontrolled. The next study was that of Chapman and Duggan¹⁶ who examined 295 patients admitted to hospital for uncomplicated peptic ulcer. Of the 61 females with gastric ulcer, 52 took at least two doses of an aspirin preparation each week and, in a large majority of these, the intake was at least two daily. This habit of aspirin taking was marked in middle-aged women. No such association between the presence of a gastric ulcer and aspirin taking was seen in men. In those taking aspirin, 80% took it in the form of a compound analgesic powder almost invariably as a proprietary preparation containing aspirin, phenacetin, and caffeine. The data suggested that the patients with gastric ulcer took between three and five times as much as controls from other Australian sources. In this study, females taking two or more doses weekly exceeded males to a highly significant degree and in females with gastric ulcer aspirin taking was present in 92%; no association of duodenal ulcer and aspirin usage was present. A comparison of the duration of aspirin taking and of dyspepsia was possible in 29 patients and in only one did ulcer pain precede analgesic ingestion. In duodenal ulcers in both sexes and gastric ulcer in males no correlation between duration of dyspepsia and duration of aspirin intake was present, although there was a general correspondence of duration of the two in females with gastric ulcer. This study also confirmed a fall in the male to female ratio for gastric ulcer noted by Billington. This is in most marked contrast with the ratios of 2.4:1¹⁷ and 1.7:1¹⁸ in Britain. This study also suffers from the defect of lacking control data.

The studies of Gillies and Skyring¹⁹ have done much to redress this. They examined 100 patients with gastric ulcer and 50 patients with duodenal ulcer and compared them with a control population of inpatients matched for age and sex in the same ward. Overall, 57% of patients with gastric ulcer took aspirin daily, the figures being 44% in males and 75% in females compared with 22% in the controls. In comparison with the controls, more of the patients with gastric ulcer took aspirin ($P < 0.001$), in larger doses ($P < 0.01$), for a longer time ($P < 0.001$). Once again the question of the validity of using inpatients as controls was raised and in a subsequent study²⁰ they interviewed 1405 workers representing all ages and social groups. More patients with gastric ulcer than controls took aspirin daily ($P < 0.001$). While aspirin ingestion was more common in duodenal ulcer than in controls, the difference was not statistically significant. The prevalence of daily aspirin

ingestion was 9.8% in control workers and was greater among women than men ($P < 0.001$) and was greater among those of lower than those of high social class ($P < 0.001$).

Alp and his colleagues²¹ carried out a retrospective survey of 638 patients with chronic gastric ulcer admitted to two large South Australian teaching hospitals and compared the findings with a control group selected from hospital patients, domestic staff, and other apparently well people. In 363 patients, comparison with a control group showed a highly significant increase in the incidence of regular aspirin ingestion at three or more doses per week compared with controls ($P < 0.0005$) and females took more aspirin than males ($P < 0.025$).

A report from the Boston Collaborative Drug Surveillance Programme has done something to overcome the problem of controls²². This study concerned some 25000 consecutive admissions to 24 Boston hospitals. There were 26 cases of newly diagnosed uncomplicated gastric ulcer of whom 19% took aspirin on at least four days a week compared with 6.9% of controls. After controlling for age and sex, the difference remained significant ($P < 0.05$). The yearly incidence rate of hospital admission for newly diagnosed benign gastric ulcer in those not taking aspirin regularly was 3/100,000 per annum, and for those taking aspirin on at least four days a week regularly was 13/100,000 per annum; the incidence of hospital admission for gastric ulcer attributable to regular aspirin at this dosage level was therefore 10/100,000 per annum. There was no significant evidence of any association between duodenal ulcer and aspirin use nor that aspirin taking in lesser amounts produced any significant incidence of hospital admissions for ulcer or bleeding.

More recently, Dagradi and his colleagues²³ in California have reviewed the question. Of 119 patients with benign gastric ulcer demonstrated at gastroscopy, 30% had multiple ulcers, 70% had single ulcers; 92% of those with multiple ulcers but only 38.5% with single benign lesions had taken ulcerogenic drugs in close proximity to the onset of symptoms. Considering aspirin alone, the frequencies were 83% and 37% respectively. The corresponding figure in routine hospital admissions was 16.5%. The increase in the proportion of patients taking regular aspirin preparations among those with multiple ulcers compared with those with single gastric ulcers was highly significant ($P < 0.0005$).

Cameron²⁴, in a prospective study at the Mayo clinic, compared 61 outpatients with gastric ulcer with age and sex matched controls suffering from non-ulcer alimentary disease and found that 52% of the patients compared with 10% of the controls took 15 or more aspirin preparations each week ($P < 0.001$). This difference persisted when patients taking aspirin for relief of alimentary symptoms or when those whose symptoms preceded aspirin were excluded. The regular use of aspirin was especially associated with ulcers of the pre-pyloric area. The association was less strong in patients with combined gastric and duodenal ulcer and the association of gastric ulcer with aspirin was stronger than that with smoking or other potentially ulcerogenic drugs.

These six studies from widely separated areas in the United States and Australia employing varied methodologies have one feature in common—all have shown significant associations between the regular intake of aspirin and the presence of chronic gastric ulcer. A different approach to the problem

is the study of the gastric manifestations in those patients known to take sufficient analgesics to produce analgesic nephropathy. There are at least five such studies.

In 1966 Dawborn and his colleagues²⁵ reported 30 patients with peptic ulcer, renal disease, and a history of analgesic abuse and in the same year Olafsson and his colleagues^{25,26} from Iceland reported 14 patients with similar syndrome. Shortly after, Gault and his colleagues⁷ from Canada reported 22 patients with renal disease and a history of analgesic abuse and noted that 12 had had a gastrectomy, the commonest indication being gastric ulcer. Fellner and Tuttle²⁷ from the United States reviewed 35 patients with analgesic nephropathy and noted the striking incidence of peptic ulcers. More recently, an Australian report of 63 patients of analgesic nephropathy and peptic ulcer, has appeared⁸. The commonest lesion in the gastrointestinal tract was a gastric ulcer but 25% had duodenal ulcer. A feature of the ulcers was a tendency to complications; 43% of the patients had overt gastrointestinal haemorrhage, 24% had perforated an ulcer, and 60% had a history of gastric surgery. Twenty-one patients had had emergency surgery for a perforation or bleeding and four patients had an hour-glass stomach: the 63 patients had a total of 54 gastric operations. A more recent report from the same unit²⁸, has reviewed the aspirin intake of 19 consecutive patients with hour-glass stomach. In two, where the hour-glass deformity was due to carcinoma, there was no history of aspirin intake. In the remainder, many of whom were middle-aged women, the ulcer was benign and in all 17 there was a history of prolonged aspirin abuse. The incidence of complications was high and again there was supporting evidence of analgesic abuse in the form of analgesic nephropathy in six patients.

The study of patients with the analgesic syndrome has highlighted a feature not previously recognised in studies of analgesic abuse. Many of the patients with the analgesic syndrome deny analgesic abuse when subsequent evidence shows that in fact they were taking analgesics^{7,8}. It would appear that this denial may account for some of the discordant results present in the literature, particularly as those abusing these drugs as part of a disordered psychosocial situation may sometimes take vast quantities.

No discussion concerning the role of aspirin in chronic gastric ulcer is complete without reference to the rheumatic diseases in which salicylates are widely used. Unfortunately, clear evidence is not forthcoming. Cooke²⁹, in reviewing the role of steroids in ulcerogenesis, concluded that the incidence of peptic ulcer in rheumatoid patients was probably increased but that it was not certain that this increase was due to the administration of steroids. Subsequently, Emmanuel and Montgomery³⁰ reviewed the association of gastric ulcer and the anti-arthritic drugs and concluded that the increased prevalence of peptic ulcers in patients receiving anti-arthritic drugs was confined to gastric ulcers. Aspirin is often given serially or in combination with other non-steroidal anti-inflammatory agents such as indomethacin, phenylbutazone, or ibuprofen which have demonstrably harmful effects on the gastric mucosa³¹. It therefore becomes impossible, in the light of the available data, to draw any conclusion concerning the significance of aspirin in the production of ulcers in patients with chronic rheumatic disorders.

To summarize, some 30 years ago in eastern Australia there appeared in young and, subsequently, middle-aged women an epidemic of gastric ulcer the characteristics of which suggested an environmental cause. Several sub-

sequent studies have shown a strong statistical association between women with gastric ulcer and aspirin taking in eastern Australia where abuse of compound analgesic powders containing aspirin is widespread in women especially in the lower socioeconomic classes. Simultaneously, there has been a relative increase in admissions to a large general hospital of women with perforated gastric ulcer in whom there is a strong association with analgesic abuse. In gastrointestinal haemorrhage likewise, analgesic abuse was associated not only with acute gastric erosions but with chronic gastric ulcer. Three studies from the United States and three from Australia concerning patients with uncomplicated ulcer again show an association of regular aspirin usage and gastric ulcer. This association was also seen in all 17 patients with hour-glass stomach due to benign gastric ulcer, and studies from north America, Iceland, and Australia on patients abusing analgesics containing aspirin have all emphasized the frequency of peptic and especially gastric ulcers with a high complication rate. Studies of this association have been made difficult by two phenomena: variations in the prevalence of aspirin use on a geographical basis and a more recently recognized phenomenon of denial of the habit by those abusing analgesics. In view of unsatisfactory features in the data for the control group in many of these studies, it is suggested that further progress is likely to be forthcoming only from prospective studies employing some form of biochemical validation of the extent of aspirin use. At present, it would appear that, just as there is probably some association between aspirin and gastric bleeding, likewise there is probably an association of chronic aspirin usage and chronic gastric ulcer. No such evidence exists for duodenal ulcer.

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