Aspirin and uncomplicated peptic ulcer¹

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Evidence will be presented of an association between uncomplicated gastric ulcer in younger women, and the consumption of large quantities of aspirin-containing preparations, usually proprietary powders containing aspirin, phenacetin, and caffeine (APC), taken for the relief of headache.

Billington (1960a, 1960b, 1963, 1964a, 1965a, 1965b) has demonstrated a rising incidence and mortality rate for gastric ulcers in young women. This change is confined to New South Wales and Queensland, and began about 1943. It has not occurred in any other part of the world, where the rates for ulcers at all sites for both men and women are falling (Susser and Stein, 1962; Susser, 1967). The rates for men in New South Wales and Queensland are similar to those elsewhere. Billington postulated that an exogenous, ulcerogenic factor was responsible, and that this was 'dependent on some aspect of [the women's] behaviour'. Douglas and Johnston (1961) suggested that this factor was aspirin, taken for chronic headache. Duggan demonstrated an association between perforation (1965, 1967) and bleeding (1968) of gastric ulcers in young women on the one hand, and the taking of excess aspirin on the other.

MATERIAL AND METHODS

A retrospective study was made from the records of the Royal Newcastle Hospital, a 730-bed general hospital with 15,000 admissions per year, which serves a population of 330,000 chiefly dependent upon heavy industry and coal-mining. The records of all patients—public, intermediate, and private—discharged or dying between 1 July 1960 and 30 June 1966 inclusive, whose final diagnosis included that of any form of peptic ulcer, were examined. From these, cases were accepted for study if (1) the purpose of admission was the treatment of symptoms of ulcer; (2) no complication of ulcer in the form of haemorrhage, perforation, or stenosis was present at the time of admission; and (3) the diagnosis of ulcer was confirmed within 12 months of the index admission by means of barium meal examination,

gastroscopy, laparotomy or necropsy, and the symptoms could reasonably be ascribed to the ulcer. Two cases of peptic ulcer of the oesophagus were excluded. The index admission was the first, during the period of the study, in which these criteria were fulfilled, and the age was that at the time of the index admission.

The data were transcribed from the records onto punch cards, which were analysed by means of a sorting machine.

DEFINITIONS

Duodenal ulcer was diagnosed if ulcer, deformity, scarring or spasm of the first part of the duodenum, with or without local tenderness, was reported, and symptoms were present at the time. Pyloric canal ulcers were counted as duodenal. Prepyloric ulcer was diagnosed if the ulcer was between the pyloric ring and the antrum, and gastric ulcer if it was elsewhere in the stomach. Since prepyloric and gastric ulcers were found to behave similarly in regard to sex, age distribution, and aspirin intake, they were combined as 'gastric' ulcers. Postsurgical ulcers were those following gastroduodenal surgery. Combined ulcers were diagnosed in cases with ulcers at more than one site at the same time.

When acetylsalicylate in any form was the only pharmacologically active ingredient, the preparation was defined as aspirin.

Preparations containing aspirin, phenacetin, and caffeine were defined as APC.

When aspirin or an aspirin-containing preparation was taken twice a day regularly for at least six months of the year before admission the intake was defined as one of 'two or more doses per day'.

When two or more doses were taken per week, but less than two per day, regularly for a similar period of time the intake was defined as 'two or more doses per week'.

Intake was defined as occasional when fewer than two doses were taken per week.

The reason for ingestion could be for organic disease (disease present, for which the taking of the drug was considered reasonable) or for the relief of headache (without either organic cause or such functional cause as migraine).

¹Based on material presented to the Gastroenterological Society of Australia on 10 October, 1967 (*Gut*, 1968, 9, 249).

TABLE I

DISTRIBUTION BY SEX AND SITE OF ULCERATION

Sex	Duodenal Ulcer	Gastric ¹ Ulcer	Combined ²	Postsurgical	All Sites
M	99	55	3	4	161
F	51	79	1	3	134
M + F	150	134	4	7	295

¹Gastric ulcers included 19 prepyloric ulcers (M 11, F 8).²Combined ulcers consisted of active gastric ulcers in all four cases, with duodenal scarring in three and ulcer in one.

TABLE II

DISTRIBUTION BY AGE, SEX, AND SITE OF ULCERATION

Ulcer	Sex	Age in Years									Total
		10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	
Duodenal	M	1	10	21	26	19	8	13	1	—	99
	F	—	5	9	21	7	5	4	—	—	51
Gastric	M	—	—	9	13	18	10	4	1	—	55
	F	—	4	14	21	17	8	11	2	2	79
All sites	M	1	10	30	40	41	20	17	2	—	161
	F	—	9	25	42	25	14	15	2	2	134
	M + F	1	19	55	82	66	34	32	4	2	295

For the statistics χ^2 was calculated in all cases using Yates' correction.

RESULTS

SITE AND SEX There were 295 cases, and Table I shows the distribution by site and sex. The ratio of duodenal to gastric ulcers was 1.1:1 (Table VIII). In males it was 1.8:1. By contrast, in females it was as low as 0.7:1, and 0.6:1 when combined ulcers were added to gastric. The male to female ratio overall was 1.2:1 (Table IX), being 1.9:1 for duodenal ulcers and a low 0.7:1 for gastric ulcers.

Later discussion will show that, compared with other series, there was a diminished ratio of duodenal to gastric ulcers, due to an excess of gastric ulcers in women.

AGE The maximum age incidence, which for the series was in the fifth decade, differed between the sexes (Table II). Males had virtually equal numbers of cases in the fifth and sixth decades, but females had a sharp maximum in the fifth decade, which outnumbered any decade in males. For duodenal ulcers, the age distribution was similar for both sexes, with peaks in the fifth decade, males outnumbering females. In the case of gastric ulcers, however, the age distribution differed between the sexes. In males, there was an even curve, with a sharp peak in the sixth decade. In females, there was a broad peak in the fourth, fifth, and sixth decades, and a smaller one in the eighth decade. In the sixth and seventh decades, the numbers of males and

females were similar, but in the third, fourth, and fifth decades, and in the eighth, females greatly outnumbered males.

The excess of female gastric ulcer patients occurred chiefly in the menopausal and premenopausal age groups, and to a lesser extent in the elderly.

ASPIRIN Aspirin taking, and its relationship to ulceration, was examined. The aspirin habit was recorded in 79% of all cases, and this frequency did not vary with sex, site of ulceration, or year of the study. More than half of the patients in whom the information was available took two or more doses per day, females greatly outnumbering males (Table III), especially in the younger age groups (Table IV).

TABLE III

QUANTITY OF ASPIRIN-CONTAINING PREPARATION INGESTED

Dose	Male		Female		Male and Female	
More than two/day	54	(43.9%)	70	(67.3%)	124	(54.6%)
More than two/week	6	(4.9%)	7	(6.7%)	13	(5.7%)
Occasional	16	(13.0%)	8	(7.7%)	24	(10.6%)
None	47	(38.2%)	19	(18.3%)	66	(29.1%)
Total	123	(100%)	104	(100%)	227	(100%)

It is evident that compared with men there was an excess of both gastric ulcers and of aspirin taking, in younger women. An exploration of a possible causal relationship between these factors was undertaken.

TABLE IV

AGE DISTRIBUTION OF THOSE TAKING TWO OR MORE DOSES PER DAY

Sex	Age in Years									Total
	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	
M	—	1	9	20	12	7	5	—	—	54
F	—	6	18	25	13	4	2	2	—	70

TABLE V

QUANTITY OF ASPIRIN-CONTAINING PREPARATION INGESTED, BY AGE, SEX, AND SITE OF ULCERATION

Sex		Age in Years									Total
		10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	
Duodenal Ulcer											
M	≥2 doses/day + ≥2 doses/week	—	1	7	11	5	3	4	—	—	31
	Occasional + none	1	5	8	12	10	1	4	—	—	41
F	≥2 doses/day + ≥2 doses/week	—	3	6	12	1	1	—	—	—	23
	Occasional + none	—	2	3	5	3	4	1	—	—	18
Gastric Ulcer											
M	≥2 doses/day + ≥2 doses/week	—	—	4	10	6	4	1	—	—	25
	Occasional + none	—	—	4	3	8	3	1	1	—	20
F	≥2 doses/day + ≥2 doses/week	—	3	11	15	14	4	3	2	—	52
	Occasional + none	—	—	1	3	1	—	4	—	—	9

ASPIRIN, SITE, AND SEX The figures for those taking two or more doses per day and per week were combined, as were those admitting to taking an occasional aspirin or none. Those taking the larger quantities were compared with those taking the smaller, by site and sex (Table V). With duodenal ulcers in both sexes there was no difference in incidence, nor in age distribution, between those taking the larger and smaller quantities of aspirin. In females with gastric ulcers, the difference was striking. Fifty-two patients took at least two doses per week, while only nine took small quantities. While four of the latter were in the eighth decade, four-fifths of those who took large amounts were aged 30 to 59. In males there was no clear difference.

The abundance of gastric ulcers in younger women was strongly associated with the taking of excessive quantities of aspirin compounds.

ASPIRIN PREPARATION AND SITE The pattern of aspirin taking was examined. The type of aspirin preparation taken was known in 77% of the cases in which the aspirin habit was recorded. Of these, 80% took APC, almost invariably in the form of proprietary powders (Table X). Apart from a few who took a mixture of preparations, the remainder took aspirin alone, usually in a tablet form. These proportions were the same for all sites and both sexes.

The excess of aspirin was predominantly in the form of APC powders.

DURATION OF INGESTION In an attempt to determine

which was causative, the aspirin taking or the ulcer pain, the duration of drug ingestion was compared with the length of ulcer history. In only 29 cases were the records adequate for this comparison to be made. With gastric ulcers in females (Table VI), the two lengths of time showed a general correspondence. In most cases it could not be determined which was the longer. However, when there was a difference, in only one case did ulcer precede analgesic ingestion. With duodenal ulcers in both sexes and gastric ulcers in males there was no correlation.

TABLE VI

DURATION OF ASPIRIN INGESTION AND LENGTH OF ULCER HISTORY IN FEMALE GASTRIC ULCER PATIENTS¹

Duration of Ingestion (years)	Length of Ulcer History			
	≤One Year	Two to five Years	Six to 15 Years	>15 Years
≤1	1	—	—	—
2-5	—	5	1	—
6-15	—	2	3	—
>15	—	—	1	2

¹Three patients who took no aspirin had histories of two to five years.

INDICATION FOR ASPIRIN The indication for aspirin was also examined. In those who customarily took two or more doses per day, the reason for which the drug was taken was known in 53% of cases (Table VII). Tension headaches was by far the commonest indication, accounting for 90% of those in whom the information was available. Those who took aspirin preparations for ulcer pain and those

TABLE VII
INDICATION FOR AND FORM OF ASPIRIN-CONTAINING
PREPARATION IN THOSE TAKING TWO OR MORE
DOSES PER DAY

Indication for Aspirin	Aspirin	APC	Total
Pain in old fractures	1	—	1
Ulcer pain	—	2	2
Backache (see text)	—	2	2
Headache	9	48	57 ¹
Sedative	—	1	1
Liked taste	—	1	1
Total	10	54	64

¹One can be more than 99% confident that, of the 124 patients taking two or more doses per day of an aspirin preparation (Table III), between 100 and 117 took it for headache.

who took them for backache, probably the result of posteriorly penetrating gastric ulcers, together made up only 6% of those whose habit was known.

This strongly suggests that ulcer pain did not cause the aspirin taking, but that the reverse was true.

DISCUSSION

The ratio of duodenal to gastric ulcers in this series (Table VIII) was low compared with that in unselected peptic ulcer cases, without haemorrhage or perforation, treated in London (Avery Jones and Pollak, 1945). The ratio was higher in these authors'

cases than it would be for inpatients alone, because of the inclusion of outpatients. The latter contain greater numbers of the less frequently complicated, and hence admitted, patients with duodenal ulcer (Nicol, 1941; Jamieson, Smith, and Scott, 1949; Watkinson, 1960; Billington, 1960b). Cases in the present series, however, were comparable with those in a study of unselected British inpatients with peptic ulcer (Daintree Johnson, 1962). Compared with those patients who had neither haemorrhage nor perforation, the present series had a low duodenal to gastric ulcer ratio. This ratio in males was the same as that in the English series, but in females it was only 0.6:1. Statistical analysis confirms that the ratio in males was the same in the two series, while it was significantly different in females ($\chi^2 = 4.8$; $P < 5\%$).

Male predominance in numbers over females was considerably less than in these English series (Table IX), though for duodenal ulcers it was more comparable. The male to female ratio for gastric ulcers was very low compared with that applying in England and in Australia before 1945. The ratio of 0.7:1, however, is remarkably close to that of 0.8:1 found by Billington (1965a) for inpatients with gastric ulcer admitted to four Sydney teaching hospitals between 1959 and 1961. These patients, like those in his earlier Sydney study, included many with complications of ulcer, but ratios of 0.6 to

TABLE VIII
RATIO OF DUODENAL TO GASTRIC ULCERS IN PRESENT AND OTHER SERIES

Series	Place	No. of Relevant Cases	Ratio					
			Duodenal: Gastric Ulcer			Duodenal to Gastric and Combined Ulcer		
			M + F	M	F	M + F	M	F
Avery Jones and Pollak (1945)	London	952	2.5:1	3.1:1	1.2:1	—	—	—
Daintree Johnson (1962)	England and Wales	7,310	—	—	—	1.4:1	1.7:1	0.9:1
Present	Newcastle, N.S.W.	288	1.1:1	1.8:1	0.7:1	1.08:1	1.7:1	0.6:1

TABLE IX
RATIO OF MALES TO FEMALES AND PEAK AGE INCIDENCE IN PRESENT AND OTHER SERIES

Series	Place	Period	No. of Cases	Ratio of Males to Females			Peak Age Incidence in Years					
				All Sites	Duodenal Ulcer	Gastric Ulcer	All Sites		Duodenal Ulcer		Gastric Ulcer	
							M	F	M	F	M	F
Avery Jones and Pollak (1945)	London	1943-44	952	4.6:1	6.5:1	2.4:1	40-49	40-49	30-39	30-39	40-49	40-49
Daintree Johnson (1962)	England and Wales	1956-57	7,480	2.5:1	3.2:1	1.7:1 ¹	45-54	45-54	45-54	45-54	45-54 ¹	55-64 ¹
Billington (1960a)	Sydney, N.S.W.	1930-39	427	—	—	2.5:1	—	—	—	—	45-54	45-64
Billington (1960a)	Sydney, N.S.W.	1945-55	1,388	—	—	1.3:1	—	—	—	—	55-64	35-44
Douglas and Johnston (1961)	Townsville, Qld.	1956-59	77	—	—	1.2:1	—	—	—	—	40-60	40-60
Billington (1965a)	Sydney, N.S.W.	1959-61	963	—	—	0.8:1	—	—	—	—	55-64	45-54
Present	Newcastle, N.S.W.	1960-66	295	1.2:1	1.9:1	0.7:1 ²	40-59	40-49	40-49	40-49	50-59	40-49

¹Including combined gastric and duodenal ulcers.

²Inclusion of combined gastric and duodenal ulcers does not alter this ratio.

0.8:1 were also found for city and country outpatients in New South Wales in 1962 and 1963 (Billington, 1964a, 1965a, 1965b). These were, for the most part, uncomplicated cases, whereas in the series of Daintree Johnson (1962) and of Avery Jones and Pollak (1945), the male to female ratio for gastric ulcer was the same whether complications were present or not. There was a statistically highly significant difference when the Newcastle ratio was compared with that prevailing in Sydney before 1939 ($\chi^2 = 40.1$, $P < 0.05\%$), but none compared with that about 1960.

The diminished ratio of duodenal to gastric ulcers in this series, due to an excess of gastric ulcers in females, supports Billington's findings (1960a, 1963, 1964a, 1965a, 1965b). Since the data for males, and for duodenal ulcers, were the same as in the English series of comparable cases, the striking difference for females with gastric ulcers is a valid observation, independent of the geographical variations for the incidence of peptic ulcer reported by many authors (Nicol, 1941; Avery Jones and Pollak, 1945; Doll, 1952; Avery Jones, 1957; Eusterman, 1959; Watkinson, 1960; Shay and Sun, 1963).

The age distributions (Table IX) for cases overall, and for duodenal ulcer cases, were generally similar to those for cases outside the regions affected by the change in gastric ulcer in Australia. For male gastric ulcer patients, the age distribution in our series resembled that in recent series elsewhere in New South Wales and Queensland. The excess of gastric ulcers in females occurred in the pre- and post-menopausal age groups, being spread over three decades (Table II). Its peak was a decade earlier than in the large British series (Daintree Johnson, 1962), but it corresponded with that in the most recent Sydney study (Billington, 1965a).

Billington (1960a) predicted that the excess of gastric ulcers in younger women would become greater, that the decade chiefly affected would advance with time, and that the number of decades involved would increase. Examination of Tables II and IX shows that these predictions are all coming true. The male to female ratio for gastric ulcer has been falling progressively in New South Wales and Queensland since 1945. It may be argued that such a comparison of data from three cities spread over two states is invalid. However, Billington (1965a) has demonstrated this trend in data drawn from the same four hospitals. Furthermore, Hennessy (1969) has noted a similar, statistically highly significant trend, in a 21-year series of cases of perforated peptic ulcer from the Royal Newcastle Hospital.

In general, the belief of Shay and Sun (1963) that 'there is no conclusive evidence that aspirin *per se*

is a cause for peptic ulcer' has prevailed. Nicol (1941) postulated that duodenal ulcers were the result of intrinsic factors, usually inherited, while gastric ulcers were due to extrinsic factors acting locally to injure the gastric mucosa. Billington (1960a), in seeking to explain his discovery of an increase in gastric ulcers in premenopausal women, deduced statistically that it was due to an exogenous factor whose action was to cause ulcers rather than to prevent their healing. He considered (1965a) that this was related to some newly acquired aspect of the women's behaviour. Douglas and Johnston (1961) suggested that this was the taking of aspirin, and presented the first evidence that this could cause chronic gastric ulceration. Furthermore, peptic ulceration is often associated with analgesic nephropathy (Dawborn, Fairley, Kincaid-Smith, and King, 1966), and a perusal of these authors' published data shows that the stomach is commonly affected.

The consumption of aspirin-containing compounds in the present series appeared great, but a control group free from ulcer was not available. However, compared with a series of unselected medical and surgical in- and outpatients in six Sydney hospitals (Lavan, Benson, Gatenby, and Posen, 1966), many more of our patients took aspirin (Table X). Although regularly taken aspirin was analysed to different quantities in these two studies, and in one, documenting the analgesic intake of unselected country town dwellers in Queensland (Purnell and Burry, 1967), it is probable that between three and five times as many of the ulcer patients as the unselected ones took large amounts. Females outnumbered males in all three series. In the present one, females taking two or more doses per week exceeded males (Table III) to a statistically highly significant degree ($\chi^2 = 13.9$, $P < 0.05\%$).

The greatest incidence of aspirin taking was in patients with gastric ulcers, 82% of whom took some aspirin, the incidence in females being 92% (Table X). These figures are remarkably close to those in the series of Douglas and Johnston (1961), who calculated that the intake of their patients was between three and seven times that of the general population in Townsville. The proportion of patients in Newcastle taking large doses was also the same as theirs. In females with gastric ulcers, the excess of those who took large amounts of aspirin over those who took little (Table V), compared with patients with duodenal ulcers, was highly significant statistically ($\chi^2 = 9.1$, $P < 0.5\%$). By contrast, in males there was no difference. Fewer duodenal ulcer patients took aspirin-containing preparations but they took more than the unselected Sydney hospital cases (Lavan *et al.*, 1966). However, Tables V and

TABLE X
ASPIRIN HABIT IN PRESENT AND OTHER SERIES

Series	Type of Case	No. of Cases	Amount (%)										Form	
			Any		>Two Doses/Week		>One Dose/Day		>Two Doses/Day		>Three Doses/Day		Percentage of Aspirin Takers Taking APC	
			M	F	M	F	M	F	M	F	M	F		
Purnell and Burry (1967) (Queensland country town)	Unselected general population	4,100	—	—	—	—	—	—	—	—	—	—	—	74
		1,004	—	—	—	—	11	15	—	—	—	—	—	—
							(13)							
Lavan, Benson, Gatenby, and Posen (1966) (Sydney)	Unselected in- and outpatients	514	—	—	—	—	13	26	—	—	—	—	—	86
							(19)					(11)		
Douglas and Johnston (1961) (Townsville)	Gastric ulcer	77	66	94	—	—	—	—	—	—	—	—	—	81
			(80)		(72)				(61)					
Present (Newcastle)	Gastric ulcer	134	70	92	56	85	—	—	48	75	—	—	—	82
			(82)		(73)				(66)					
	Duodenal ulcer	150	56	66	43	56	—	—	39	54	—	—	—	75
			(59)		(48)				(44)					
	All sites	295	62	82	49	74	—	—	44	67	—	—	—	80
			(71)		(60)				(55)					

¹Percentages are of the cases with information available. Combined sexes are shown in parentheses.

X show that there was not the same difference between those taking little aspirin and those taking large quantities nor between the sexes as was the case in patients with gastric ulcers.

The available data do not support the argument that the pain of a previously existing ulcer led to the patient taking aspirin. This would not account for the age difference between those taking excess aspirin and those taking little, nor its limitation to women with gastric ulcers. To explain the significant difference in the aspirin intakes of patients with gastric and duodenal ulcer, a profound difference in the nature of the pain from ulcers at the two sites would have to be postulated. Clinical experience does not support this. The correlation, in the cases with adequate data, between the duration of aspirin ingestion and the length of ulcer history, which occurred only for females with gastric ulcers (Table VI), suggested a causal relationship. In most cases it could not be determined which preceded the other, the aspirin or the ulcer, but in three of the four in which this was possible, aspirin came first. The reason for ingestion was recorded in more than half of the cases taking two or more doses a day (Table VII) but in these ulcer pain was an insignificant (3%) indication, and remained so even if those whose backache was probably the result of posteriorly penetrating gastric ulcer (3%) were included. For 90% of cases, the indication was tension headaches. Calculation of the confidence limits shows that this is highly likely to be the true percentage (Footnote, Table VII). In their gastric ulcer patients, Douglas and Johnston (1961) likewise

found that in only 4% of the cases with available information was ulcer pain the indication. In 66% it was headache. Sixteen per cent took an aspirin compound as a stimulant, an indication surprisingly absent from the present series. Since there is no reason to suppose that the patients took aspirin for ulcer pain, when they stated that they took it for headache, the available data strongly suggest that the ulcers were the result, rather than the cause, of the aspirin ingestion.

The evidence suggests that the late peak in the female gastric ulcer patients resulted from those unknown factors that usually cause ulcers, while the early one was due to aspirin. The age distribution (Tables IV and V) of the large proportion (85%) of female gastric ulcer patients taking excessive quantities of aspirin corresponded with those decades, except the eighth (Table II), in which females with gastric ulcers outnumbered males, and resembled that of the females in Billington's latest study for Sydney (Table IX). On the other hand, the few (15%) who took little aspirin were older, as in areas not affected by the gastric ulcer change (Billington, 1960a, 1963, 1965b). This age difference between the takers of excess aspirin and those who took little was similar to that found by Duggan (1967, 1968) for perforated and bleeding gastric but not duodenal ulcers. The age distribution curve of female gastric ulcer patient overall was reminiscent of the bimodal curve in Billington's series.

The excess of gastric ulcers in younger women was associated with the taking, not of aspirin preparations generally, but of those which contain

phenacetin and caffeine (Table X). A remarkably constant four-fifths of the aspirin takers in different series use APC. Douglas and Johnston (1961) found that the proportion of the different preparations taken reflected the amounts sold in their district. The corresponding information for Newcastle was unobtainable.

No patient in the present series was known to take APC for organic disease (Table VII). Only one had a complaint for which analgesics might reasonably be taken, and he took aspirin alone. The symptoms for which the remainder took them were those of stress, mainly tension headaches. Similarly the patients of Lavan *et al* (1966) took them for reasons 'in no way related to pain or illness'. Like Douglas and Johnston (1961), we considered, even though none of our patients mentioned taking them as stimulants, that continued consumption of these drugs was due to the readily occurring habituation to caffeine (Ritchie, 1965) and sometimes possibly to phenacetin (Woodbury, 1965).

Aspirin appears to be the noxious agent (Menguy, 1966; Croft and Wood, 1967). We are not aware of any evidence incriminating phenacetin. Although caffeine stimulates gastric secretion, there is no evidence that it causes ulcer (Segal, 1960). However, aspirin, when taken alone, was a numerically less important cause of ulcer in our series than APC. This, presumably, was because aspirin is not addicting (Woodbury, 1965), and therefore is not likely to be taken in such large quantities nor by so many patients. Patients taking APC consumed larger quantities than those taking aspirin, eight to 12 doses per day being common, and the occurrence of acute gastric erosions and bleeding at least is dependent upon the amount administered (Pierson, Holt, Watson, and Keating, 1961; Croft and Wood, 1967), and that of chronic atrophic gastritis may be also (Edwards and Coghill, 1966).

It is hard to reconcile the strong association of aspirin taking with gastric ulcers in females and the apparent lack of correlation in males. Susceptibility to salicylate-induced gastric haemorrhage varies between individuals in humans (Pierson *et al*, 1961) and in dogs (Davenport, 1967). However, this is not sex-linked in the former, although the amount of blood lost, in distinction to the occurrence of bleeding, is greatest in women aged 19 to 30. More women than men in the general population take aspirin-containing preparations, and they take greater quantities (Purnell and Burry, 1967). The comparatively greater exposure to aspirin which results may well account for the sex difference in ulcer incidence.

The consumption of large amounts of aspirin-containing preparations dates from the last war, and appears to be increasing, especially in women

(Purnell and Burry, 1967). The excess of gastric ulcers in women began about 1943 (Billington, 1960b), has increased progressively since, and has involved, with the passage of time, an increasing number of cohorts of women (Billington, 1965a).

The question arises why the excess of gastric ulcers in women is confined to New South Wales and Queensland. An inter-state difference in the aspirin-taking pattern would account for the variation but little information could be obtained. In New South Wales in 1964-65, medical practitioners prescribed for pensioners, under the National Health Service, considerably greater quantities per head of APC than their Victorian colleagues, who tended to prescribe aspirin instead, and this in smaller quantities (Redshaw, 1966). It is perhaps significant that the headquarters of the two principal manufacturers of APC powders are in Sydney, while that of the best known proprietary aspirin maker is in Melbourne. However, further studies of the aspirin-taking habits of the populations of the different states of the Commonwealth will be necessary in order to explore the significance of this. There is therefore strong evidence in favour of the hypothesis that aspirin, in the guise of the APC powder, is the cause of the Australian gastric ulcer change.

SUMMARY

Two hundred and ninety-five patients admitted to the Royal Newcastle Hospital in the period 1960 to 1966 for treatment of uncomplicated, proven, peptic ulcer were studied. There was an excess of gastric ulcers in women aged 30 to 59 years. There was a statistically highly significant association with the consumption of large quantities of aspirin-containing preparations, usually aspirin-phenacetin-caffeine (APC) powders taken for tension headaches. There was no such correlation in the case of duodenal ulcers in either sex, nor of gastric ulcers in males. The data suggested that the ulceration was the result, rather than the cause, of the aspirin ingestion. The evidence of this series strengthens the hypothesis that the cause of the Australian gastric ulcer change is the aspirin in the APC powder.

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REFERENCES

- Billington, B. P. (1960a). Gastric ulcer: age, sex, and a curious retrogression. *Aust. Ann. Med.*, 9, 111-121.
- (1960b). The Australian gastric ulcer change: further observations. *Med. J. Aust.*, 2, 19-20.
- (1963). The Australian gastric ulcer change: interstate variations. *Aust. Ann. Med.*, 12, 153-159.
- (1964a). Gastric ulcer in N.S.W.: a radiological investigation. *J. Coll. Radiol. Aust.*, 8, 131-133.
- (1964b). Death and gastric ulcer. *Med. J. Aust.*, 2, 485-492.
- (1965a). Observations from New South Wales on the changing incidence of gastric ulcer in Australia. *Gut*, 6, 121-133.
- (1965b). Eighty miles of first class sheep and wheat country: a further report on the Australian gastric ulcer change. *Lancet*, 2, 378-379.
- Croft, D. N., and Wood, P. H. N. (1967). Gastric mucosa and susceptibility to occult gastrointestinal bleeding caused by aspirin. *Brit. med. J.*, 1, 137-141.
- Davenport, H. W. (1967). Salicylate damage to the gastric mucosal barrier. *New Engl. J. Med.*, 276, 1307-1312.
- Dawborn, J. K., Fairly, K. F., Kincaid-Smith, P., and King, W. E. (1966). The Association of peptic ulceration, chronic renal disease, and analgesic abuse. *Quart. J. Med.*, n.s., 35, 69-83.
- Doll, R. (1952). Peptic ulcer. Epidemiology. In *Modern Trends in Gastroenterology*, edited by F. Avery Jones, pp. 361-379. Butterworth, London.
- Douglas, R. A., and Johnston, E. D. (1961). Aspirin and chronic gastric ulcer. *Med. J. Aust.*, 2, 893-897.
- Duggan, J. M. (1965). The relationship between perforated peptic ulcer and aspirin ingestion. *Med. J. Aust.*, 2, 659-662.
- (1967). The association between aspirin ingestion and perforated peptic ulcer. *Aust. Ann. Med.*, 16, 263.
- (1968). Gastrointestinal haemorrhage, gastric ulcer and aspirin abuse. *Ibid.*, 17, 188.
- Edwards, F. C., and Coghill, N. F. (1966). Aetiological factors in chronic atrophic gastritis. *Brit. med. J.*, 2, 1409-1415.
- Eusterman, G. B. (1959). Symposium on Epidemiologic and clinical features of peptic ulcer disease throughout the world. In *Proceedings of the (1st) World Congress of Gastroenterology, 1958*, vol. 1, pp. 1-87. Williams and Wilkins, Baltimore.
- Hennessy, E. J. (1969). Perforated peptic ulcer. Mortality and morbidity in 603 cases. *Aust. N.Z. J. Surg.*, 38, 243-252.
- Jamieson, R. A., Smith, W. E., and Scott, L. D. W. (1949). Peptic ulcer in Glasgow. A hospital survey. *Brit. med. J.*, 1, 298-300.
- Johnson, H. D. (1962). Peptic ulcer in hospital. An analysis of a 10% in-patient enquiry throughout England and Wales. *Gut*, 3, 106-117.
- Jones, F. A. (1957). Clinical and social problems of peptic ulcer. *Brit. med. J.*, 1, 719-723.
- , and Pollak, H. (1945). Civilian dyspepsia. *Ibid.*, 1, 797-800.
- Lavan, J. N., Benson, W. J., Gatenby, A. H., and Posen, S. (1966). The consumption of analgesics by Australian hospital patients. *Med. J. Aust.*, 2, 694-695.
- Menguy, R. (1966). Gastric mucosal injury by aspirin. *Gastroenterology*, 51, 430-432.
- Nicol, B. M. (1941). The geographical distribution of gastric and duodenal ulcers in the British Isles, with notes on the aetiology of peptic ulcer. *Brit. med. J.*, 2, 780-782.
- Pierson, R. N., Jr., Holt, P. R., Watson, R. M., and Keating, R. P. (1961). Aspirin and gastrointestinal bleeding. Chromate⁵¹ blood loss studies. *Amer. J. Med.*, 31, 259-265.
- Purnell, J., and Burry, A. F. (1967). Analgesic consumption in a country town. *Med. J. Aust.*, 2, 389-391.
- Redshaw, G. M. (1966). Personal communication.
- Ritchie, J. M. (1965). Central nervous system stimulants. II. The Xanthines. In *The Pharmacological Basis of Therapeutics*, 3rd ed., edited by L. S. Goodman and A. Gilman, pp. 354-366. Macmillan, New York.
- Segal, H. L. (1960). Ulcerogenic drugs and technics: experimental and clinical. *Amer. J. Med.*, 29, 780-792.
- Shay, H., and Sun, D. C. H. (1963). Etiology and pathology of gastric and duodenal ulcer, In *Gastroenterology*, 2nd ed., vol. 1, edited by H. L. Bockus, pp. 420-465. Saunders, Philadelphia and London.
- Susser, M. (1967). Causes of peptic ulcer. A selective epidemiologic review. *J. chron. Dis.*, 20, 435-456.
- , and Stein, Z. (1962). Civilisation and peptic ulcer. *Lancet*, 1, 115-119.
- Watkinson, G. (1960). The incidence of chronic peptic ulcer found at necropsy: a study of 20,000 examinations performed in Leeds in 1930-49 and in England and Scotland in 1956. *Gut*, 1, 14-30.
- Woodbury, D. M. (1965). Analgesics and antipyretics. In *The Pharmacological Basis of Therapeutics*, edited by L. S. Goodman, and A. Gilman, pp. 312-344. Macmillan, New York and London.