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PEPTIC ULCERATION

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Guest Editor

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Foreword

Peptic ulcer disease which afflicts 10 millions in the United States and, at some time in their lives, 20 per cent of all adults in the U.K. and Northern Europe, presents a social and economic problem of gargantuan proportions and a continuing challenge to researchers and practitioners in gastro-enterology. We have to confess a disquieting ignorance of the aetiology of the disease and, up to now, a largely empirical approach to treatment. At last, however, the tide may be turning and a much more exciting prospect lies before us than ever before in the century since peptic ulcer received clinical recognition.

Interestingly, as so often in the history of medicine, the advance towards understanding of the normal state as well as the pathophysiology of the upper alimentary tract has in large measure been born out of the urgency of enquiry into syndromes of intractable peptic ulceration so gross and lethal as those associated with peptide-secreting tumours. The resulting revelation of the existence of a second endocrine system mostly located between the gastric incisura and the ligament of Treitz, includes such an elaboration of biologically active polypeptides with intimate relationship to upper alimentary secretory and motility function and to neuro-humoral mechanisms, that a vast array of questions and hypotheses has now appeared, the hot pursuit of which is afoot.

In the chapters which follow, the new landscape of enquiry is laid out. Its contours are already hinted by the catchwords of the new colloquial which include the incompetent pylorus, the lower oesophageal sphincter, reflux gastritis, parietal-cell vagotomy, Bulbogastrone, cyclic AMP and healing rate factor among the many others which the readers will encounter. It is particularly encouraging that the advance in knowledge pointing the way to the roots of aetiology are now closely followed by changes in both conservative and surgical management devices but in a pasture of controlled trial and long-term reappraisal on which sacred cows of ulcer therapeutics graze less easily.

For the purpose of this volume I have, therefore, chosen such areas relating to ulcer disease as have enjoyed the advancing frontier of the past few years or which, remaining controversial, benefit by incisive and critical review. Each writer has previously made significant and authoritative contributions to his subjects and I believe this exposition by basic scientists, physicians and surgeons represents just the conjunctive approach which offers the possibility that the problem of peptic ulcer may be resolved in the next decade.

W. SIRCUS

1

Changing Patterns in the Epidemiology of Peptic Ulcer

M. J. S. LANGMAN

Environmental factors are of prime importance in the aetiology of peptic ulcer, but they are poorly understood. Clues to these aetiological factors may be obtained if greater attention is paid to the changing and variable patterns of ulcer incidence.

GENERAL PROBLEMS OF ASSESSMENT AND INTERPRETATION

A number of difficulties interfere with the assessment of the frequency and predisposing causes of peptic ulcer.

Many analyses have not distinguished between gastric and duodenal ulcer despite the fact that there is overwhelming clinical and other evidence that these are separate diseases. A second problem has arisen in finding satisfactory standard bases upon which data obtained in various areas, or even in the same area and at different times, can be reliably compared.

The clinical diagnosis of gastric or duodenal ulcer can be based upon radiological, endoscopic or operative criteria. Radiological assessment of gastric ulcer is probably fairly reliable (though no measurements of observer variation seem to have been made), but is of limited value in duodenal ulcer. In particular the detection of active ulceration in a deformed cap can be little more than guesswork. Few ulcers are likely to be undetected at operation, but most patients do not come to surgery, and endoscopy is not a technique which can be applied to all patients.

Ulcer mortality

Deaths due to gastric and duodenal ulcer are few relative to total disease frequency, thus, even when complications of haematemesis or melaena occur, mortality rates are seldom greater than 8 per cent of the total.

Ulcer mortality both from gastric and duodenal ulcer varies greatly with socio-economic status, and this trend has, if anything, become more obvious recently (Table 1a). These differences may result partly from variations in the quality of medical care obtained (or sought) by individuals of different social classes. They also probably reflect general variations in ulcer incidence for ulcer frequency statistics (Weir, 1960) and population survey results show the same trend (Table 1b).

Table 1a. *Social class and mortality from gastric and duodenal ulcer in England and Wales*

	Social class[a]				
	I	II	III	IV	V
Gastric ulcer					
1949–51	56	81	97	99	144
1959–63	46	58	94	106	199
Duodenal ulcer					
1949–51	105	78	106	82	126
1959–63	70	84	113	102	136

[a]Figures are standardised mortality ratios, the observed divided by the expected rates multiplied by 100.
(Registrar General 1958, 1971)

Table 1b. *Observed and expected frequency of gastric ulcer in south-west Scotland, 1957 to 1959*

	I	II	III	IV	V
Gastric ulcer					
observed	0	11	12	13	28
expected	2	11	30	14	7
Duodenal ulcer					
observed	13	41	125	136	158
expected	14	80	218	108	52

(Litton and Murdoch, 1963)

Ulcer morbidity

HOSPITAL STATISTICS. Patients are admitted to hospital with simple uncomplicated ulcers relatively infrequently, except for operation, and the criteria for elective surgical or, more uncommonly, medical treatment probably differ so much from one time or place to another that useful comparisons are seldom possible. The 10 per cent sample obtained in the Hospital Inpatient Enquiry (HIPE) in the United Kingdom is a valuable index of all varieties of disease resulting in admission and can supply useful longitudinal data showing temporal trends in admission rates. These figures may not however be directly comparable with inpatient statistics obtained elsewhere in the world.

Postmortem surveys conducted on patients dying suddenly or in hospital from all causes can also supply information about ulcer frequency, provided that the pathologist is prepared to pay special attention to the stomach and duodenum irrespective of the actual cause of death (Watkinson, 1960). There is no certainty that such surveys will identify the scars of all healed ulcers as well as active craters, but they can supply useful indices of the prevalence of active ulcer at different ages and minimal estimates of previous ulcer frequency (provided it is remembered that patients dying suddenly or in hospital are very far from being a random sample of the population).

POPULATION SURVEYS. Deliberate attempts to determine ulcer frequency by population surveys probably produce the most reliable estimates of ulcer incidence and prevalence. However the work involved in such surveys is considerable and consequently they are likely to be conducted where there is prior evidence that ulcer presents an especially frequent or unusual problem and seldom, if ever, where ulcer is uncommon or apparently uninteresting in its clinical characteristics.

Table 2. *Prevalence of ulcer and dyspepsia observed during surveys conducted in different areas*

	Percentage frequency of:		
	Diagnosed ulcer	Likely ulcer	All dyspepsia and ulcer
Australia			
Melbourne, 1968			
(Gillies and Skyring, 1969)	7·2	—	—
India			
Assam, 1960			
(Malhotra, Majumdar and Bardoloi, 1966)	—	15·1	28·4
United Kingdom			
London, 1946	5·2	1·3	31·0
Aberdeen, 1961	9·9	5·2	35·2
(Doll and Jones, 1951; Weir and Backett, 1968)			
U.S.A.			
1965 to 1967			
(Mendeloff and Dunn, 1971)	—	—	25·4

POPULATION PREVALENCE. Table 2 gives the results obtained in five surveys conducted at different times and places in the world. The measurements are incomplete as survey methods varied and are also, therefore, not necessarily directly comparable with each other. The figures indicate however that ulcer can be an extremely common problem. Such figures, as already stated, give an unreal appearance of uniformity. Thus there is strong reason to believe that duodenal ulcer is now more common in Scotland than in England, in Southern than in Northern Nigeria and in Southern than in Northern India (at least in part). By contrast gastric ulcer is relatively uncommon in much of India, Africa, and the U.S.A., is more frequent in the United Kingdom and most of Western Europe, and seems to be a particular problem in Australia in young women.

Chronological trends

During the last hundred years there has been a dramatic change in the pattern of ulcer frequency. In the nineteenth century duodenal ulcer seems to have been a rare disease whereas gastric ulcer was extremely common, especially in women. However at the turn of the century duodenal ulcer seemed to become a well defined if still relatively infrequent problem. Thereafter duodenal ulcer prevalence increased steadily so that in almost all areas it became more common than gastric ulcer with a probable peak, at least in

Table 3. *Proportions of men and women dying with gastric ulcers*

Age	Perforated ulcer[a]	Ulcer deaths[b]		
	1867	1912	1918	1924
Less than 35 years				
Men	18	182	167	151
Women	96	338	214	109
M:F ratio	0·2:1	0·5:1	0·8:1	1·4:1
35 years or more				
Men	42	691	900	1219
Women	43	635	713	620
M:F ratio	1·0:1	1·1:1	1·3:1	2·0:1

[a]Brinton (1867)
[b]Registrar General Statistical Reviews (1912, 1918 and 1924)

the United Kingdom, in the late 1950s. These trends have been evident in mortality rates (Table 3) as well as in morbidity figures (Table 4) obtained generally in different parts of Europe. Estimates obtained from the HIPE strongly suggest that changes are continuing. Table 5 shows those which have occurred in admission rates between 1956 and 1967 in England and Wales. Gastric ulcer admissions of all clinical types have fallen by rather

Table 4. *Male to female ratio of peptic ulcer in hospital patients in Copenhagen*

	No. of patients	Ratio (M:F)
1901–05	471	0·3:1
1911–15	964	0·9:1
1921–25	1493	1·8:1
1931–35	2559	3·1:1

(Hansen, 1937)

over a quarter whilst, by contrast, duodenal ulcer admissions of all clinical types combined have fallen by less than 10 per cent. Such changes may reflect real changes in ulcer frequency, or else may occur secondary to alterations in medical treatment, such as the introduction of liquorice derivatives. A clue to the likely possibility can be obtained by analysing ulcer perforation figures, for perforation is often the first clinical manifestation of ulcer. Furthermore

Table 5. *Estimated annual admission rates with gastric and duodenal ulcer in England and Wales, 1956 to 1967*

Period	Gastric ulcer		Duodenal ulcer	
	All cases	perforating only	All cases	perforating only
1956–58	28 380	2682	41 179	6272
1965–67	20 886	1846	37 587	5037
Per cent change	−26·4	−31·2	−8·7	−19·7

(HIPE, unpublished data)

perforation is a mandatory cause of admission and is therefore closer to being a true measure of ulcer frequency in the community than elective admissions. The fall of almost a third in the gastric ulcer perforation figures in the period under review suggests that ulcer frequency has decreased. The duodenal ulcer perforation rate has also fallen by almost a fifth, despite a more modest reduction in total admissions. Further evidence that the falling perforation rate is an indication of a real change in ulcer frequency comes from data obtained in York (Table 6), where total annual diagnoses of duodenal ulcer fell considerably between 1952 and 1963 (Pulvertaft, 1968).

Table 6. *Mean annual incidence of duodenal ulcer per 1000 population aged 35 to 54 in York, England*

	Men	Women
1952–54	3·1	1·0
1955–57	2·3	1·0
1958–60	1·8	1·0
1961–63	1·7	0·6

From data of Pulvertaft (1968)

Changes in the pattern of ulcer frequency have also been recorded in other areas. Thus in India comparison of the clinical characteristics of operative ulcer patients in the 1940s and 1960s has shown a fall in the male to female ratio and also a fall in the overall proportions with pyloric stenosis, though haemorrhage and perforation still seem to be relatively uncommon, at least in some areas (Table 7). In examining data obtained in such places, where the overall quantity of medical care offered is relatively small, it is difficult to know whether the variations described are due more to administrative and social changes in the acceptance and delivery of care than to any other factor.

Table 7. *Comparison of operative cases of gastric and duodenal ulcer in Madras*

		1942–45	1962–66
Duodenal ulcer	Total number	1047	1034
	Male:female ratio	26·9:1	13·3:1
	Clinical pyloric stenosis	51·3%	30·7%
Gastric ulcer	Total number	66	68
	Male:female ratio	22·0:1	9·7:1

Madanagopalan, Subramaniam and Krishnan, 1968)

PREDISPOSING FACTORS

Genetic influences

There has been ample confirmation of the original findings of associations between the ABO blood groups and secretion status and gastric and duodenal ulcer (McConnell, 1966). Further investigations have indicated that the basic association between blood group O and ulcer is strongest in those with

complications, especially of haemorrhage (Langman and Doll, 1965). These relationships will be discussed in more detail in a future issue. Even though genetic effects on ulcer frequency or behaviour are clearly demonstrable, they can account for only a very small proportion of total ulcer incidence.

Smoking

Smoking is known to diminish the healing of gastric ulcers, and there is suggestive evidence that it also predisposes to ulcer (Doll, Jones and Pygott, 1958; Monson, 1970). It is difficult to distinguish when questioning patients between those who smoke and develop ulcers and vice versa. However the data obtained in U.S. physicians indicate that smoking is followed by ulceration. The underlying mechanism is unclear, but as smoking can reduce gastric secretory responses (Wilkinson and Johnston, 1971) then an increased liability to ulcer must be explained by another mechanism.

Alcohol

Though ulcer is relatively common in cirrhotics there is no sound evidence that mild to moderate drinking predisposes to ulcer.

Diet

Though environmental influences are of primary importance in affecting ulcer incidence, and dietary factors are of special interest, disappointingly little progress has been made in elucidating them.

Broad epidemiological comparisons have been used to suggest that a high fibre and protein content and a low refined carbohydrate content is associated with a low ulcer frequency (Cleave, 1962) and by contrast a low protein and high carbohydrate diet (irrespective of fibre content) have been put forward as treatments which are less likely to stimulate gastric acid output (Saint Hilaire et al, 1960; Dekkers, 1965).

The hypothetical advantage of a high fibre content has been claimed to be due to its stimulant effect on salivary secretion during chewing. Though clear proof is lacking, examination of ulcer frequency in India in particular suggests that a bland sloppy diet (not unlike traditional ulcer diets) is customarily taken in some areas with a high ulcer frequency and a rough diet with a high fibre content (and often many spices) where ulcer is uncommon (Malhotra, 1964). One individual item of diet which can cause a severe antral gastritis is a variety of Japanese pickle (MacDonald, Anderson and Hashimoto, 1967) and may be a clue to one possible aetiological factor in gastric ulcer.

Drugs

ASPIRIN. Salicylate preparations are commonly thought to exacerbate dyspepsia and evidence has frequently been adduced to suggest that aspirin will predispose to ulcer bleeding. Though at first sight attractive these epidemiological studies leave more room for doubt than might be thought (Langman, 1970), and it may be that aspirin is less important as a cause of haematemesis and melaena than has initially been claimed. It has been estimated that 2000 tons of aspirin are taken annually in the United Kingdom

but it has yet to be proved that aspirin causes chronic ulceration. The same may not however be true elsewhere, and in Australia a tendency for gastric ulcer to develop in young and middle aged women has been linked to habitual analgesic consumption (Gillies and Skyring, 1969). Table 8 shows the recent change noted in the sex ratio of gastric ulcer patients in Sydney which has been attributed to analgesic intake by women. It is as yet uncertain that aspirin itself is the offending drug, for the preparations abused, often taken as non-specific pick-me-ups, usually contain several pharmacological compounds.

Table 8. *Male to female ratio of gastric ulcer patients admitted to hospitals in Sydney, New South Wales*

	Number of patients	Male:female ratio
1930–39	427	2·5:1
1946–55	1388	1·3:1
1959–61	963	0·8:1

(Billington, 1963 and 1965)

OTHERS. Though steroid and other anti-rheumatic preparations are commonly thought to exacerbate peptic ulceration and possibly to cause it to develop, they can be responsible for no more than a very small proportion of total ulcer incidence.

REFERENCES

Billington, B. P. (1963) The Australian gastric ulcer change: interstate variations. *Australasian Annals of Medicine*, **12**, 153–159.

Billington, B. P. (1965) Observations from New South Wales on the changing incidence of gastric ulcer in Australia. *Gut*, **6**, 121–133.

Brinton, W. (1867) *On the Pathology Symptoms and Treatment of Ulcer of the Stomach.* London: Churchill.

Cleave, T. L. (1962) *Peptic Ulcer.* Bristol: John Wright.

Dekkers, H. J. N. (1965) Carbohydrate diet for duodenal ulcer, some remarks about the mechanism of pain in duodenal ulcer. *Gastroenterologia*, **86**, 496–504.

Doll, R. & Jones, F. A. (1951) Occupational factors in the aetiology of gastric and duodenal ulcers. *Special Report Series of the Medical Research Council*, No. **276.**

Doll, R., Jones, F. A. & Pygott, F. (1958) Effect of smoking on the production and maintenance of gastric and duodenal ulcers. *Lancet*, **i**, 657–662.

Gillies, M. A. & Skyring, A. P. (1969) Gastric and duodenal ulcer. The association between aspirin ingestion, smoking and family history of ulcer. *Medical Journal of Australia*, **2**, 280–285.

Hansen, J. L. (1937) Investigations on frequency of peptic ulcer with special regard to distribution between 2 sexes. *Ugeskrift für Laeger*, **99**, 1145–1151.

Langman, M. J. S. & Doll, R. (1965) ABO blood groups and secretion status in relation to clinical characteristics of peptic ulcer. *Gut*, **6**, 270–273.

Langman, M. J. S. (1970) Epidemiological evidence for the association of aspirin and acute gastrointestinal bleeding. *Gut*, **11**, 627–634.

Litton, A. & Murdoch, W. E. (1963) Peptic ulcer in south-west Scotland. *Gut*, **4**, 360–366.

MacDonald, W. C., Anderson, F. H. & Hashimoto, S. (1967) Histological effect of certain pickles on the human gastric mucosa; a preliminary report. *Canadian Medical Association Journal*, **96**, 1521–1525.

McConnell, R. B. (1966) *The Genetics of Gastrointestinal Disorders*. London: Oxford University Press.

Madanagopalan, N., Subramaniam, R. & Kirshnan, M. N. (1968) Comparative study of operated cases of peptic ulcer in Madras in the 1940s and 1960s. *Gut*, **9**, 69–74.

Malhotra, S. L. (1964) Peptic ulcer in India and its aetiology. *Gut*, **5**, 412–416.

Malhotra, S. L., Majumdar, C. T. & Bardoloi, P. C. (1964) Peptic ulcer in Assam. *Gut*, **5**, 355–358.

Mendeloff, A. I. & Dunn, J. P. (1971) *Digestive Diseases. Vital and Health Statistics Monographs*. American Public Health Association. Cambridge, Mass: Harvard University Press.

Monson, R. R. (1970) Cigarette smoking and body form in peptic ulcer. *Gastroenterology*, **58**, 337–344.

Pulvertaft, C. N. (1968) Comments on the incidence and natural history of gastric and duodenal ulcer. *Postgraduate Medical Journal*, **44**, 597–602.

Registrar General's Statistical Reviews for 1912, 1918 and 1924. London: H.M.S.O.

Registrar General's Decennial Supplements on Occupational Mortality for 1951 and 1961 for England and Wales. London: H.M.S.O., 1958, 1971.

Saint Hilaire, S., Lavers, M. K., Kennedy, J. & Code, C. F. (1960) Gastric acid secretory values of different foods. *Gastroenterology*, **39**, 1–11.

Watkinson, G. (1960) The incidence of chronic peptic ulcer found at necropsy. *Gut*, **1**, 1–14.

Wilkinson, A. R. & Johnston, D. (1971) Inhibitory effect of cigarette smoking on gastric secretion stimulated by pentagastrin in man. *Lancet*, **ii**, 628–632.

Weir, R. D. (1960) Perforated peptic ulcer in north-east Scotland. *Scottish Medical Journal*, **5**, 257–264.

Weir, R. D. & Backett, E. M. (1968) Studies of the epidemiology of peptic ulcer in a rural community: prevalence and natural history of dyspepsia and peptic ulcer. *Gut*, **9**, 75–83.