Drugs for Peptic Ulcer

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There is now a range of treatments that can be shown to accelerate the short-term healing of ulcer, and some of these will also prevent relapse during continued administration. Desirable as this extension of the benefits of medical treatment may be, is there any reason for believing that the fundamental course of ulcer disease has been altered?

Duodenal Ulcer

The advent of endoscopy has been followed by the formal testing of a variety of regimes in ulcer treatment. As a result, evidence has been brought forward to support the use of four main remedies: carbenoxolone, cetrated bismuth, cimetidine and intensive antacid treatment.

Treatment with any of these regimes seems to be associated with roughly a doubling in the proportion of ulcers healed during short-term treatment, and Table 1 illustrates this trend by reference to carbenoxolone and cimetidine. There is, however, a variation in treatment responses; thus, in the USA, drug effects are notoriously hard to demonstrate because of high placebo response rates. The merits and disadvantages of each treatment depend in part upon an assessment of their adverse effects, and in part upon the longer term outcome. Short-term healing is a desirable objective, but there is little to be gained if ulcer breakdown is prompt, and either further and prolonged courses of treatment are needed, or else surgery is ultimately required.

Antacids

In the USA it has been shown that antacids given in doses in excess of 1,000 mmol daily will induce ulcer healing (Peterson et al., 1977). A high proportion of patients developed diarrhoea. The regime prescribed, 30 ml of antacid eight times a day, would need an intensely obsessional patient to complete it, and a small suitcase in which to carry the drugs home. Relapse rates on stopping treatment are not clear, but as the fundamental conditions predisposing to ulcer are unaltered, recurrent symptoms must be expected.

| Table 1. Duodenal ulcer: outcome of short-term treatment trials. |
|---------------------------------------------------------------|
| **Carbenoxolone capsules**                                   | **No. treated** | **% Healed** | **Ratio of No. healed** |
| Sahel et al., 1977 (France)                                   | 68             | 65           | 3.4 : 1         |
| Young et al., 1978 (Australia)                                | 40             | 60           | 2.4 : 1         |
| Nagy, 1978 (Australia)                                        | 44             | 66           | 2.2 : 1         |
| Davies and Reed, 1977 (UK)                                   | 40             | 75           | 1.9 : 1         |
| Archambault et al., 1977 (Canada)                            | 41             | 68           | 1.9 : 1         |
| Hirschowitz, 1976 (USA)                                      | 60             | 61           | 1.1 : 1         |
| **Cimetidine**                                                |                |              |                 |
| Gray et al., 1975 (UK)                                        | 40             | 85           | 3.3 : 1         |
| Bardhan et al., 1977 (UK)                                    | 89             | 73           | 2.5 : 1         |
| Bodemar and Walan, 1976 (Scandinavia)                        | 44             | 90           | 2.4 : 1         |
| Hetzel et al., 1977 (Australia)                               | 67             | 82           | 2.5 : 1         |
| Semb et al., 1977 (Scandinavia)                              | 40             | 85           | 1.4 : 1         |
| Binder et al., 1978 (USA)                                    | 52             | 76           | 1.2 : 1         |

Carbenoxolone

Delayed release capsules of carbenoxolone have now been well proven to promote ulcer healing. The merits of the capsule as a delivery vehicle, it being designed to liberate its contents directly into the duodenum after bursting in the gastric antrum, have never been properly tested. It may be that ordinary carbenoxolone tablets are equally effective.

Adverse effects of salt and water retention with oc-
casional hypokalaemia and raised blood pressure are well described. These are predictable as natural outcomes of the drug’s mode of action, and can usually be simply and safely managed by concurrent administration of a thiazide diuretic with a potassium supplement. However, the adverse effects limit drug use to those who have good cardiorespiratory, hepatic and renal function, and who are under the age of 70, adverse effects being common in the elderly. Furthermore, maintenance treatment is impracticable because of the risks engendered by electrolyte imbalance.

The outcome on stopping treatment is not clear. The drug is thought to induce ulcer healing through an increase in mucosal resistance on the grounds that no action on acid output has been found. How long any change in resistance persists is unknown, as relapse rates on stopping treatment have not been reported.

Chelated Bismuth

There is reasonable, if quantitatively limited, evidence that this preparation will promote duodenal ulcer healing (Moshal, 1974; Coughlin et al., 1977). It is assumed to do so by coating the ulcer, but this has never been proved. The drug is free from adverse effects, and bismuth encephalopathy has not yet been reported. Relapse rates are unknown.

Cimetidine

A large body of evidence now exists to show that this histamine H₂ antagonist promotes gastric ulcer healing. Doses greater than one gram daily do not improve healing rates, which are comparable with those obtained with carbenoxolone (Table 1).

Relapse is frequent on stopping treatment, and can be prevented by maintenance doses of 400 to 800 mg daily. However, when such treatment ceases relapse still occurs and it is clear that six months’ to a year’s treatment after one to two months’ initial treatment designed to heal the ulcer has had no fundamental effect on the course of the disease (Table 2).

Adverse effects in the short term are few. Those that can reasonably be ascribed to treatment include occasional gynaecomastia, raised serum creatinine and, possibly, uric acid and transaminase levels, all reversing on stopping treatment. Those possibly ascribable to treatment include mental confusion and, on stopping the treatment, ulcer perforation. The true pattern of adverse effects of treatment will not, however, become clear until considerably more clinical experience is available. Histamine H₂ receptors are widely distributed in the body, and the consequences of interference with, say, those in the cardiovascular system are not known. Also unknown are the consequences of long-term treatment, with the reduction of gastric acidity and encouragement of bacterial proliferation in the stomach.

As matters stand, cimetidine seems best reserved for patients with symptoms resistant to conventional measures, and then in courses of limited duration. In those where treatment needs to be continued for long periods the desirability of gastric surgery should be considered.

**Symptoms and Ulcer Activity**

In duodenal ulceration the prime need is to relieve symptoms. Unfortunately, we know little of the causes of pain in ulcer patients. Examination of the use of antacids for symptomatic relief shows wide variation between individuals with apparently identical disease. Furthermore, ulcer healing does not necessarily correlate with symptom remission. In the presence of such confusion it seems best to reserve potent drug treatment for patients with objectively demonstrable disease. However, some patients tend to fare well regardless of the visible activity of the disease. Thus, the patient who has an episode of acute bleeding has little chance of further bleeding in the next five to ten years, and also is likely to have little in the way of pain. Treatment for visibly active disease in this group may therefore be unnecessary.

**Gastric Ulcer**

The treatments for which there is good evidence of efficacy in inducing short-term healing are carbenoxolone sodium, chelated bismuth salts and cimetidine. With all of these, ulcer healing can be induced at least twice as often as during placebo treatment (Table 3). The major problems of gastric ulcer management which remain are three—

1. Can a malignant lesion be distinguished from a benign ulcer confidently?
2. Can the high mortality rate ascribed to a bleeding gastric ulcer be reduced?
3. Can the high relapse rate of chronic gastric ulceration be reduced?

1. **Distinction of Ulceration: Benign and Malignant**

In the past, a satisfactory response to treatment has been used as an indicator of a benign ulcer. This method of distinction has fallen into disuse with the advent of endoscopy and biopsy, though it is still suggested that all ulcers should be followed up until healing is established. However, this does not guarantee the benignity of the disease, for there are descriptions of complete healing of malignant ulcers during treatment with cimetidine (Taylor et al., 1978), and there is no fundamental reason for believing that such spurious healing can occur only with this drug.

The use of clinical response to assess the nature of disease may be misplaced in the presence of cancer. It can also mislead in patients with functional dyspepsia

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**Table 2. Duodenal ulcer: outcome of maintenance cimetidine treatment.**

|                | No. treated | % remaining relapse-free | Maintenance period | Post-maintenance |
|----------------|-------------|--------------------------|--------------------|------------------|
| Dronfield et al., (1978) ¹ | 42         | 75                       | 25                 |                  |
| Gudmand Hoyer et al., (1978) ² | 57         | 88                       | 47                 |                  |

¹ 800 mg daily for six months, then eight months follow-up
² 800 mg daily for twelve months, then three months follow-up
who have typical ulcer-like symptoms; thus Horrocks and de Dombal (1978) found that a quarter of all patients with functional dyspepsia had symptoms relieved by antacids, and a third had pain in relation to meals. The likelihood must be that many of these patients would have their symptoms equally relieved by potent anti-ulcer drugs, which would clearly be unnecessary.

2. Reduction of Mortality from Bleeding Gastric Ulcer

The chances of death from bleeding peptic ulceration increase steeply with age. This pattern has led to the advocacy of surgery in the hope of reducing such mortality, though the evidence in support of such action is indifferent. Drugs that promote ulcer healing cannot logically be expected to reduce mortality from immediate complications. The ulcer that bleeds because it has a large artery in its base is unlikely to have the risk of bleeding altered in the short term.

3. Reduction of Relapse Rate

When patients with gastric ulcer are reviewed ten or more years later a high proportion will have had operations. Thus, Mowat and his colleagues (1975) found that 69 out of 151 (46 per cent) with chronic gastric ulcers followed up a minimum of four years later had been operated upon, and Doll (1966), on reviewing the natural history of ulcer, found that between just under a quarter and over a third of patients had been operated upon, while only a half or less had none or only minor symptoms.

So far there is only fragmentary evidence about the relapse rates of gastric ulceration following cimetidine or any other treatment (Macchell et al., 1978), either during maintenance treatment, or after treatment has stopped.

It has been conventional clinical practice to try to induce early ulcer healing in the hope of reducing relapse rates. Little evidence exists to support this practice, but Piper and his colleagues (1978) have recently found that, after four years, clinical relapse was over twice as uncommon in individuals who healed their ulcers at initial hospital admission as in those who did not. There is some limited clinical evidence (Langman, 1968) to suggest that patients whose ulcers heal during carbon- oxolone treatment do not break down any more or less rapidly than those who received conventional treatment. Since more ulcers healed with carbon-oxolone treatment, this suggests that some benefit from treatment is retained after stopping it. Finally, in a small trial, cimetidine prophylaxis has been found to reduce the frequency of relapse, but what happens when treatment is ultimately stopped is not known (Macchell et al., 1978).

Relapse of symptoms and return of ulceration are common once treatment of gastric ulceration has ceased and, given the high proportion of individuals who ultimately have relapses, there remains good reason for recommending surgery after a relatively short period of medical treatment.

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**Book Review**

Advanced Medicine 14. Edited by D. J. Weatherall. Pitman Medical, Tunbridge Wells, 1978. Price £8.50.

This book is based on the Advanced Medicine Conference at the College of Physicians in February 1978. Thirty-seven authors combine to produce 36 chapters. This represents an achievement, since the book is published after such a short time. Chapters are grouped into sections which may contain subjects as diverse as dietary fibre and liver failure. But possibly this is temporary since, having conquered constipation, diverticulosis, haemorrhoids and varicose veins elsewhere, fibre here tackles diabetes, hypercholesterolaemia and gallstones. One feels liver failure may well be next.

Some chapters assume that the reader is abreast of the appropriate jargon, e.g., ‘the aberration resulted from adjacent segregation of a parental reciprocal translocation’ is stated without further qualification. Another author takes us back to the basics of DNA and the genetic code, for those who have not heard of Watson or Crick. But on the whole all the authors make their material most readable, particularly the chapters on liver disease. There are light-hearted illustrations, such as an analogy of a football crowd for a platelet aggregation in the section on Prevention of Thrombosis. Some chapters offer practical advice: how to manage asthma; use H1 antagonists; diagnose Lassa fever; suspect resistant malaria; treat cardiac arrhythmias; manage liver failure, or portal venous hypertension. It is a pity that a more practical note did not enter the section on hypertension.

The scientific advances are well covered; the chapter on new techniques of chromosome analysis was fascinating and those on genetics and medical sciences well worth reading.

A volume compiled in relative haste will always contain some misprints. None was sufficient to obscure meaning, I found ‘ovalocytosis’ rather endearing. (How green was my ovalocyte?) But my favourite must be ‘cardiac morality’ which was, we were told, reduced. Evidently a new type of heart failure.

Altogether a most worthwhile book.

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**Dreams before Freud**

Sir Thomas Browne, watching his friend die, observed that as the end approached his friend was ‘now past the healthful Dreams of the Sun, Moon, and Stars in their Clarity and proper Courses.’ Twas too late to dream of Flying, of Limpid Fountains, smooth Waters, white Vestments, and fruitful green Trees, which are the Visions of healthful Sleeps, and at a good distance from the Grave.’ He was saddened by the dying man’s dream of his dear friends and how he would not long be parted from them. Browne could never resist musing on any subject and reflected on the nature of dreams without the dubious benefit of Freudian interpretation. ‘Some Dreams I confess may admit of ease and feminine Exposition: he who dream’d that he could not see his right Shoulder, might easily fear to lose the sight of his right Eye; he that before a Journey dream’d that his Feet were cut off, had a plain warning not to undertake his intended Journey. But why to dream of Lettuce should presage some ensuing Disease, why to eat Figs should signify foolish Talk, why to eat Eggs great Trouble, and to dream of Blindness should be so highly commended, according to the Onetricritical Verses of Astrampycus and Nicephorus, I shall leave unto your Divination.’