Current Practice

DISEASE OF THE DIGESTIVE SYSTEM

Duodenal Ulcer—I

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It is the purpose of this paper to discuss duodenal ulcer under three headings: diagnosis, medical management, and indications for elective operation. The treatment of emergency complications such as perforation and haemorrhage will not be considered.

Diagnosis

Duodenal ulcer continues to be a common disorder in Britain. It still shows a predominance in males, though there is a suggestion that the difference in incidence between the two sexes may not be as great as it was 20 years ago. Reliable data on the overall incidence of peptic ulceration is understandably difficult to acquire in view of the very variable severity and natural course of the disease. If the incidence of perforation is one factor capable of fairly precise measurement, there is evidence¹ that at least in one part of the country there has been a real decrease in the number of such complications in the last ten years. Although several interpretations of this finding are possible, it may be that it reflects a recent change in the incidence of duodenal ulcer, just as there is evidence that the pattern of gastric ulcer, at least in Australia, may also be changing.²

The diagnosis of duodenal ulcer is usually strongly suspected from the clinical history alone. The chief and often sole complaint is of epigastric or right hypochondriac pain or discomfort most frequently experienced when the patient is hungry, and by the time he seeks medical advice he has generally noted that eating a meal affords substantial relief for an hour or two. There may also be recurrence of the upper abdominal pain during the night, and if this causes interruption of sleep the patient often has noticed that drinking a glass of milk or taking a small snack will let him return to his sleep. Vomiting is not as common an occurrence in patients with duodenal ulcer as it is with gastric ulcer, but in a minority of duodenal ulcer patients even without pyloric stenosis some vomiting does from time to time occur. Usually this is of partly digested food or clear gastric juice, and the act of vomiting often brings relief of abdominal discomfort. A few patients may deliberately induce vomiting to obtain such relief. Repeated attacks of copious vomiting, particularly of retained gastric contents, do of course suggest the occurrence of pyloric stenosis.

By the time the patient seeks medical help he has usually experienced several episodes of his pain or discomfort with remissions of variable length intervening. Since a large variety of antacid and other "indigestion" preparations are widely advertised, and readily available, most patients will have tried one or several of such preparations. Most will have experienced at least partial relief from this self-selected medication, and a good proportion will claim that a dose of bicarbonate of soda is as good as anything to ease the pain.

Radiation of the pain through to the back usually occurs only in the most severe relapses of ulcer pain, and this feature is

generally taken to indicate a posterior ulcer irritating or penetrating into the retroperitoneal tissues.

There does not seem to be any particular group of food substances which are regularly blamed for the onset of ulcer dyspepsia. Many patients complain, however, that spicy or greasy foods do bring on their symptoms, though intolerance of such foods seems to be a non-specific feature of most disorders of the upper digestive tract. An individual patient with a duodenal ulcer may relate the somewhat abrupt onset of his symptoms with the ingestion of a particular food substance and therefore believe that it was responsible for the symptoms. However, the variety of foods blamed in this way is so large that no set pattern emerges.

Barium-meal examination will confirm the diagnosis in the majority of cases, and it is reasonable to expect a diagnostic accuracy of over 90%. The largest ulcers will usually be clearly shown directly, and for the remainder the indirect signs of deformity of the duodenal cap, abnormalities of the mucosal pattern, or difficulty in satisfactory filling of the duodenal cap will give the diagnostic indications. It is not an uncommon experience for those clinicians and radiologists who regularly jointly review ulcer patients to find quite gross disparity between the x-ray findings and the severity of the clinical history at the time of the examination. Quite minimal deformity of the duodenal cap may be seen in a patient having severe pain almost incapable of relief by medical measures, while by contrast a large ulcer crater with gross scarring of the duodenal cap is found in a patient having minimal dyspepsia. Because of this variable relation between clinical history and radiological findings, when a patient has convincing symptoms of a duodenal ulcer but an apparently normal barium meal it is reasonable to repeat the examination after an interval of a few months should the symptoms persist. Even with repeated expert radiological examination a few duodenal ulcers may escape x-ray detection and come to light only at a subsequent laparotomy. This is unusual, and is more likely when the ulcer is abnormally situated.

Who Do the Barium Meal?

It might be argued that if the symptoms are quite typical and clear-cut there is no necessity to perform the barium meal. This argument is not valid. It is important to have the x-ray results in all suspect cases for several reasons. Firstly, it is virtually impossible on symptomatology alone to differentiate with any confidence between duodenal and gastric ulcer, and since there are some important differences in the management of the two types of disorder it is essential to know the location of the ulcer. Secondly, the concurrent presence of both duodenal and gastric ulcers is being recognized increasingly frequently, and it is important to detect this. Thirdly, other abnormalities of the upper alimentary tract such as hiatus hernia, congenital abnormalities, or diverticula may be present and have a bearing on treatment.

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In most patients the diagnosis is adequately established by barium-meal examination, but a number of further diagnostic aids may be valuable in special circumstances.

Gastroscopy.—Inspection of the gastric lumen by the flexible fiberscope or the direct-viewing gastro-camera is indicated in patients with a strong dyspeptic history and a normal barium-meal examination. The gastroscopic examination may reveal a small undetected gastric ulcer or other gastric lesions but will of course not normally permit direct inspection of the duodenum itself.

Acid Secretion Measurements.—The diagnostic application of these tests is quite limited. Assessment of the maximal acid response to either histamine³ or more recently the synthetic gastrin-like pentapeptide pentagastrin⁴ has replaced other tests of acid secretion. Though the maximal acid response of duodenal ulcer patients is twice that of normal controls there is a very large range of individual values in each group and considerable overlap between the two groups. Thus a high value for the maximal acid response in an individual patient will not clearly establish the diagnosis of duodenal ulcer, but will only make the diagnosis more likely. In return for the high order of close supervision, thoroughness, and time-consuming care which must be expended to obtain reasonably accurate secretory measurements the diagnostic usefulness of these tests is disappointingly small.

Where the clinical history may raise the suspicion of the very rare Zollinger-Ellison syndrome (unusually severe ulcer dyspepsia, multiple ulcers on radiological examination, and/or severe watery diarrhoea), comparison of the unstimulated gastric acid secretion with that obtained after maximal stimulation with histamine or pentagastrin may add considerable support to the diagnosis. In this condition it is characteristic, though not invariable, to find a very large output of acid in the unstimulated phase as a result of the continuously large production of the gastrin-like secretagogue from the pancreatic tumour, and the additional administration of a "maximal" dose of histamine or pentagastrin does not bring about much further increase in the gastric acid secretion.

There has been much interest in the relationship between peptic ulceration and blood group distribution. The present position, recently reviewed by Langman,⁵ may be briefly summarized as follows. Both duodenal and gastric ulcers are more likely to occur in persons belonging to blood group O, particularly if they are incapable of secreting the blood group substances in their mucus secretion. The increased risk of these group O non-secretors, though statistically significant, is relatively slight, and a knowledge of the blood group and secretor status of an individual patient with duodenal ulcer does not at present help in establishing the diagnosis or in planning the clinical management.

Medical Management

Most duodenal ulcer patients are treated in the first instance by conservative measures: advice regarding diet, drugs for symptomatic relief—such as alkalis, anticholinergic drugs, and sedatives, and some advice regarding the general pattern of daily life, work routine, and social activities.

Diet

Traditionally patients have been advised to restrict their dietary intake to "bland" constituents with a predominance of milk, milk-containing foods, and carbohydrates. In the past quite detailed restrictions have been advocated, such as milk and fish for prolonged periods. There is no good evidence that such strict limitation of diet is of any real value in achieving symptomatic relief or in preventing further relapses. Detailed advice should not be given on foods to be preferred or avoided. Many patients find it difficult if not impossible to stick to a grossly limited diet during a normal day. The patient should

be told simply to avoid any particular items which have regularly caused a bout of dyspepsia. Foods which are highly seasoned should probably be avoided, as many spices are known to have a local irritant action on the gastric mucosa, unless the patient is inordinately fond of them and has found that he can eat them without any discomfort.

Since nearly every duodenal ulcer patient finds that a drink of milk will give prompt relief of the ulcer pain, an increased intake of milk or milk-containing drinks spaced frequently throughout the day is often recommended. However, there is no real evidence that milk is better than other substances in neutralizing gastric acid or in any other way. The patient with a duodenal ulcer may be advised to take extra milk if he likes it, with and between meals, but there seems no justification in insisting that those patients who strongly dislike milk should take it.

Timing of Meals

The timing of meals is probably much more important than the actual food. Lennard-Jones and Babouris⁶ have shown that there is much less fluctuation in intragastric pH when a diet of the patient's own selection is fed at two-hourly intervals as compared with four-hourly. Translated into practical terms this means that the patient should be urged to have a mid-morning and mid-afternoon snack in addition to the three main meals, and that he should also have something to eat in the middle of the evening and last thing at night before retiring to bed. Sometimes the patient's occupation makes this regimen difficult, but it is generally possible to persuade him to carry some packaged food with him and to take this at the appropriate times.

For how long should such a diet pattern be followed? There is unfortunately no clear-cut guide on this question, but it is probably unnecessary to prolong it beyond a few weeks after complete remission has occurred. A gradual return could then be made to normal spacing. The patient should be told that it is unwise for him to miss a meal or go for much longer than three to four hours without something to eat.

This advice is likely to lead to an increase in weight, and on occasions to gross obesity. Fortunately patients with duodenal ulcer on average tend to be a bit underweight, and the weight gained as a result of the dietary measures may not always pose too much of a problem.

What advice should be given about the taking of alcohol? Alcohol is known to stimulate the gastric secretion of acid, and it is also known that excessive quantities of ingested alcohol can cause a diffuse gastritis. It is doubtful whether it is necessary to forbid the taking of alcohol altogether, but patients should avoid spirits and should not take any alcohol when fasting.

Drugs

Alkalis.—Most patients find that one or other of the very numerous alkaline preparations available will give effective symptomatic relief. Perhaps the most popular remedies contain aluminium hydroxide, phosphate, silicate, or glycinate, magnesium trisilicate, hydroxide, or carbonate, calcium carbonate, or bismuth aluminate. It is common clinical experience that though some preparations enjoy a fairly wide popularity among duodenal ulcer patients there is considerable variation in the apparent effectiveness of different drugs and mixtures from one individual to another. Again it is often found that whereas one alkaline preparation will regularly afford relief for months or years it may eventually lose in usefulness and the patient will switch to another preparation which apparently then proves superior. This in turn through time may eventually be superseded by yet another antacid, and yet all three

preparations might have virtually the same capacity to neutralize acids. It is often surprising how rapid and prolonged is the relief obtained from a relatively small dose of an alkaline preparation, a dose which would be able to neutralize only a very small quantity of acid. It seems that the symptomatic relief afforded by alkalis is not solely explained by their acid-neutralizing properties, since the quantities theoretically required to keep the stomach contents at an alkaline pH for prolonged periods throughout the day are many times the doses normally taken by duodenal ulcer patients.

Since the aim of giving antacid preparations is simply to give temporary symptomatic relief and not to secure continuous acid neutralization, the alkali should be taken by the patient only as and when required for relief of pain. There seems no virtue in taking doses regularly throughout the day at set times or in relation to meals, and there is no justification for giving alkalis during a period of remission in the hope that they will minimize the chance of recurrence of symptoms.

To some extent side-effects will dictate the choice of an antacid preparation. Those containing magnesium tend to cause mild diarrhoea, whereas aluminium hydroxide may have the opposite effect. If taken in very large dosage calcium carbonate and bicarbonate and sodium bicarbonate may cause alkalosis.

Anticholinergic Drugs.—Though not so popular as alkalis anticholinergic drugs are also widely used in the symptomatic treatment of ulcer dyspepsia. If given in adequate dosage it can be shown that such drugs will both reduce gastric acid and pepsin secretion and also diminish gastric motility. For this last reason the anticholinergic drugs have often been referred to as "antispasmodics," there being a belief that muscular spasms may cause or contribute to duodenal ulcer pain. Among the most commonly prescribed anticholinergic agents are atropine and hyoscine and their derivatives, poldine, propanthelene, dicyclomine, and glycopyrrolate. It is probably fair to say that such agents are not as commonly effective as the antacid preparations, but a proportion of patients do find anticholinergic drugs completely effective in obtaining prompt relief. This variation in the usefulness of different symptomatic remedies may reflect individual variation in the mechanism of ulcer pain.

There is evidence^{7,8} that anticholinergic drugs should be given in maximal tolerable dose in order to obtain significant relief of symptoms. Dryness of the mouth, blurring of vision, and occasionally difficulty in emptying the bladder may occur if excessive dosage is taken, and it may not always be possible to obtain satisfactory relief of the dyspeptic symptoms with a dose which does not cause these unpleasant, and at times risky, side-effects.

Sedatives.—The idea behind giving sedation to patients with duodenal ulcer arose from the concept that patients with this disorder were unduly prone to worry excessively, to be over-active, agitated, and introspective, and that this pattern was in some way causally related to their duodenal ulcer. It was also argued that, since a period of rest in bed would virtually always result in the disappearance of even the most severe ulcer symptoms, sedation might go at least some way towards achieving a more tranquil background for the patient and so encourage the healing of his ulcer. Small doses of sedatives, notably phenobarbitone, are commonly added to proprietary antacid preparations. There is, however, no good evidence that sedation will improve the chances of obtaining satisfactory remission or prevent further symptoms. However, such drugs may well be beneficial in a selected minority of patients displaying signs of gross hyper-excitability.

Oestrogens.—In recent years the effect of oestrogens has been studied in men with duodenal ulcer, following the reasoning that women have a much lower incidence of duodenal ulcer than men and therefore female sex hormone might protect against ulceration. It was shown by Truelove⁹ in a carefully controlled clinical trial that stilboestrol 0.5 mg. b.d. exerted a

beneficial effect on the symptom course and radiological findings in men with duodenal ulcers. Unfortunately, as might be expected, a relatively high incidence of feminizing side-effects weighed heavily against widespread use of such treatment. A few further recent attempts have been made to evaluate other oestrogen preparations with less feminizing side-effects, but the results have been inconclusive. While further evaluation is awaited with interest, there seems no indication at present for oestrogen therapy in the routine management of duodenal ulcer patients.

Carbenoxolone.—Carbenoxolone is an anti-inflammatory agent isolated from liquorice extract, and a variety of similar preparations have been used for many years in the medical management of peptic ulceration. While there is some evidence that carbenoxolone may facilitate the healing of gastric ulcer in ambulant patients, there is at present no indication that it exerts a favourable influence in duodenal ulcer. Most liquorice preparations, including carbenoxolone, cause retention of water and sodium when given in moderate or high doses, a property incidentally shared by oestrogens. It may well be that this fluid-retaining property is an essential aspect to the therapeutic value of these drugs.

Anti-pepsin Agents.—A number of agents have been found to inhibit the proteolytic enzyme action of pepsin under laboratory conditions. However, to date none has been shown to perform this role satisfactorily *in vivo*, and such a therapeutic approach is not promising.

General Aspects

Rest.—It is common experience that peptic ulcer symptoms rapidly remit when the patient is put to bed. Whether the physical inactivity or the isolation from "stresses" of occupational, social, domestic, and other responsibilities is the more important factor is uncertain. Whereas it is not always practical or indeed possible for a patient in relapse of duodenal ulcer symptoms to take to bed, it is on occasion worthwhile advice to a patient who is having increasingly severe pain which proves intractable to other measures. The response of symptoms to a short period of bed rest is also sometimes used to determine whether the pain is genuinely due to duodenal ulcer or some other lesion. If the pain does not subside when the patient is confined to bed this is usually taken as an indication that the pain is not due to peptic ulceration. While this is not an absolute rule it is often a useful guide.

Psychological Factors.—The importance of psychological factors in the aetiology and natural course of duodenal ulcer remains uncertain and controversial. Opinions vary from the extremes of the belief that virtually all peptic ulcers are the expression of emotive disorder and conflict, to the view that any expressions of reaction or behaviour abnormalities are the consequences of the peptic ulcer state. The compromise view is that psychic disturbance is of importance in a proportion of patients only. Many clinicians can readily recall patients whose symptoms regularly flared up on exposure to a particular emotional problem and promptly settled once more on the problem being overcome. Where such factors can be clearly recognized it may be possible to help the patient avoid exposure to the precipitating factors by some simple commonsense advice, or to modify the patient's reaction to the particular circumstances by enlisting the aid of the professional psychotherapist. In many instances, however, though there may be aggravating work or social factors, it may be quite impractical to alter the situation.

Smoking.—There are many good reasons for advising the cigarette smoker to give up the habit, and these apply no less in the duodenal ulcer patient than in any others. Doll, Jones, and Pygott¹⁰ showed in 1958 that stopping smoking accelerated the healing of gastric ulcer. There is still a surprising lack

of information on the effects of cigarette smoking on the course of duodenal ulcer. At present, therefore, any advice to stop smoking is based on general grounds.

Gastric Freezing.—The initial enthusiasm for gastric mucosal freezing has not been sustained. Clinical experience with this technique has been reviewed by Forrest,¹¹ who concludes that there is no place for this method of treatment in the management of chronic duodenal ulcer at the present day.

(This article will be concluded next week with an account of the surgical management of duodenal ulcer together with a list of references.)

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Analgesics and Monoamine-oxidase Inhibitors

Q.—What untoward reactions may occur when analgesic drugs are given to patients who have been taking a monoamine-oxidase inhibitor drug? How may severe pain of acute onset be treated in such patients?

A.—There have been a number of reports of untoward reactions when analgesics have been given to patients who were receiving monoamine-oxidase inhibitors such as iproniazid, phenelzine, nialamide, pargyline, and tranlylcypromine.¹⁻³ In most of the reported cases the analgesic concerned has been pethidine.

The more alarming type of reaction occurs within minutes of the administration of pethidine. The patient becomes restless, even violent, with twitching of muscles, sweating, cyanosis, hypertension, increased tendon reflexes, extensor plantar responses, and Cheyne-Stokes respiration. In some cases, however, the narcotic and hypotensive effects of pethidine are potentiated, and the patient has a prolonged period of unconsciousness with hypotension.⁴ In at least three cases death has been attributed to the interaction of the two drugs.⁵

An additional hazard concerns the administration of compound preparations which contain both an analgesic drug and a sympathomimetic drug such as amphetamine or one of its derivatives. The Committee on the Safety of Drugs issued a warning,⁶ directed particularly to dentists, about the dangers of using these preparations in patients who have been taking monoamine-oxidase inhibitors.

Therefore for the treatment of severe acute pain in a patient who is known to be receiving or to have recently had a monoamine-oxidase inhibitor both pethidine and compound preparations containing sympathomimetic agents should be avoided. Other narcotic analgesics may be used with caution. Morphine has been given without untoward effect to a patient who subsequently had an alarming reaction to pethidine.¹ The smallest therapeutic dose should be used and the patient watched carefully for 15 to 20 minutes after the analgesic has been given. If nothing untoward happens within this time an acute reaction is unlikely, but the patient may have a more prolonged sedative response than is usual. Should an acute

reaction occur prednisolone 25 mg. should be given intravenously. The other measure which has been recommended is the prompt acidification of the urine to increase the elimination of pethidine. The action of ammonium chloride given orally is too slow for this purpose, and the intravenous administration of sodium acid phosphate or lysine or arginine hydrochloride is suggested.⁵

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Inheritance of Ankylosing Spondylitis

Q.—What are the chances of a man affected with ankylosing spondylitis having a child who will also be affected?

A.—Ankylosing spondylitis has a multifactorial aetiology, and shows a definite concentration within families. There are not enough empirical data to give a risk for the children of affected males, but data from sibs¹⁻³ indicate that the risk will be of the order of 3%, whereas the incidence in the general population is of the order of 0.5 per 1,000. The risk is likely to be higher for sons than for daughters, and higher when the mother (and not, as in this case, the father) is the affected parent.

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Antidepressant Drugs and Muscular Weakness

Q.—Imipramine given for depression in a case of progressive muscular atrophy seems to increase the muscle weakness. Which group of antidepressants are least likely to affect muscle power in these cases?

A.—Muscular weakness is recognized as a side-effect which may occur in some patients treated with imipramine or other antidepressant

sant drugs of the dibenzepine (tricyclic) group such as amitriptyline. It is not therefore surprising that a patient with progressive muscular atrophy should respond in this way. One of the other drugs which have antidepressant properties, such as phenelzine (a monoamine-oxidase inhibitor) or a small dose of amphetamine (a sympathomimetic drug), might be tried, but it may be questioned whether in this case the use of antidepressant drugs is the correct approach to the problem. Presumably the patient's depression is secondary to his organic disease, and the response to antidepressant drugs in such cases is not likely to be as favourable as in endogenous depression.

Notes and Comments

Treatment of Chronic Brucellosis.—Surgeon Commander H. M. DARLOW (Microbiological Research Establishment, Porton, near Salisbury, Wilts) writes: The value of ampicillin in the treatment of chronic brucellosis ("Any Questions?" 30 September, p. 847) was dismissed as a failure on the strength of two cases. I have been involved with two mild and one severe case which were successfully treated with this antibiotic given in doses of 250 mg. four times a day for 28 days. The result was particularly dramatic in the severe case. The patient had been a semi-invalid for several years with frequent bouts of pyrexia and spinal changes. She has been symptom-free now for four years and leads a normal life.

While not disputing the possibility, that the tetracycline-streptomycin regimen is the sheet anchor in the treatment of this distressing complaint, it is not infrequently ineffective, and one wonders if it really is superior to ampicillin or to other antibiotics and nalidixic acid, not quoted in the article, which have been used less frequently but nevertheless with some success. In view of my own experience I think that ampicillin should be given a fair trial, and I should be interested to hear through your pages of the opinions and experiences of others with this antibiotic.

OUR EXPERT replies: Claims for the success of other agents rest on reports of small numbers of individual cases such as Surgeon Commander Darlow gives. They are difficult to assess without more details of criteria, length of follow-up, and total number of patients treated. It is relatively unusual to find similar reports of individual failures, and it is unfortunate for ampicillin (which looks, on the basis of in-vitro studies, a very promising agent) that a few failures have been reported but not a few successes. Surgeon Commander Darlow is quite right: what is needed is a fair trial—if by that he means a properly conducted comparison of the tetracycline-streptomycin regimen (the only one so far submitted to extended critical examination) with other likely-looking agents.