Medical management of peptic ulcer

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Introduction

Sir Francis Avery Jones (FAJ—for once the abbreviation means something to everyone) has been actively involved in the practical and research aspects of management of peptic ulcer throughout his long and productive career. Some of FAJ's earliest publications (Avery Jones, 1939a and b, 1943, 1947) deal with management of acute upper alimentary bleeding and he was instrumental in introducing modern concepts of fluid and electrolyte balance into the treatment of these acutely ill patients. Accurate diagnosis was always one of FAJ's interests and in addition to exploiting together with F. Pygott the potential of the emergency barium meal, he did research in the field of endoscopy (Fletcher and Avery Jones, 1945). The endoscopy sessions at Central Middlesex Hospital, before the introduction of fiberoptic instruments made life much easier for practitioners of this art, were one of the focal points of the week, with FAJ enjoying the doing and the teaching, usually with a large group of acolytes in attendance.

FAJ's contribution in the peptic ulcer area include not only research into the treatment and prognosis of complications of the disease (Avery Jones and Doll 1953; Avery Jones, 1956), but he also encouraged the then novel and revolutionary approach to the statistical evaluation of the results of treatment through the controlled therapeutic trial. Working in the Department of Gastroenterology at Central Middlesex Hospital Dr (now Sir) Richard Doll was given facilities to conduct the studies that eventually culminated in evaluating the first agent shown to significantly accelerate the healing of gastric ulcer (GU)—carbenoxolone sodium (Doll *et al.*, 1962). Environmental factors, such as smoking, were also investigated (Doll, Avery Jones and Pygott, 1958) and FAJ's sustained interest in carbenoxolone is documented in serial publications (Avery Jones and Sullivan, 1972; Avery Jones and Parke, 1975; Avery Jones, Langman and Mann, 1978).

These important researches established the background for the rapid progress and far-reaching

changes in management of peptic ulcer that have taken place during the past 10 years. Progress in this area has been due to several factors. The development of fiberoptic endoscopy has improved the accuracy of diagnosis and the assessment of the effects of treatment on the healing of ulcers. The use of controlled clinical trials for evaluation of treatment has led to a vast accumulation of data on ulcer healing under various medical regimes. Only those trials which take complete ulcer healing as the endpoint of treatment should be considered as valid. This is because endoscopic measurements of ulcer size are inaccurate and also because a partly healed ulcer is a doubtful therapeutic benefit.

Further progress in the medical management of duodenal ulcer (DU) and GU has been due to a fresh interest in the pharmacology of ulcer-healing drugs. The development of agents that powerfully inhibit gastric acid secretion by blocking the action of endogenous histamine at H_2 receptors, or by blocking $H^+K^+ATPase$ in parietal cells has led to intense research activity. This has produced a wealth of new data, new drugs and new insights into older remedies, sometimes with unexpected results. Faster healing of DU or GU is now attainable with many drugs. Moreover, medical treatment has for the first time been able to decrease significantly the relapse rate of DU and GU. The number of therapeutic strategies available for the management of DU or GU has increased, making the decision making process more interesting, but also more difficult.

Short-term treatment of peptic ulcer

Diet, smoking and alcohol

The commonsense advice to eat a well-balanced diet as frequent small meals, to avoid smoking and to take no, or only moderate quantities of alcohol is good advice. There are data from some, but not all, trials suggesting that smoking decreases the chances of healing in DU. Low dietary fibre intake may worsen the prognosis in DU according to one study:

much more information is needed before this idea can be accepted.

Antacids

Antacids remain as the main symptomatic treatment for DU and GU for temporary, but fast relief from dyspepsia, as shown by the vast number of antacid preparations available without prescription in chemists' shops.

The recent development in the use of antacids in peptic ulcer is the demonstration that, if given in high enough doses—approximately 1000 mmol/day—antacids will significantly accelerate the rate of healing of DU in comparison with placebo to a similar extent as cimetidine (Table 1). Unfortunately patients' compliance with such high antacid dose is likely to be poor, and unwanted effects of constipation or diarrhoea are likely to be frequent—30% in one study. The practical use of antacids is likely to remain in the area of symptomatic, rather than therapeutic, management of chronic DU. No data are available with regard to therapy of GU, but antacids are useful for symptoms in this disease.

TABLE 1. Healing of duodenal ulcer on high-dose antacid therapy

	n	% healed		
		Placebo	Antacid	Cimetidine
Peterson <i>et al.</i> , 1977	80	40	76	—
Ippoliti <i>et al.</i> , 1978	94	—	86	76

There is no point in advising the patient to take antacids during periods of remission from DU or GU, as they have not been shown to decrease the frequency of relapse. Patients usually take 10 ml of liquid antacid, or chew an antacid tablet after meals. This time-honoured dose is too small. Patients should be encouraged to take 20–30 ml of liquid antacid 2-hourly until symptoms are relieved. Antacids vary greatly in their neutralizing capacity, but the doctor's reasons for choosing a particular preparation are seldom influenced by this. This is, perhaps one area where medical management could be simply improved.

Anticholinergics

The use of anticholinergic compounds in the treatment of peptic ulcer has been limited by their unwanted effects on other cholinergically mediated functions, such as ocular accommodation, salivation, and bladder emptying in men. These limitations have precluded the widespread use of these drugs in the treatment of peptic ulcer, although a number of small trials have shown a decrease in the long-term incidence of various complications in patients with

DUs; these have been recently reviewed by Walar (1980).

A potentially important development has been the hypothesis that subpopulations of cholinergic muscarinic receptors may exist and that these could be differentially inhibited by suitable anticholinergics. This is the basis of the claims made for pirenzepine which is said to block selectively muscarinic receptors on or near gastric parietal cells (Chierichetti, Gaetano and Petrin, 1979).

Pirenzepine has been shown in a number of trials to have a similar effect on DU healing as cimetidine (Trotman *et al.*, 1982) and shows a statistically significant advantage over placebo-treated control groups. Unfortunately the drug is not entirely specific for gastric muscarinic receptors and unwanted effects of cholinergic blockade do occur, although in general they tend to be mild. Pirenzepine can certainly be added to the list of agents available for the short-term medical management of DU.

Bismuth

Therapy with bismuth salts can be neurotoxic and therefore has no place in the treatment of DU or GU. Chelated bismuth compounds, however, seem safe. A good example is tri-potassium di-citrate bismuthate (TDB). A number of controlled trials, summarized in Table 2, have shown that TDB significantly speeds the healing of DU or GU when compared with placebo. The rate of healing during 4 to 6 weeks of outpatient treatment is 80–90% and comparable to the healing rates achieved with histamine H₂-receptor blocking drugs (Table 2). Martin *et al.* (1981) reported that relapse rates of DU may be lower after treatment with TDB than with other drugs. If confirmed, this is potentially a very important development in medical management of DU. It is possible that treatment with TDB allows a more complete epithelialization of the ulcer crater than other drugs, but this is speculative.

Carbenoxolone sodium

Twenty years ago, carbenoxolone sodium, a synthetic derivative of glycyrrhizic acid, which is a constituent of liquorice, was the first drug shown to accelerate the healing of GU. The studies, done by Doll *et al.* (1962), were performed in Sir Francis Avery Jones' Department at Central Middlesex Hospital and ushered the modern era of scientific evaluation of results of treatment in peptic ulcer disease. Doll and colleagues had previously tested several compounds in controlled trials with negative results. The positive results of treatment of GU with carbenoxolone were unexpected and were therefore tested again, in a separate trial (Doll, Hill and Hutton, 1965). Carbenoxolone has now declined in

importance in comparison with newer, safer compounds. The mode of action has not been worked out in detail, but available evidence suggests that it slows down gastric epithelial cell turnover, alters the chemical composition of mucus and affects the metabolism of prostaglandins. It may also have antiviral properties.

Carbenoxolone is presumed to act topically on the ulcer—hence its presentation as tablets for the treatment of GU and as 'positioned release' capsules for the treatment of DU.

Table 3 sets out results of controlled short-term trials in DU or GU. The results are comparable to those attained with other drugs. The main limitation to the use of carbenoxolone sodium in routine short-term treatment of DU or GU are the unwanted effects, which comprise sodium and water retention, hypertension and hypokalaemia. These are potentially dangerous, necessitate careful and frequent supervision of the patient, and are especially marked in the elderly and in those with cardiorespiratory or renal insufficiency. Attempts to separate the unwanted from the therapeutic effects of carbenoxolone by treatment with aldosterone antagonists (spironolactone) (Doll, Langman and Shawdon, 1968), or by

synthesizing analogues of carbenoxolone, have not so far been successful (Fraser *et al.*, 1972). Controlled long-term trials of carbenoxolone therapy are not available.

Sucralfate

Sucralfate joins the range of mucosal protective drugs available for the treatment of DU. The drug, an aluminium salt of a sulphated disaccharide, is not absorbed and is presumed to act locally, protecting the ulcer crater from the damaging effects of acid, pepsin or bile. Moshal, Spitaels and Khan (1980) and others, in studies involving 328 patients, have shown healing rates of DU treatment with sucralfate ranging from 75 to 98%, compared to 44 to 66% healing on placebo. Comparisons of sucralfate with cimetidine in DU (Table 4) have yielded similar results (Martin *et al.*, 1982). In a 6-month maintenance study, Classen *et al.* (1982) reported a recurrence rate of 22% on sucralfate and 51% on placebo in 122 DU patients, a significant difference. By contrast, sucralfate 2 g daily and placebo given for 6 months to 55 patients with GU yielded similar results. Only minor side effects have been reported so far and the drug

TABLE 2. Healing of duodenal (DU) and gastric (GU) ulcers on chelated bismuth

	Lesion	n	Treatment period (weeks)	% healed	
				TDB	Placebo (P) or cimetidine (C)
Salmon <i>et al.</i> , 1974	DU	16	4-5	88	13 (P)
Shreeve 1975	DU	38	4	74	21 (P)
Moshal 1974	DU	36	6	94	20 (P)
Vissoulis <i>et al.</i> , 1975	DU	47	4	72	32 (P)
Lee and Nicholson 1977	DU	37	4	85	35 (P)
Cannon 1977	DU	35	4	79	38 (P)
Coughlin <i>et al.</i> , 1977	DU	42	4	83	42 (P)
Martin <i>et al.</i> , 1981	DU	58	4	66	60 (C)
			8	89	85 (C)
Lee <i>et al.</i> , 1977	GU	19	4	89	20 (P)
Boyes <i>et al.</i> , 1975	GU	20	4	90	30 (P)
Sutton 1982	GU	50	4	72	36 (P)

TABLE 3. Healing of duodenal (DU) and gastric (GU) ulcers on carbenoxolone sodium

	Lesion	n	Treatment period (weeks)	% healed	
				Carbenoxolone	Placebo
Nagy 1978	DU	44	6	66	30
Archambault <i>et al.</i> , 1977	DU	119	6	75	48
Davies & Reed 1977	DU	34	12	75	39
Multicentre 1977	DU	68	6	65	20
Young <i>et al.</i> , 1978	DU	40	12	60	25
Brown <i>et al.</i> , 1972	DU	31	12	66	58
Gilbert 1976	GU	69	5	67	44
Lorber 1976	GU	66	4	36	33*
Stadelmann <i>et al.</i> , 1972	GU	41	4	45	33

* Result not significant.

TABLE 4. Healing of duodenal ulcers on sucralfate: comparison with cimetidine (Martin *et al.*, 1983)

n	Treatment period (weeks)	% healed	
		Sucralfate	Cimetidine
46	4	80	76
52	8	90	86

appears to be safe. More extensive evaluation of this compound is needed.

H₂-histamine receptor antagonists

Drugs that specifically block the H₂ receptors for histamine (Black *et al.*, 1972) provide the means of powerful control of gastric acid secretion and hence treatment of peptic ulcer. Cimetidine has been widely used in clinical practice and is now joined by ranitidine, another major H₂-receptor blocker. The two drugs are chemically distinct: cimetidine is based on the imidazole ring, while ranitidine is a furan; there are also differences in the side chain. These dissimilarities confer pharmacological differences on the two drugs. Ranitidine is approximately five times as potent an inhibitor of gastric acid output in man than cimetidine. Cimetidine is specific in binding to histamine H₂-receptors, but also binds at other sites. Cimetidine binds to the P450 mixed function oxygenase enzyme system in the liver and this interferes with metabolism of drugs such as warfarin, propranolol, or theophylline. Cimetidine also binds at androgen receptors, thus occasionally exhibiting antiandrogenic properties. Administration of cimetidine may cause reversible mental confusion in the elderly or gynaecomastia in other patients. Ranitidine, on the other hand, is more specific and so far has not exhibited any of the above unwanted actions of cimetidine, or indeed any other unwanted pharmacological effects at ordinary dose levels. Both drugs are very safe.

Both drugs act therapeutically by inhibiting gastric acid secretion. The main physiological stimulus that increases acid output is food; the nocturnal acid secretion which seems important in DU patients is probably mediated by the vagus. H₂-receptor antagonists inhibit gastric acid output stimulated by histamine, gastrin, or the vagus and also suppress meal-stimulated acid output (Pounder *et al.*, 1976).

Short-term treatment of DU

Cimetidine and ranitidine are both highly effective in the short-term medical treatment of DU and short-term results of cimetidine in DU have been recently analyzed by Wormsley (1981) (Table 5). These results have been obtained mainly with doses of

cimetidine 1 g/day in the U.K. and Europe, and 1.6 g/day in the U.S.A. Table 6 shows that, although the rate of DU healing is always higher on cimetidine than on placebo, the differences between cimetidine and controls do not reach statistical significance in studies from Norway, Switzerland, West Germany and the U.S.A. These differences are due to high placebo healing rates in Europe and to low cimetidine healing rates in the U.S.A. The causes responsible are probably multifactorial. Selections of patients must play a part. Where generous endoscopic facilities exist many patients with high probability of spontaneous ulcer healing may be included in the studies. Spontaneous remissions may be frequent in such population samples, tending to blur differences between the active and control treatments. The reason for the low healing rate of DUs on cimetidine in the U.S.A. is more difficult to explain.

TABLE 5. Healing of duodenal ulcers on cimetidine in various countries: (from Wormsley, 1981)

	n	Treatment period (weeks)	% healed		
			Cimetidine	Placebo	P
U.K.	441	4	73 (44-85)	31	S
U.K.	118	6	69 (62-96)	21	S
Italy	395	4	77	36	S
Sweden	54	6	87	34	S
Norway	20	4	85	60	NS
France	109	4	69	55	S
Switzerland	101	4	81	58	NS
F.R. Germany	99	4	76	62	NS
S. Africa	55	6	75	42	S
Australia	43	6	84	38	S
U.S.A.	264	4	58	41	NS

S = statistically significant; NS = statistically not significant.

TABLE 6. Healing of duodenal ulcers on cimetidine 1 g/day compared with cimetidine 400 mg twice daily (bd) (Kerr, 1981)

n	Treatment period (weeks)	% healed	
		1 g/day	400 mg bd
92	4	69	
78	4		66
90	8	90	
76	8		88

One multicentre study in the U.K. and Ireland compared the effect of cimetidine 1 g/day with cimetidine 400 mg twice daily in the short-term treatment of DU (Kerr, 1981, Table 6). There was no difference between the results of the two doses of cimetidine, but before accepting these results more studies in other centres are needed.

Short-term treatment of DU with ranitidine consists of twice daily administration of 150 mg of this more powerful drug. Results are similar to those with cimetidine, and up to now all studies comparing ranitidine with placebo show a significant advantage for the active treatment (Table 7). Comparisons of ranitidine 150 mg bd with cimetidine 1 g/day yield very similar results with either drug (Table 7): in one large trial (Zeitoun and d'Azemar, 1982) ranitidine was just significantly better than cimetidine ($P < 0.05$).

TABLE 7. Healing of duodenal ulcers on ranitidine 300 mg/day: comparison with placebo or cimetidine 1 g/day

	n	Treatment period (weeks)	% healed	
			Ranitidine 150 mg bd	Placebo
Lee <i>et al.</i> , 1982	50	4	92*	29
Bianchi Porro <i>et al.</i> , 1982	164	4	77*	29
Gibinski <i>et al.</i> , 1982	177	3	86*	52
Paré <i>et al.</i> , 1982	41	4	90*	52
			Cimetidine 1 g/day	
Zeitoun & d'Azemar	794	4	74*	68
Barr <i>et al.</i> , 1982	50	4	72	64
Van Dommelen <i>et al.</i> , 1982	59	4	69	60
Schiller 1982 (UK trials)	281	4	75	74

*Statistically significant difference.

Short-term treatment of GU

Short-term treatment of chronic benign GU with H_2 histamine receptor antagonists gives somewhat variable results (Table 8). Not all trials of cimetidine

versus placebo show an advantage for the active treatment. In general, cimetidine and carbenoxolone perform equally well in the short-term management of GU, but cimetidine is safer (Table 8). A large multicentre trial shows ranitidine to have a significant advantage over dummy tablets, while comparisons of ranitidine versus cimetidine yield virtually identical results (Table 8).

ATPase inhibitors Omeprazole

This is the latest, and most powerful, addition to the range of drugs that decrease gastric acid secretion. Omeprazole is a substituted benzimidazole, which acts by inhibiting the $H^+K^+ATPase$ at the secretory membrane of the parietal cell, and thus inhibits the proton pump. Omeprazole can produce complete inhibition of pentagastrin-stimulated acid output (Lind *et al.*, 1983) and can virtually eliminate intragastric acidity in patients with DU eating normal meals (Walt *et al.*, 1983); early results of short-term clinical trials in DU look promising (Gustavsson *et al.*, 1983).

Which drug for short-term treatment of peptic ulcer?

There is thus now a very wide range of drugs listed in Table 9 available for the short-term (4–12 weeks) management of peptic ulcer. Despite profound differences in the pharmacological properties of these agents, the short-term results appear very similar (Table 9). The choice of short-term therapy for peptic ulcer might therefore be governed not so much by efficacy, which appears to be similar, but by safety,

TABLE 8. Healing of gastric ulcers on cimetidine (comparison with placebo or carbenoxolone) or ranitidine (comparison with placebo or cimetidine)

	n	% healed		P
		Cimetidine	Placebo	
Bader <i>et al.</i> , 1977	53	69	37	0.02
Frost <i>et al.</i> , 1977	45	78	27	0.002
Ciclitira <i>et al.</i> , 1979	60	66	52	NS
Dyck <i>et al.</i> , 1978	59	60	41	NS
Englert <i>et al.</i> , 1978	130	59	61	NS
	60	70 (+ antacid)		NS
		Cimetidine	Carbenoxolone	
La Brooy <i>et al.</i> , 1979	54	78	52	NS
Porro & Petrillo 1979	51	76	72	NS
Morgan <i>et al.</i> , 1978	21	100	58	0.039
Coughlin <i>et al.</i> , 1979	50	58	50	NS
		Ranitidine	Placebo	
Ryan 1982 (multicentre)	328	65	44	0.01–0.001
		Ranitidine	Cimetidine	
Wright <i>et al.</i> , 1982	65	58	57	NS
Belgian Study Group 1982	145	66	67	NS

NS = statistically not significant.

cost and acceptability to the patient. The weight of evidence, however, is at present strongest with respect to the H_2 receptor antagonists and they are the most widely used agents. However, as Table 9 shows, no drug is capable of healing 100% of DUs. Why this is so, is not known.

TABLE 9. Healing of duodenal ulcers on 12 different drugs and on placebo (modified from Wormsley, 1981)

Drug	No. of patients	No. of trials	% healed
Placebo	1893	—	42
Cimetidine	1739	46	73
Ranitidine	241	8	80
Pirenzepine	505	20	56
Anticholinergics	83	5	72
Antacids	172	7	66
DeNol	266	12	78
Caved S	53	2	62
Carbenoxolone	258	13	64
Trithiozine	324	7	53
Trimipramine	109	3	70
Sucralfate	297	9	75
Gliptide	54	2	63

Prevention of relapse of duodenal ulcer or gastrointestinal ulcer

Prevention of relapses of DU (or of GU) is a major problem for medical treatment and it is the failure to control the symptoms that in the uncomplicated case ultimately results in operation. Apart from one study of maintenance therapy of DU with sucralfate (Classen *et al.*, 1982), ranitidine and cimetidine are the only drugs shown in controlled trials to decrease the rate of relapse of DU or GU during periods of 6 to 12 months. Table 10 summarizes studies in DU with cimetidine 400 mg daily or 400 mg twice daily during one year. Long-term therapy with cimetidine substantially decreases the chances of a symptomatic relapse, but despite continued medication the relapse rate may reach 25%. The reason for this is not clear. Low compliance with the treatment must be a factor, although it has never been studied systematically in substantial numbers of patients. There is an appreciable incidence of asymptomatic recurrence of DU in the cimetidine and in the placebo-treated patients. Symptom-free recurrence means nothing to the patient, who is interested in relief of the dyspepsia and pain. The doctor, however, will be concerned that even a symptomless reappearance of the DU crater may herald an early return of pain, or continued risk of complications. How to manage these symptomless recurrences is at present not clear. Nor is it certain how many patients, after an apparently successful vagotomy for DU, have had silent recurrences and eventually present as operative failures.

Maintenance treatment of DU with ranitidine is

carried out with one 150 mg bedtime dose. Hunt *et al.* (1982) compared ranitidine 150 mg with cimetidine 400 mg, given at night to 61 patients with healed DU. The results were very similar on both treatments—a 25% annual recurrence rate, with three and five asymptomatic recurrences on ranitidine and cimetidine respectively. In a study of 248 patients with healed DU treated with ranitidine 150 mg at night, Boyd *et al.* (1982) reported an annual symptomatic relapse rate of 14%, which compares with the reported 19% symptomatic relapse rate of patients maintained on cimetidine 400 mg. Inclusion of asymptomatic re-ulcerations increased the relapse rate to 25% per year.

TABLE 10. Summary of maintenance trials of cimetidine in duodenal ulcer: comparison with placebo (Burland *et al.*, 1978)

Patients at entry	Cimetidine g/day	Recurrences	
		% symptomatic	% asymptomatic
179	0.4	13.4 (24)	5.3 (75)
184	0.8	13.0 (24)	9.3 (75)
333	Placebo	47.4 (158)	30.0 (73)

The number of patients examined is given in parentheses.

Published experience of long-term maintenance trials with H_2 histamine receptor antagonists in GU is less abundant. Each of three studies comprising a total of 75 patients with healed GU given 0.8 or 1 g cimetidine daily for one year reported a significantly lower relapse rate (0–18%) on cimetidine than on placebo (44–64%) (Birger Jensen *et al.*, 1979; Kang Canalese and Piper, 1979; Machell *et al.*, 1979). However, in another 6-month trial on 31 GU patients, cimetidine 800 mg daily was no better than placebo in preventing GU relapse (La Brooy *et al.*, 1980). The relapse rate of GU on ranitidine 150 mg at night for 6 months was 7% (1 of 15 patients), while it was 44% (7 of 16 patients) on placebo. An open, multicentre study showed a cumulative relapse rate of GU on ranitidine of 17% at one year (Cockel Dawson and Jain, 1982).

Thus the relapse rate of DU, and probably also of GU, can be significantly decreased during medication with ranitidine or cimetidine. Studies of incidence of recurrent ulcer after maintenance therapy with histamine H_2 receptor antagonists is stopped do not suggest that the natural history of the disease is altered by a period of successful maintenance therapy. As the DU diathesis persists for many years, the patient is therefore faced with a very prolonged period of medical treatment. For how long and in what manner this should be done has not yet been settled. In some patients, for example in those with cardiorespiratory insufficiency, the risks of operation are unacceptable and long-term medication is the

answer, but the solution is less clear in others. On clinical grounds, those with continuous symptoms should be given continuous treatment, while it is perhaps best to treat those with well-defined relapses and remissions with intermittent short courses.

Now that there is a choice between surgical and medical management of uncomplicated DU, the decision whether or not to operate has to be arrived at with the fullest participation of the patient, following a careful and detailed explanation of advantages and disadvantages of each course of action. In GU most physicians would still advise early operation if the ulcer does not heal, or recurs after a period of medical treatment.

Modern medical management of peptic ulcer is now seen to provide opportunities of treatment with many drugs possessing widely differing pharmacological properties and modes of action. In the short term, these compounds alter the balance between attack by acid, pepsin, bile and other environmental and intraluminal agents on the one hand, and mucosal defence on the other. This heals ulcer in most patients. Healing can be maintained by long-term therapy with ranitidine, or cimetidine, but there is no evidence that the natural history of ulcer disease is affected and the relapse rate is appreciable. The long-term effect on the incidence of surgery in peptic ulcer is as yet unknown, although decreased rates of ulcer operations have been reported from various centres. Another factor may be a change in the clinical attributes of peptic ulcer diathesis. Despite all these changes and advances, the principles established by FAJ of early and accurate diagnosis and vigorous, scientifically based treatment, remain valid. The close cooperation between medical and surgical gastroenterologists which has been FAJ's practice in his Department at Central Middlesex Hospital continues to be important in the treatment of patients with acid-pepsin disease.

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