The amount of cimetidine used by hospitalized patients is more difficult to estimate directly, but such use is widespread. In addition to being used in patients with ulcer disease, the drug has been used to prevent and treat stress-related gastritis and bleeding (39,100). Many physicians are probably using cimetidine in seriously ill patients who are susceptible to gastrointestinal hemorrhage (48). A recent randomized trial of patients hospitalized in an intensive care unit found that regular antacid therapy is more effective than cimetidine in preventing gastrointestinal bleeding (117).

From a commercial viewpoint, cimetidine is a spectacularly successful product. In 1977, cimetidine was marketed in 65 countries; in 1978, it was sold in 90 countries. In 1977, SmithKline reported sales of gastrointestinal drugs of $90.5 million; in 1978, sales of these drugs were $315 million. In its 1978 annual report, SmithKline stated that Tagamet® was its most important single product (135). Worldwide sales to hospitals and pharmacies in 1979 probably exceeded $400 million. This translates into a rough estimate of 10 million patients per year consuming cimetidine worldwide .10 A conservatively estimated 1.5 million to 2 million ambulatory U.S. patients with ulcer disease and ulcer-like symptoms were treated with cimetidine in 1978.[11]

Cimetidine has thus become one of the most widely used pharmaceuticals in the world in a remarkably short time. Part of the reason for this success rests in the widespread prevalence of ulcer disease and ulcer-like symptoms. SmithKline pioneered and persevered in developing and marketing a new class of pharmaceutical agents. Furthermore, as discussed in the next part of this case study, a substantial number of controlled trials attest to the effectiveness and relative safety of this drug in the treatment of ulcer disease.

[10]This estimate follows from high and low estimates, as shown:

	High estimate	Low estimate
Retail value of sales	$500 million	$300 million
– Retail price per tablet	$0.25	$030
= Number of tablets (A)	2 billion	1 billion
Weekly number of tablets	28	28
x Mean weeks of treatment	5	6
= Number of tablets patient (B)	140	168
Estimated number of patients (A/B)	14,300,000	6,000,000

[11]This estimate is based on a conservative projection of the numbers of Americans living at home who report ulcer disease in 1968 and 1975 and the proportion who visit their physicians for this problem at least once in the year (36).

THE BENEFIT-AND-COST MODEL APPLIED TO CIMETIDINE

Elements in the Analysis

The major components of the benefit-and-cost model presented earlier in this case study are shown in table 9. Listed under each component are a number of measures pertinent to cimetidine. Ideally, benefit and cost estimates would be made separately for each class of patients that might be treated with cimetidine. The basis for separating groups of patients could be demographic features (e.g., age, race, sex), clinical diagnosis (e. g., duodenal ulcer, gastric ulcer, Zollinger-Ellison syndrome), or stage of disease (e.g., number of days since diagnosis, previous treatments, complications).

Figure 4 is a paradigm decision-tree that displays the sequence of decisions and chance events that follow from the initial choice of intervention in a particular group of patients with ulcer disease. Clearly, the model requires a very large amount of data. It is not possible in this review to discuss potential sources of data for every estimate that follows each choice of strategy. Rather, we select for discussion the major elements of information required by the model and the available evidence.

Our primary emphasis is on patients with duodenal ulcer, the most common form of ulcer disease; we discuss patients with gastric ulcer in less detail. In addition to being used in these patients, cimetidine is sometimes used in patients with gastrinoma.[12] The traditional treatment for patients with gastrinomas includes gastrectomy

[12]This is a gastrin-secreting tumor, usually located in the Pancreas. It causes the Zollinger-Ellison syndrome of severe ulcers, intractable pain, and diarrhea. First described in *1955*, the Zollinger-Ellison syndrome has been recorded in more than *2,000* cases in the literature (101).

Table 9.—Components and Measures of Components in a Benefit-and-Cost Analysis of Cimetidine

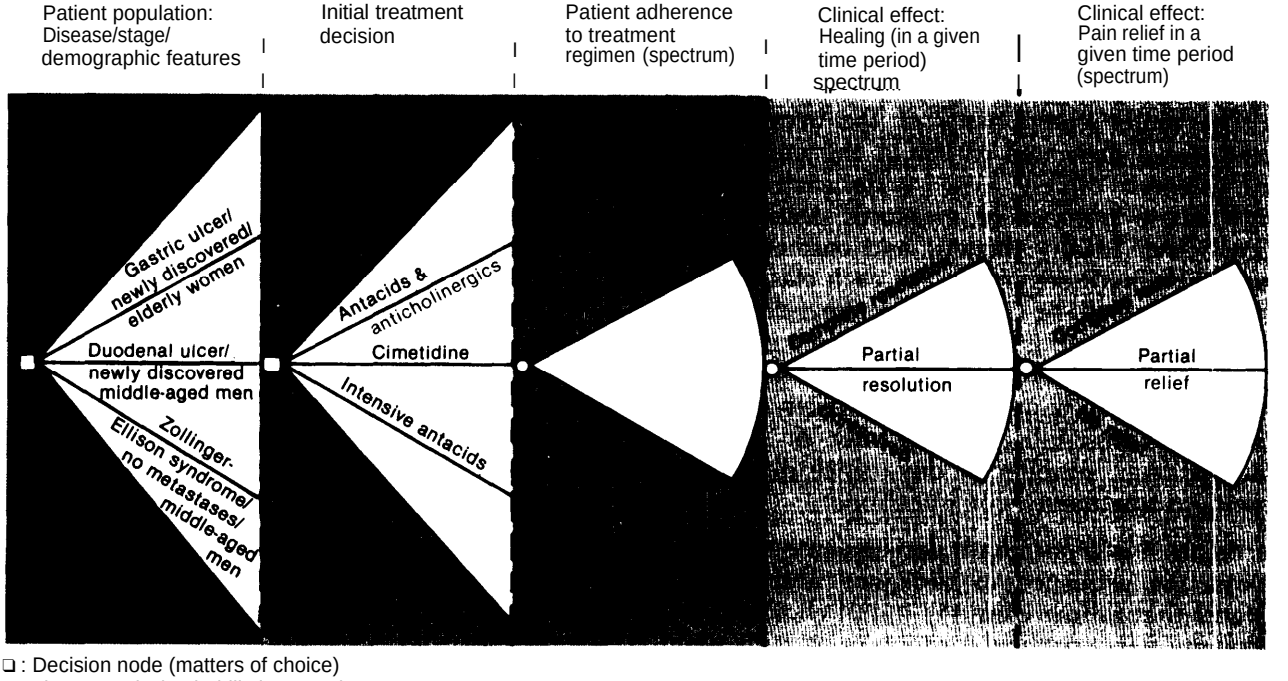
Clinical *effects*	• Number/time period
Short-term	Hospitalization
• Healing	• Number/time period
• Relief of symptoms	• Duration
• Side effects and adherence	Surgery
• Complications	• Number/time period
• Recurrence	• Type
Long-term	Other
. Recurrence	• Non-M. D. provider visits
• Side effects and adherence	• Nursing care
• Complications	Outcome
Health system effects	Health
Medication	. Mortality
• Antacids	—Number of deaths
• Anticholinergics	—Age-adjusted mortality
. Diet	—Years of life lost
. Other	• Morbidity
Diagnostic tests	—Days and severity of pain
Ž Laboratory	— Days of disability
• Monitoring chemistries	Resource costs and savings
. Imaging	• Days of work lost
—X-ray	—Premature death
—Endoscopy	—Temporary and permanent disability
• Physiologic function	• Cimetidine purchase
• Gastric acid	• Implications of health system effects
Physician visits	

(excision of the whole or part of the stomach) time of surgery for the primary tumor, but cimetidine has been employed successfully **as an** alternative to gastrectomy in these patients (99,138). Because of the rarity of gastrinoma as a cause of ulcer disease, the costs and benefits of the use of cimetidine in patients with this disease are not significant from a societal viewpoint. Since the clinical value of cimetidine for nonulcer disease such as dyspepsia (94) and upper gastrointestinal hemorrhage (41) is outside the scope of this report, we do not address it below. We limit our focus to elements of the cost effectiveness of cimetidine in peptic ulcer disease and do not attempt a global assessment of the value of this drug.

Clinical Effects

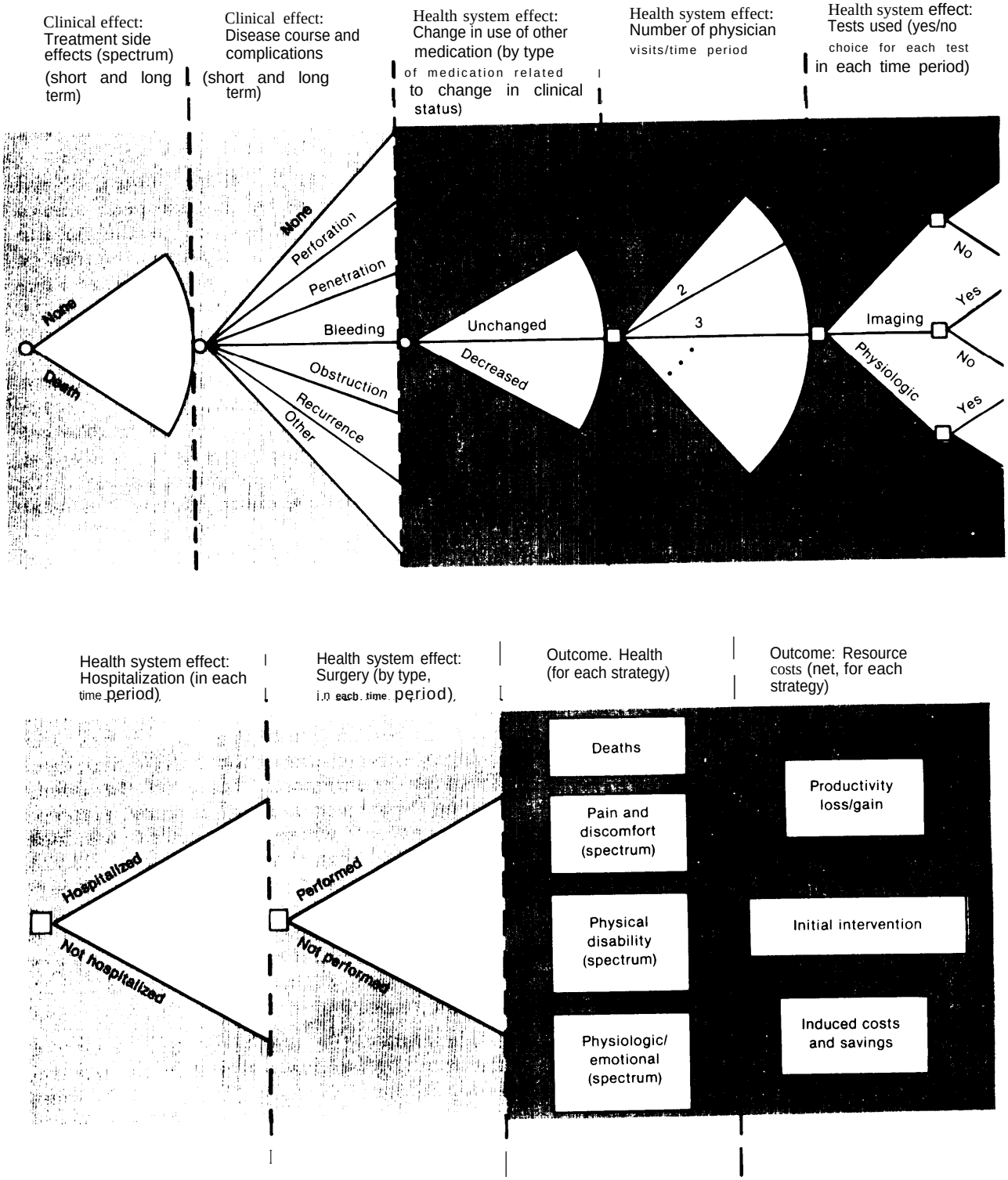
No treatment for duodenal ulcer has been subjected to as many randomized, controlled, double-blind studies as cimetidine has (68). These studies of cimetidine vary in their methodological stringency and completeness. In a review of the quality of 10 published, randomized, controlled trials of H_2 antagonists (includ-

Figure 4.—Paradigm Decision Tree: Cimetidine and Alternative Intervention Strategies



❑ : Decision node (matters of choice)
O: Chance node (probabilistic events)

Figure 4.— Paradigm Decision Tree: Cimetidine and Alternative Intervention Strategies (Continued)



❑ Decision node (matters of choice)
O Chance node (probabilistic events)

ing several on metiamide), Chalmers, et al. (25) rated only one "poor"—a record that compared quite favorably with Chalmers, et al. 's assessment of clinical trials of other treatments for ulcer disease.

There is one important methodological difference between the controlled studies of ulcer disease done in the 1970's and those done earlier. In the more recent studies, fiberoptic endoscopy replaced gastrointestinal X-rays as the means used to verify the presence and healing of ulcers. This direct visual confirmation of ulcer status can reduce diagnostic errors and consequent variability in experimental results. As a result, endoscopy-controlled studies may be more likely to find statistically significant differences in the clinical effectiveness of various treatments,

In addition to controlled studies, several symposia have been devoted to cimetidine (22,52, 150), and a number of review articles have appeared in major medical journals (e.g., 48,126). This work has provided reliable information that can contribute to estimates of clinical benefits and risks in a CEA, but a number of important areas of uncertainty remain.

Short-Term Clinical Effects

HEALING

At least 10 double-blind, placebo-controlled studies examining the short-term clinical effects of cimetidine in patients with duodenal ulcers have been published in the English language. Together these 10 studies (see table 10) provide compelling evidence that cimetidine promotes healing of duodenal ulcers. Overall, the rate of healing in 4 to 6 weeks among cimetidine-treated patients was approximately 70 percent, almost twice the level achieved by placebo-treated patients (36 percent). Similar results were obtained in a half-dozen additional studies conducted in France, West Germany, Italy, and Spain (7).

One notable exception to the almost uniformly significant findings of cimetidine's superiority over placebo is the large, multicenter U.S. study by Binder, et al. (11). Among outpatients assessed at the end of 4 and 6 weeks (57 on cimetidine; 54 on placebo), no significant differences were observed in the proportions healed (67 and 56 percent, respectively). [t is evident that the statistical conclusions from this study are different from the others not because of worse performance of cimetidine, but because of a substantially higher rate of healing within the placebo group.

It is possible that the patients in the U.S. trial differed from those in the European studies either because of differences in the natural history of the disease in different countries or because the U.S. subjects tended to be at a different stage of illness. For example, some of the earlier European studies were restricted to patients who were considered candidates for surgery. The importance of criteria for patient selection and evaluation, as well as possible variation in the course of disease in different countries, was stressed in a Swiss study that found a very high proportion of patients with peptic ulcer healing under placebo treatment (125).

It is possible that the discrepant results are partly related to differences in antacid consumption. With one exception (108), all the controlled studies permitted ad libitum antacids for all patients. Patients in the European studies were usually provided tablet antacids, which are less potent than the type of liquid antacid used in the U.S. study (81,106). Overall, the U.S. patients consumed more antacid than their European counterparts. More to the point, among the subjects in the U.S. study, placebo-treated patients whose ulcers healed consumed more antacid than those whose ulcers did not heal. (Mean antacid consumption was 12 percent higher among inpatients whose ulcer healed and 112 percent higher among outpatients than in those whose ulcers failed to heal; differences in median antacid consumption were 68 and 21 percent, respectively.)

This raises the possibility that a partial therapeutic effect was realized in the placebo group in the U.S. study. Underlying this possibility is the assumption that antacids promote ulcer healing. Antacids have been shown in at least two endoscopy-controlled studies to have a greater effect than placebo on healing of duodenal ulcer (93,116). One, a study by Lam, et al.

Table 10.—Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect **on Duodenal Ulcer Healing**

Study	Investigator[a] year/country	Cimetidine daily dose (grams)	Duration (weeks)	Placebo		Cimetidine		Cimetidine v. placebo; significant difference (ps0.05)
				Number of patients[b]	Number/o/. healed	Number of patients[b]	Number/o/o healed	
D1	Bank, et al. (6) 1976/South Africa	1.2 1.6	6	19 (19)	8 (420/o)	8 (8) 11 (11)	7 (86%) 9 (82°/0)	Yes (p< 0.01)
D2	Bardhan, et al. (8) 1979/United Kingdom	1 2	4	46 (50)	13 (28°/0)	70 (78) 64 (72)	43 (61 %) 45 (70%)	Yes (p< 0.001)
D3	Binder. et-al. (11) 1978/United States	12	2 (inpatient)	49 (53)	18 (37%)	43 (45)	24 (56%)	Yes (p< 0.05)
			2 (outpatient)	27	7 (260/.)	26	12 (46%)	Yes (p< 0.05)
			4 (outpatient)	27 (103)	13 (48°/0)	28 (107)	16 (570/')	No
			6 (outpatient)	27	17 (63%)	29	22 (76%)	No
D4	B-lack wood, et al. (13) 1976/United Kingdom[c]	1.6	6	12 (NA)[d]	3 (25%)	11 (NA)[d]	9(82%)	Yes (p< 0.025)
D5	Bodemar and Walan(15) 19761 Sweden	0.8 1.2	6	14 (15)	2(1 4°/0)	15 (15) 15 (15)	12 (80°/0) 14 (93°/0)	Yes (p< 0.001)
D6	Gray, et al. West Germany	1	4	20 (20)	5 (20°/0)	20 (20)	17 (850/o)	Yes (p< 0.0005)
D7	Hetzel, et al, (76) 1978/Australia	1.2	6	42 (44)	16 (380/o)	43 (44)	36 (840A)	Yes (p< 0,001)
D8	Moshal, et al. (108) 1977/South Africa	0.8 1.2	6	19 (21)	8 (42°/0)	19 (40) 17	14 (74°/0) 11 (65%)	Yes (p< 0.05)
D9	Northfield and Blackwood (1 10) 1977/United Kingdom[e]	1.6	6	21 (NA)[d]	4 (19°/0)	21 (NA)[d]	13 (620/o)	Yes (p< 0.05)
			12	15)	4 (27%)	17	15 (88°/0)	
D10	Semb, et al. (129) 1977/Norway	1.2	4	20 (20)	12 (60°/0)	20 (22)	17 (850/o)	No

[a]Numbers in parentheses refer to references listed at the end of this case study
[b]Numbers, n parentheses are numbers entering study
[c]Patients included in study D9
[d]NA Not available
[e]Includes Patients from study D4

SOURCE Modified after K D Bardhan Cimetidine in Duodenal Ulceration '' 1978 (7), and D H. Winship, ''Cimetidine in the Treatment of Duodenal Ulcer,'' 1978 (154)

(93) found that 20 (77 percent) of 26 Chinese patients experienced ulcer healing after 4 weeks' treatment with aluminum-magnesium antacid tablets (25 mEq per dose; seven doses per day). Only 8 of 24 patients treated with placebo experienced healing at the end of 4 weeks, a significantly lower fraction ($p < 0.005$). Relatively low doses of antacids were effective in the Lam study; Chinese patients have similar parietal cell masses and lower acid production than Occidental patients (93). The second study, by Peterson, et al. (116) in the United States, used higher doses of liquid aluminum-magnesium antacid (150 mEq per dose; seven doses per day). In this double-blind trial, 28 (78 percent) of 36 patients on high-dose antacids experienced healing ulcers at 28 days, compared to 17 (45 percent) of 38 patients on placebo ($p < 0.005$). A recent British review, prompted by the lesser reliance on antacids by British clinicians com-

pared to Americans, concluded that antacids were effective in promoting healing of duodenal ulcer (106).

Notice that the rates of healing with antacids in the Lam (93) and Peterson (116) studies (77 and 78 percent, respectively) are much higher than the healing rate (56 percent) in the placebo group using ad libitum antacids in the multicenter U.S. trial of cimetidine (11). In fact, the healing rates with antacids in the Lam and Peterson studies were even higher than the rate of healing with cimetidine (67 percent) in the U.S. multicenter trial (11)

This observation leads to an important question: Is cimetidine more effective than a concerted antacid program in promoting ulcer healing? The question is important because a CEA should seek to compare the incremental effects of competitive alternatives with one another, as well as with a do-nothing strategy.

It is statistically unsound and maybe misleading to compare selected groups from different studies. Fortunately, at least one randomized, double-blind study has compared cimetidine with intensive antacid therapy in patients with duodenal ulcers (80). This multicenter trial found that in 15 (52 percent) of 29 patients taking antacids seven times daily, and in **40 (62** percent) of 65 patients taking cimetidine, ulcers healed after 4 weeks .13 The rate of healing in patients taking cimetidine was not significantly better than the rate in patients taking antacid ($p > 0.1$), and the authors concluded that "800 and 1,200 mg of cimetidine daily produced duodenal ulcer healing and pain relief equivalent to 210 ml of Al-Mg antacid daily" (80).

This conclusion should be qualified. Conventional tests of significance, as employed by these investigators, are concerned with the risk of falsely rejecting the null hypothesis of "no difference" between treatments (the a or type I error). In the Ippoliti study, the observed difference did not justify a conclusion to reject the hypothesis of "no difference" at a 95-percent level of confidence. However, also of concern is the complementary error, namely the failure to reject the null hypothesis when in fact a difference in treatment outcomes in present (the B or type 11 error) (49). This error, which may be clinically important, has been overlooked frequently in trials of the treatment of duodenal ulcer (27), as well as in other medical research (54).

We have estimated that if cimetidine truly healed 10 percent more ulcers than did antacids (62 v. 52 percent, the findings of the Ippoliti study), then, given the number of patients in the trial, there was less than one chance in three that the investigators would have found a statistically significant difference.[14] This would argue for a more tentative clinical conclusion. It argues as well for more extensive research on the questions of the relative clinical effectiveness of cimetidine and antacids. [15]

Several double-blind randomized trials have compared cimetidine to placebo in patients with gastric ulcer. These are summarized in table 11. (A number of additional reports of interim results (150) and studies without endoscopic assessment of healing (95) are excluded.) Two of the European trials—one by Bader, et al. (5), the other by Frost, et al. (56)-—found a statistically significant improvement in healing with cimetidine at 4 and 6 weeks, respectively. However, this finding was not borne out in the trials by Ciclitira, et al. (28) and Dyck, et al. (40). The latter trials did tend to favor cimetidine (14 percent more patients healed at 4 weeks in the Ciclitira study (28) and 19 percent more at 6 weeks in the Dyck study **(40)),** but these differences were not statistically significant. The point made above concerning the chance of B-error applies to the interpretation of these studies as well. Also pertinent is the earlier discussion of the tendency of U.S. patients to consume greater

[13] The cimetidine patients were divided into two groups with different dosage regimens: 33 patients received 1,200 mg daily and 21 (64 percent) experienced healing; 32 patients received 800 mg daily and 19 (59 percent) experience healing.

[14] More precisely, given the stated assumptions, the power of the experiment $(1 - \beta)$ is estimated to be 0.68.

[15] Ippoliti has conducted a second, unpublished randomized trial of patients with duodenal ulcers, treating 65 patients with cimetidine and *62* patients with an intense antacid regimen. In this study, the proportion showing healed ulcers at 4 and *6* weeks was virtually identical in the two groups. At 4 weeks, the proportions with healed ulcers were 62 percent for patients taking cimetidine and 66 percent for patients taking antacids; at 6 weeks, the proportions were 85 percent and 84 percent, respectively (67).

Table 11 .—Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Gastric Ulcer Healing

Study	Investigator[a] year/country	Cimetidine daily dose (grams)	Duration (weeks)	Placebo		Cimetidine		Cimetidine v. placebo; significant difference (p<0.05)
				Number of patients[b]	Number/O/O healed	Number of patients[b]	Numberl% healed	
G1	Bader, et al. (5) 19771 France	1	4	27	10 (37°/0)	26	18 (690/o)	Yes (p <0.02)
G2	Ciclitira, et al. (28) 1977 United Kingdom	1	4	25	13 (52%)	35	23 (66°/0)	No
G3	Dyck, et al. (40) 19781 United States	1.2	2	28	4 (14%)	29	7 (24%)	No
G4	Frost, et al. (56) 1977/ United Kingdom	1	6	22	6 (270/o)	23	18(78°/0)	Yes (p< 0.002)

[a]Numbersin parentheses refer to references listed at the end of this case study

SOURCE Based on J W Freston, "Cimetidinein the Treatment of Gastric Ulcer Review and Commentary," 1978 (55), and H R Wulff and S J Rune, "A Comparison of Studies on the Treatment of Gastric Ulceration WithCimetidine, 1978 (156)

amounts of antacid, which hinders comparison among studies done in the United States and Europe.

The effectiveness of antacids alone in the healing of gastric ulcer is debatable, with controlled studies reaching conflicting conclusions (55). One multicenter, randomized study of patients with gastric ulcer in the United States compared three treatment regimens: cimetidine alone, antacid alone, and cimetidine plus antacid (43). This study found no significant differences in healing among these three groups at 12 days or 6 weeks.[16] N. control group taking placebo only was included, apparently because of ethical concerns about withholding a potentially effective treatment (i. e., antacids) from all patients (55). This omission, subsequently lamented by at least some of the investigators (53), leaves open the question of whether treatment with either cimetidine or antacids is superior to placebo in patients with gastric ulcer.

In summary, cimetidine has been shown conclusively to promote healing of duodenal ulcer, and some evidence suggests it is more effective than placebo in patients with gastric ulcer .17 In general, European studies have found more favorable results with cimetidine than have U.S. trials. In patients with gastric ulcers, cimetidine has not been shown convincingly to be more effective than an intense course of antacids. Whether cimetidine is more effective than an intense antacid program in healing duodenal ulcers is still open to question. Of course, promotion of healing is only one aspect of short-term clinical performance (see table **9,** p. **26).**

PAIN RELIEF

Seven of the 10 randomized, controlled studies of duodenal ulcer listed in table 10 also compared cimetidine to placebo in terms of pain relief. Those findings are summarized in table 12. Comparison across studies is complicated by the variety and subjectivity of measures employed. These measures include frequency of painful days and nights, number of pain-free weeks, severity of pain, proportion of asymptomatic patients, and days of treatment required to achieve symptom relief. An additional *com*plication arises because the time frame for meas-

[16]After 12 days, 16 percent of 67 patients taking antacids, 20 percent of 71 patients taking cimetidine, and 25 percent of 65 patients taking both experienced ulcer healing: after 6 weeks, the results were, respect ivel y, 61 percent of 62 patients, 59 percent of 68 patients, and 70 percent of 60 patients.

[17]In addition to cimetidine and antacids, three other drugs have been shown in controlled clinical trials to promote healing of ulcers better than a placebo: colloidal bismuth, carbenoxolone, and trimipramine *(139).* None is now used for this purpose in the United States.

Table 12.—Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Duodenal Ulcer Pain Relief

Study[a]	Summary of results
D1	Cimetidine group asymptomatic for mean of 4 out of 6 weeks; placebo group free of symptoms for a mean of 2.4 out of 6 weeks; in other words, the cimetidine group had a 44% reduction in the mean number of weeks with some pain. (Statistical significance not reported.)
D2	Cimetidine group experienced a 34% reduction in days with pain and a 36% reduction in nights with pain compared to the placebo group. Differences in the frequency of pain were significant in each of the 4 weeks of the study ($p < 0.005$).
D3	Inpatients: significantly more patients taking cimetidine than taking placebo had day and night pain relief at the end of 3 days (61 v. 30%; $p < 0.01$); difference not significant at the end of 1 week (69 v. 55%). Outpatients: significantly more patients taking cimetidine had day and night pain relief at the end of 1 week (45 v. 31 *o/c; p < 0.05);* difference not significant after the first week.
D4	Not reported.
D5	Cimetidine group had "significantly lower pain score" (p range < 0.02 to < 0.1) both day and night during the first 3 weeks (method of measurement and computation not fully explained). After 3 weeks, cimetidine group had "significantly" ($p < 0.1$) less day pain in weeks 5 and 6.
D6	Cimetidine group had significantly more pain-free days each week of the study ($p < 0.01$).
07	Not reported.
Da	At the end of 6 weeks, cimetidine group had significantly more asymptomatic patients (780/') than did the placebo group (47°/0) ($p < 0.025$).
D9	Not reported.
D10	Cimetidine group required significantly fewer days to achieve symptom relief (8.1 ± 9.9 [S. D.]) than did the placebo group (20.6 ± 9.1 [S.D.]) ($p<$ 0.01).

[a]See table 10 for investigator, year, and country

urement varies from study to study. Nonetheless, these studies fairly consistentl$_y$ report greater pain relief with cimetidine than with placebo. Again, the multicenter U.S. trial (11) shows less striking differences than the other trials.

The Ippoliti study (80) comparing cimetidine to antacid found prompt symptom relief with both treatments (55 percent of cimetidine-treated patients and 58 percent of antacid-treated patients became asymptomatic by day). At the end of 4 weeks' treatment, 63 percent of patients taking antacids and 80 percent of those taking cimetidine were asymptomatic, a difference that was not statisticall$_y$ significant ($p > 0.1$).

Placebo-controlled studies of patients with gastric ulcer varied in the extent to which cimetidine-treated groups experienced more rapid or complete pain relief than those treated with antacids (see table 13). The Englert study (43) comparing antacids and cimetidine found similar symptom response in all groups.

Investigators differ in their conclusions about the correspondence between ulcer healing and pain relief. Several investigators report a poor correlation between healing and symptom relief (e.g., 6,62,108), and others say the correlation is good (e.g., 8,61,80). Part of the reason for differing assessments may be a difference in what various investigators consider a good or a poor correlation. For example, Bardhan (8) found the association between healin$_g$ and symptom relief to be significantl$_y$ different from what would have been expected to occur by chance. On the other hand, the same data show that the abilit$_y$ of pain relief to predict ulcer healing is not very strong. [18]

As in our discussion of B-error above, this points out the important distinction between the interpretation of results based on statistical criteria and that based on clinical criteria: Results that fail a test of statistical significance may still be clinicall$_y$ meaningful; conversely, statisticall$_y$ significant differences may not be particularl$_y$ meaningful clinically. The degree of association between healing and pain relief is pertinent to a cost-effectiveness assessment, because a patient's decision to return to normal activity depends at least as much on symptoms as on the physical repair of the ulcer. If estimates of a drug's comparative effectiveness in returnin$_g$ patients to work are based primaril$_y$ on healing, the$_y$ may be misleadin$_g$ insofar as

[18]The probability of ulcer healin$_g$ given symptom improvement is *50 60 = 0.77,* and the probabili t y of nonheal ing given no improvement in symptoms is 42/72 = 0.58. These are not particularly large predictive values. In the Ippoliti study (80), the corresponding values are a bit lower in the first case (42 '60 = O 70) and somewhat higher in the second (18 20 = 0.90).

Table 13.—Short-Term, Double-Blind, Placebo.Controlled Studies of Cimetidine: Effect on Gastric Ulcer Pain Relief

Study[a]	Summary of results
G1	Patients taking cimetidine tended to have more rapid and greater relief of pain, but differences were not statistically significant.
G2	Cimetidine-based group had significantly fewer attacks of pain during each week of the study.
G3	No systematic or significant differences in the severity or frequency of pain at 2 weeks or at 6 weeks between the cimetidine-treated and placebo-treated groups.
G4	Group taking cimetidine had fewer days of pain, but differences were not statistically significant.

[a]See table 11 for Investigator year and country

pain relief and healing do not correspond to one another, Almy (2) suggests a further possibility if a patient returns to work after symptoms have remitted but before healing has occurred: Workdays gained might be lost later on owing to late consequences of unhealed ulcer.

In summary, evidence from most controlled, double-blind studies suggests that cimetidine promotes faster and more complete pain relief than does a placebo in duodenal ulcer, but not necessarily in gastric ulcer. An intense antacid program appears to be about as effective as cimetidine, but more evidence on this question is needed. The correspondence between healing and symptom relief is imperfect: The association is not random, but relief of symptoms is not a reliable clinical predictor of healing.

SAFETY AND ADHERENCE

No pharmacologic agent is perfectly safe. A drug's side effects depend on its toxicity, the dosage and duration of administration, and the individual susceptibility of the patient. The importance of side effects of any one treatment should be judged in relation to the severity of the disease being treated and the risks of alternative interventions.

Before turning to cimetidine, let us briefly consider the alternative of antacid therapy as a baseline. Unlike cimetidine, the Al-Mg antacid suspensions usually prescribed are, for the most part, not systemically absorbed. The most common adverse side effect of these antacids is diarrhea, which is related to the dose of magnesium salts. In studies with intense antacid regimens, **27** percent (80) and 36 percent (43) of patients taking antacids developed diarrhea. In the Peterson study (116) comparing antacids with a placebo, 66 percent of the antacid group and 21 percent of the placebo group were switched for at least 7 days to an alternative medication because of diarrhea. Mild diarrhea may not be very important medically, but this effect, along with the need for frequent administration, does discourage patient adherence to high-dose antacid regimens. Aluminum salts bind phosphate ions, and this may produce hypophosphatemia in patients who have intestinal malabsorption problems. This rare consequence may be countered by selecting a different type of antacid or giving phosphate supplements. [19]

Cimetidine in short-term use has been associated with a wide range of side effects. The manufacturer instituted a formal, postmarked surveillance system that covered 9,907 ambulatory patients and found a total of 577 adverse events in 442 patients (4.4 percent of all patients) (59). Only a fraction of the adverse events were believed to be attributable to cimetidine; for example, 30 of 254 adverse gastrointestinal events occurred in circumstances that strongly suggested an association with cimetidine. No deaths were attributed to use of the drug. An extensive review by Kruss and Littman in 1978 (92) of publications, manufacturers' files, and submissions to FDA concluded that cimetidine was safe enough to be used in patients with duodenal ulcer disease for up to 8 weeks, and indeed, this is the use currently approved by FDA. A high proportion of patients develops clinically insignificant elevations in serum creatinine which resolves promptly with cessation of therapy (92). Gynecomastia (excessive development of breast tissue in males) has been reported in under 1 percent of patients on short-term treatment; the incidence increases

[19]A different array of metabolic problems may follow use of calcium carbonate antacid (which is absorbed systemically), but since this is not usually prescribed by physicians in the United States, we will not consider it further

with longer term use (72). Mental confusion (102), reversible hepatitis (145), and several cases of severe allergic reaction (33) have also been reported. Agranulocytosis, the principal problem with cimetidine's predecessor, metiamide, has been reported to occur transiently with cimetidine (32,90). In addition, at least one fatality due to aplastic anemia has been reported in association with cimetidine (26).

Recent bacteriological studies of the gastric juice of patients before and after 4 weeks' treatment with cimetidine found major increases in total bacterial counts, including large numbers of fecal-type organisms, following treatment (122), This effect, noted after short-term use, would be of greater concern with long-term use of cimetidine, as explained below. The principal determinant of gastric flora in humans is the acidity of the stomach, and increases in fecal types of bacteria are found in the stomachs of achlorhydric patients such as those with pernicious anemia (38). Patients with pernicious anemia have long been recognized to have a significantly increased risk of developing gastric cancer (107). Possibly, the increased incidence of cancer is related to the metabolic activity of fecal-type bacteria that reduce nitrates and may lead to the development of carcinogenic N-nitroso compounds in the stomach (123). At present, however, this long-term risk of cimetidine (or any agent that chronically reduces gastric acidity) is speculative.

In the past year, new evidence has accumulated concerning the effects of cimetidine on the reproductive function in males. Earlier animal studies had clearly shown an antiandrogenic effect of large doses of cimetidine administered for 6 to 12 months (92). During the past year, at least one case of reversible impotence has been attributed to cimetidine (155). In addition, a study of seven patients with ulcer disease, duodenitis, gastritis, or esophagitis found a 30- percent reduction in mean sperm count after 9 weeks of cimetidine treatment; the luteinizing hormone response to luteinizing hormone-releasing factor was also reduced (144).[20] This study included no control group of ill patients not taking cimetidine. Sperm counts remained within the wide fertile range, but the antiandrogenic side effects of cimetidine should be evaluated further. [21]

Thus, cimetidine used for up to 2 months appears to be a relatively safe drug, but reported increases and shifts in gastric flora and endocrinologic effects are disturbing. Cimetidine is more risky than antacids, but less troublesome to the patient. The more extensively a drug is used, the more difficult it is to impute a causal relation to sporadically reported side effects or case fatalities. On the other hand, truly associated but rare side effects can affect substantial numbers of patients if a drug is very widely prescribed, as is cimetidine. One's attitude toward the safety of cimetidine depends in part on the weight placed on the possibility of unanticipated and remotely occurring side effects such as those that have occurred with other medications like diethylstilbestrol (75).

COMPLICATIONS

The major complications of ulcer disease are bleeding from the base of the ulcer, obstruction due to swelling or fibrosis, perforation through the intestinal wall into the peritoneal cavity, and penetration into the pancreatic bed. As noted previously, these complications are relatively uncommon and rarely occur as the initial manifestation of ulcer disease.

The principal question of interest here is whether short-term use of cimetidine alters the likelihood of near-term complications. Several British investigators have reported patients who developed perforation of peptic ulcers shortly after the cessation of cimetidine therapy (60,148). An increased risk of perforation following cimetidine therapy is not substantiated by controlled studies comparing longer term use of cimetidine and placebo following an initial course of cimetidine. These studies, discussed in the section on long-term clinical effects below,

[20]The mean sperm counts were 134.3 million per ml before cimetidine and 94.0 million per ml after treatment. The investigators state that the reduction was 43 percent, but this overstatement is apparently based on dividing the difference in mean sperm count (40. 3 million per ml[3]) by the final, rather than the initial, count,

[21]Additional studies are underway, according to FDA (5 I I.

assess whether maintenance doses of cimetidine can reduce the likelihood of ulcer recurrence,

ULCER RECURRENCE FOLLOWING SURGERY

Cimetidine has been used to treat ulcers that recur following surgery for ulcer disease. We are aware of two randomized, controlled trials of cimetidine's effectiveness in preventing ulceration after surgery (71,88). These studies reached different conclusions. In Britain, Kennedy and Spencer (88) compared cimetidine with placebo in patients who had undergone one of a variety of surgical procedures (including gastrectomy and vagotomy with and without a drainage procedure) and who, after surgery, had developed ulcers at various locations (stomach, duodenum, or jejunum). The 12 patients treated with 1 g of cimetidine daily did not show significantly more healing at 6 weeks than the 12 patients treated with placebo.

A more recent study in West Germany (71) was restricted to patients who had undergone partial gastrectomy and developed ulcers at or near the site of the surgery. After 4 weeks of treatment, ulcers had healed in six of seven patients treated with 1 g of cimetidine daily, but none of the eight treated with placebo had healed (difference significant, $p < 0.01$). After 8 weeks, all seven cimetidine-treated patients, but only one of eight placebo-treated patients had healed (difference significant, $p < 0.01$). The incidence of relapse after cessation of cimetidine and effects of maintenance on preventing recurrence after surgery have not yet been reported in controlled trials.

RECOMMENDATIONS FOR TREATING NEWLY DIAGNOSED, UNCOMPLICATED ULCER

Gastroenterologists differ in their recommended treatment for patients with newly diagnosed, uncomplicated duodenal ulcers. Some, stressing comparable rates of healing, long experience with antacids, and uncertainties attending any recently introduced drug, recommend an initial trial of intense antacid therapy (140). Others, impressed with cimetidine's performance and concerned about lack of patient adherence to an antacid regimen, prefer to use cimetidine (98).

The choice between antacids and cimetidine is clearly closely balanced. Rather than adopt either approach exclusively, a conscientious clinician might better weigh the choice for each patient individually, taking account of present uncertainties as well as each patient's personality and preferences. For example, patients vary in their willingness to persevere with antacids in the face of mild to moderately uncomfortable side effects. In addition, patients, as well as doctors, vary in their attitudes toward known and unknown risks. Thus, a young man trying to start a family would surely view possible antiandrogenic effects differently than would a woman or elderly man.

As times goes on, new evidence may reduce present uncertainties about the comparative benefits and risks of cimetidine. Individual patient characteristics and values might still make the preferred treatment different for different patients who are all classified in the same general diagnostic category.

Long-Term Clinical Effects

The use of cimetidine beyond the short-term treatment of ulcer may take two forms: 1) intermittent administration if symptoms or ulcerations recur, and 2) maintenance treatment with the aim of preventing ulcer recurrence.

Cimetidine is probably very commonly used for intermittent treatment of ulcers (7), but we are aware of no controlled studies comparing cimetidine to alternative approaches. One study (64) suggests that with cimetidine, healing of a second ulcer is slower than healing of an initial ulcer. In 25 patients with recurrent ulcers, **52** percent healed after 4 weeks of treatment with cimetidine compared to 76 percent who had healed within 4 weeks after diagnosis of their first ulcer. Interpretation of the results of this study, however, is clouded by differences in the initial treatment history of these patients and ambiguity in the report. For example, the 25 patients with recurrent ulcers included a majority whose first ulcers had been treated with cimeti - dine and others whose first ulcers had healed spontaneously. In addition, most of the 25 patients had been maintained on placebo, but an

unspecified number (between 1 and 7) had been maintained on low-dose cimetidine.

We are aware of no studies comparing maintenance cimetidine to maintenance antacids. Perhaps it has been assumed that few patients would adhere to long-term treatment with effective doses of antacids. Grossman (67) suggests that this might be reconsidered in light of the recent study by Lam, et al. (93), who found that relatively small doses of antacids given in the form of tablets were effective in promoting the healing of duodenal ulcers.

Most research on long-term use has compared maintenance doses of cimetidine to placebo (with antacids ad libitum). These studies form the basis for the following discussion.

ULCER RECURRENCE

Table 14 summarizes the results of six double-blind controlled studies, published in English, comparing maintenance cimetidine to placebo for periods ranging from 80 days to 1 year. Patients in these studies were given 400 or 800 mg of cimetidine daily. Investigators consistently report a statistically significant reduction in symptoms and recurrent ulceration during the period of treatment in the cimetidine-treated group compared to those given placebo. The consistency of results is particularly striking given the range of criteria used to select patients —with some studies including patients with recently treated new ulcers (e. g., 70), others limited to chronically ill patients (e.g., 16), and others restricted to patients considered candidates for surgery (e. g., 64).

The conclusions from these studies are reinforced by a recent review by Burland, et al. (23). These authors compiled results from 15 double-blind maintenance trials, either completed or in progress, involving 695 patients. Overall, the number developing recurrent ulcers while taking placebo appears to be twice that observed with maintenance cimetidine. Approximately 10 percent of patients treated with placebo and 50 percent of cimetidine-treated patients remained in remission during 12 months of treatment.

Table 14.—Controlled Trials of Maintenance Cimetidine in Peptic Ulcer

					Symptomatic relapse		Ulcer recurrence (by endoscopy)		
Study	Investigator year/country	Initial (premaint.) treatment	Duration of maint. (months)	Maint. treatment	Number analyzed	Number/% relapse	Number analyzed	Number/% recur	Difference significant ($p < 0.05$)
M1	Bardhan, et al. (9) 1979/United Kingdom	53 cimetid. 7 other	6	P bid	31	18 (58%)	27	20 (74%)	Yes
				C 400 mg bid	29	4 (14%)			(p< 0.005) recurrence
M2	Blackwood, et al. (13) 1976/United Kingdom	Not specified	6	P hs	24	12 (50%)	24	21 (88%)	Yes
				C 800 mg hs	21	8 (380/.)	21	5 (250/.)	(p< 0.0005) recurrence
M3	Bodemar & Walan (16)/ 1978/United Kingdom	65 cimetid. 3 other	12	P bid	36	30 (83%)	36	38 (83%)	Yes
				C 400 mg bid	32	12 (38%)	32	6 (38%)	(P< 0.0005)
M4	Gray, et al.(64) 1978/United Kingdom	52 cimetid. 8 other	6	P hs	30	24 (80%)	29	24 [83%)	Yes
				C 400 mghs	26	11(42%)	22	7 (32%)	
M5	Gudmand-Hbyer, et al. (70) 19781 Denmark	Not specified	12	P bid	25	20(80%)	—	—	Yes
				C 400 mg bid	26	3(12%)	–	—	(p< 0,1301)
M6	Hetzel, et al. (78) Australia	Not specified	2 2/3	P bid	31	10 (32%)c	—	—	Yes
						14 (4570)	—	—	
				C 400 mg bid	36	0			

[a]Numbers in parentheses refer to references listed at the end of this case study.
[b]P = placebo; C = cimetidine; bid = twice daily; hs = at bedtime.
[c]The report states in the same paragraph both that 10 patients on placebo suffered relapse and that 45 percent of those on placebo had relapsed

Results were identical with 400 and 800 mg of cimetidine daily.

The performance of different maintenance regimens may depend on the initial treatment received by patients. Those whose ulcers have healed initially with placebo, antacids, or cimetidine may differ in their susceptibility to recurrence. Consider the possibility that patients with newly developed ulcers fall into two clinically indistinguishable subpopulations, one (type A) being more resistant to treatment and prone to relapse than the other (type B). Now consider the hypothetical experimental situation illustrated in table 15. Seventy patients in each of two groups are assigned randomly to initial treatment with cimetidine or with antacids. In each group of **70, 40** are type A and **30** are type B. Both treatments produce healing in 75 percent of type A patients, but cimetidine is twice as effective as antacids **(67 v. 33** percent) in producing healing in type B patients.

After initial treatment, only those patients who have healed are followed for possible relapse. (In the case of maintenance studies, only patients initially healed are tested with maintenance therapy.) Assuming that a given proportion (one-third) of all type A patients and that a larger proportion (one-half) of all type B patients both relapse within 6 months, then cimetidine-treated patients will appear to be more prone to relapse (40 v. 38 percent). This can be true even when, as shown in the last column of table 15, cimetidine results in a greater fraction of the initial population of patients remaining asymptomatic.

Empirical evidence consistent with such an adverse selection of patients whose ulcers heal initially with cimetidine may be found in the results collected by Burland, et al. (23). Among patients treated with maintenance placebo, 245 (50 percent) of 290 patients initially treated with cimetidine developed symptomatic re-ulceration, compared to 9 (30 percent) of 30 patients initially treated with placebo (difference significant, p c 0.05). On the other hand, there may not be an adverse selection of patients who heal following cimetidine treatment as compared to those who heal after antacid treatment. Ippoliti followed patients with duodenal ulcer who had been assigned randomly to treatment for up to 6 weeks with a concerted antacid program or with cimetidine. 22 Among those whose ulcers healed, the rate of recurrence at 6 months (as determined by endoscopic examination at 3 and 6 months) was 54 percent among the 41 patients who had been treated with cimetidine and 60 percent among the 35 patients who had been treated with antacids.

Following cessation of treatment, patients who had been taking cimetidine begin to relapse at the same rate as the initial rate of relapse among patients who were treated with maintenance placebo. This important finding is demonstrated in the study by Gudmand-Høyer, et al. (70). Once it is discontinued, maintenance cimetidine appears neither to accelerate recurrence nor to effect any more permanent cure.

"Unpublished study (79).

Table 15.—Results of Treatment With Two Hypothetical Subpopulations of Ulcer Patients: Type A More Resistant to Treatment and Prone to Relapse Than Type B

Initial treatment	Starting population of patients	Response to initial treatment: Number healed (o/o of those entered)	Treatment discontinued: Relapse in 6 months after treatment discontinued: Number relapsed (o/o of initially healed)	Number remaining asymptomatic (% of starting population)
Cimetidine	Total = 70	Total = 50 (71 O/.)	Total = 20 (400/.)	30 (43°/0)
	Type A = 40	Type A = 30 (75°/0)	Type A = 10 (33°/0)	20 (50°/0)
	Type B = 30	Type B = 20 (67%)	Type B = 10 (500/.)	10 (33°/0)
Antacids	Total = 70	Total = 40 (570/.)	Total = 15 (380/.)	25 (36°/0)
	Type A = 40	Type A = 30 (750/.)	Type A = 10 (330/.)	20 (50°/0)
	Type B = 30	Type B = 10 (33%)	Type B = 5 (500/.)	5(1 70/o)

The implications drawn from these studies are less consistent than are the findings. To some investigators, the high relapse rate after cessation of treatment "suggests that prolonged cimetidine therapy is necessary to retain most patients in remission" (76). Others, cognizant of the potential unknown risks in treatment for longer than 12 months, wonder whether "those patients would have been better off if surgery had been advised at a much earlier stage. A year has been wasted in which they have been taking tablets daily when the end-result was surgery after all" (Wulff, quoted in 150). But not all patients who relapse become candidates for surgery, and a key question is the likelihood of their healing without surgery. Even if maintenance cimetidine accomplished nothing more than a l-year delay in surgery, it might be worthwhile for some patients to defer the small, but definite, mortality risk from surgery in favor of the risks of cimetidine for 12 months. Indeed, as a patient's surgical risk increases, cimetidine's unknown consequences become more acceptable **(29).**

In summary, compared to placebo, maintenance treatment with cimetidine significantly reduces the chance of ulcer recurrence. Once cimetidine is discontinued, patients begin to relapse at the same rate as they would have without maintenance treatment. We found no controlled studies of maintenance cimetidine comparing alternative treatments other than placebo and no published reports studying periods longer than 1 year of maintenance therapy.

SAFETY

Long-term studies with cimetidine turn up no important new side effects other than those mentioned in relation to short-term treatment. The incidence of gynecornastia may be as high as 4 percent in patients treated for 2 months to 1 year (131). Presumably, changes in the bacterial flora of the stomach found after 4 weeks of cimetidine treatment would persist with long-term therapy (122). As discussed earlier, this raises the possibility that patients taking maintenance cimetidine might have an increased risk of developing gastric cancer. Experienced clinicians express concern that rare, but severe, side effects may not be evident in relatively small controlled trials and that risk of toxicity is greatly magnified if treatment continues for prolonged periods of time **(70).**

COMPLICATIONS

Available controlled trials tell us very little about possible effects of cimetidine on long-term complications of ulcer disease (hemorrhage, obstruction, perforation, and penetration). The reasons rest mainly in the nature of the disease, absence of reliable estimates of baseline rates (no randomly selected population of ulcer patients has been followed over many years), and the comparative rarity of severe complications, believed to be not more than a few percent per year following initial diagnosis **(140).**

As stressed by Grossman **(70),** the size of a study needed to detect clinically relevant changes in complication rates would be enormous. If, as he posits, **5** per 1,000 recurrences result in perforation, and we wanted to detect at a 0.05 significance level a treatment that would halve the rate of recurrence, we would need more than 15,000 patients in each of two experimental groups to have a 90-percent chance of finding that difference (49).

It may be that insofar as a treatment such as cimetidine therapy can reduce or delay recurrence, it will reduce or delay complications. However, insofar as patients at higher risk of complications are also more resistant to treatment that delays recurrence, reductions in complication rates will be less than reductions in recurrence. The reasons are analogous to the adverse-selection bias hypothesized above. There is little convincing evidence that cessation of cimetidine treatment can promote complications (see earlier discussion), and likewise, there are no convincing data from clinical trials that cimetidine reduces complications. Given the size of studies that would be required, it seems unlikely that compelling evidence on this question will be forthcoming from controlled clinical trials.

PENDING APPROVAL BY FDA

At the present time, FDA is considering approval of cimetidine for use longer than **8** weeks in patients with duodenal ulcer disease. Its advisory committee reportedly recommended in October 1979 the approval of maintenance cimetidine for patients who are at "high risk" for surgery (50). This probably includes both patients who are more likely to require surgery and patients who are less likely to survive surgery. We understand that final decisions on this question, as well as revised limits on the approved duration of treatment, are not yet formulated. The principal drawback to longer term use is the risk of unknown side effects. Available evidence supports the effectiveness of cimetidine in delaying recurrence. Physicians and patient attitudes toward the unknown risks of cimetidine will vary, but for those with relatively large and tangible risks from surgery, cimetidine is likely to be judged as a less dangerous course.

FDA has not yet approved cimetidine for use in patients with gastric ulcer. This is apparently related to the conflicting evidence about the efficacy of cimetidine for gastric ulcer (see table 11, p. 31) and to a more general policy concern about the possible role of nitrosoaminated compounds in the development of cancer.

Health System Effects

Empirical data on the health system effects of cimetidine are more sparse than available information about clinical effects. Some pertinent information is available, and several studies are in progress that may shed more light on these effects, but at the present time, available evidence is suggestive rather than conclusive. As discussed in the next part of this case study, the lack of empirical evidence to inform estimates of cimetidine's health system effects seriously handicaps available benefit-and-cost analyses.

Medication

Eight of the 20 placebo-controlled studies of cimetidine shown in table **16** (D1, D2, D3, D5, D6, G2, G3, M3) compared antacid consumption among patients in the experimental and control groups. Five (D2, D5, D6, G2, M3) of the eight studies were conducted in Europe and one (D1) in South Africa. In these six studies, cimetidine-treated patients consumed between 47 and 84 percent less antacid. In the remaining two studies (D3 and G3), both done in the United States, differences were less marked, and there were no consistent trends toward decreased antacid consumption among cimetidine-treated patients.

Possible effects of cimetidine use on the consumption of other drugs have not been reported.

Diagnostic Tests

Insofar as persistent or recurrent ulcer symptoms lead physicians to perform diagnostic tests, and insofar as cimetidine reduces or delays symptoms, the drug could result in fewer diagnostic tests if used without the constraints of controlled triail protocols. It is important to bear in mind that cimetidine's effectiveness in long-term use has been tested against placebo, but not, to our knowledge, against an antacid program or other regimen. To the extent that cimetidine produces biochemical or other abnormalities that physicians choose to evaluate further, it could increase the number of laboratory tests performed.

In addition, if physicians felt obliged to screen for unlikely but potentially serious side effects, such as granulocytopenia, the number of diagnostic tests in patients treated with cimetidine could increase. The presence and extent of these different effects are currently matters for speculation.

Physician Visits

The range of potential effects posited for diagnostic tests applies as well to physician visits. Secondary induced effects are also possible: If physicians are visited less often for a principal problem of ulcer disease, then less medication and fewer procedures may be used for a less troublesome problem, such as mild to moderate joint pain, that in itself might not prompt a person to seek medical care.

Hospitalization and Surgery

Costs of hospitalization and surgery are the largest single component of medical expenditures for ulcer disease (see table 6, p. 19). Hence, the effects of an intervention such as cimetidine on the rates of hospitalization and surgery are particularly important to a CEA.

Because, as discussed earlier, cimetidine was disseminated widely in a short period of time, it seems possible that its effects might be reflected in global trends of hospitalization and surgery. Data we have compiled and analyzed from NCHS do indicate an unexpectedly sharp decline in surgery in the first calendar year **(1978)** following the introduction of cimetidine in the United States. According to data from CPHA compiled by Elashoff and Grossman (42), however, the decline was less precipitous. Hospital-related effects that are linked more directly to the use of cimetidine may emerge in the next few years from several studies currently in progress, which we will describe briefly.

Table 16.—Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Antacid Consumption

Study[a]	Time period	Antacid consumption of cimetidine group compared to that of placebo group
D1	6 weeks	83% reduction
D2	4 weeks	"Significantly" fewer tablets[b]
03	First week[c]	Inpatients: no differences Outpatients: 40% reduction
D4	—	Not reported
D5	6 weeks	84% reduction
D6	4 weeks	47% reduction
D7	—	Not reported
D8	—	No antacids permitted
D9	—	Not reported
D10	—	Not reported
G1	—	Not reported
G2	4 weeks	61% reduction
G3	2 weeks 6 weeks	No significant differences
G4	—	Not reported
MI	—	Not reported
M2	—	Not reported
M3	12 months	700/. reduction (approximately)
M4	—	Not reported
M5	—	Not reported
M6	—	Not reported

[a] See tables 10, 11, and 14 for Investigator, year, and country
[b] Scatter plots of antacid consumption presented, no numbers provided or statistical tests reported.
[c] Not reported for later weeks of study

Two principal sources of nationwide hospital data are the Hospital Discharge Survey of NCHS and the Hospital Record Study of CPHA. Data from both sources are used in this analysis. Unless otherwise stated, Hospital Record Study data are taken from a review by Elashoff and Grossman (42). Hospital Discharge Survey data were obtained directly from NCHS and then compiled for this case study.

Information from NCHS and CPHA is not in perfect agreement. Estimates in both the Hospital Record Study of CPHA and the Hospital Discharge Survey of NCHS are based on samples of non-Federal, short-term hospital discharges, stratified by hospital size and location. The fraction of records sampled is inversely proportional to hospital size, so that the overall probability of selecting a particular discharge is approximately the same for each class of hospital size. Both sources estimate discharges, not patients, so multiple admissions for an individual patient are indistinguishable from one-time-only admissions.

One major distinction between the two sources is the difference in parent populations of hospitals. For the Hospital Discharge Survey, NCHS selects a representative sample from all U.S. hospitals. CPHA draws its sample for the Hospital Record Study from the more than 750 hospitals in its parent file. These hospitals comprise approximately 13 percent of all U.S. hospitals, but they account for nearly 40 percent of all hospital discharges. Thus, large hospitals are overrepresented in the CPHA parent file. The subset selected for the Hospital Record Study data is chosen to represent the size distribution for all U.S. hospitals, but the extent to which any bias is introduced by the inclusion or exclusion of U.S. hospitals in the CPHA parent set is not well defined .23

Table 4 (p. **16)** showed NCHS Hospital Discharge Survey data for peptic ulcer disease for the years 1966 and 1970 through 1978. The first-

z 'One indica tor of the represen ta t iveness of Hospital Record-Study based figures is a comparison of Hospital Record Study estimated deaths from peptic ulcer and total counts (not projections) tabulated by the NCHS Division of Vital Statistics. Between 1970 and 1978, Hospital Record Study estimates of annual deaths from peptic ulcer were *92* to 114 percent of U, S. Vital Statistics counts (42).

listed diagnoses count those discharges for which one of the ulcer diseases was listed as the primary diagnosis. These data, plotted in figure 3 (p. 17), show a distinct downward trend over the past decade for hospitalization of patients whose first-listed diagnosis was ulcer disease. The CPHA Hospital Record Survey data show a similar and significant downward trend, with an even greater difference in the total decline from **1970** to **1978 (42).**[24] According to both sets of data, the number of hospitalizations for ulcer disease in **1978** is approximately what would be expected by extrapolating the trend established through 1977.

Furthermore, both sets of data confirm that hospitalizations during the 1970's have declined for duodenal ulcer and remained constant for gastric ulcer. Between 1970 and 1978, the ratio of hospitalizations for duodenal ulcer to those for gastric ulcer declined by 37 percent according to the Hospital Record Study and by 49 percent according to the Hospital Discharge Survey. This is further evidence for the epidemiologic distinction between duodenal and gastric ulcer. The figures are incomplete because a relatively small number of diagnoses categorized as "peptic ulcer—site unspecified" is omitted, but their inclusion would not alter the trends indicated.

Data from CPHA's Hospital Record Study can also be used to estimate the number of admissions for uncomplicated ulcer disease and those for ulcer disease associated with hemorrhage or perforation (42). Between 1970 and 1978, uncomplicated duodenal ulcer admissions declined by 46 percent; admissions for hemorrhage declined by 37 percent; and admissions for perforation declined 24 percent, though failing to reach statistical significance because of the small number of admissions for perforation. Uncomplicated gastric ulcer admissions showed a small, but significant, decline (18 percent). No clear trend emerged for complicated gastric ulcer admissions.

The number of surgical procedures for ulcer disease has shown a decline during the 1970's that roughly parallels that for hospitalizations. Both NCHS and CPHA collect data on surgical procedures, but neither routinely relates operations to discharge diagnoses. The principle surgical procedures used for ulcer disease are partial gastrectomy (excision of part of the stomach) and vagotomy (cutting of the vagus nerve), with pyloroplasty (enlargement of the pyloric canal) or other drainage procedure (134). The numbers of these procedures performed during selected years from 1966 through 1978 are shown in table 17 (NCHS data). During this period, pyloroplasty and drainage procedures were almost invariably performed in association with vagotomy. Virtually all vagotomies were probably undertaken for the treatment of ulcer disease. Presumably, the great majority of partial gastrectomies were also done for ulcer disease, but there are also several less common indications for partial gastrectomy (e.g., gastric carcinoma and trauma).

[24] Elashoff and Grossman define a trend as significant if: 1) the Spearman rank order correlation is significant ($p < 0.05$), and 2) the difference between the 1970 and 1978 values exceeds the size of the 95-percent confidence interval for the median value (42).

Table 17.—Number of Selected Surgical Procedures (Partial Gastrectomy, Vagotomy, Pyloroplasty and Drainage") in the United States, 1966-78

Year	Partial gastrectomy	Vagotomy	Pyloroplasty and drainage
1966	74,500	61,000	56,800
1970	55,800	62,800	45,500
1972	63,300	59,300	42,000
1975	53,300	52,800	38,500
1976	54,200	48,300	31,200
1977	51,100	45,500	26,300
1978	39,700	29,200	20,600

[a] Ulcer disease is by far the most common indication for these surgical procedures. Over the time period shown, pyloroplasty and drainage were almost invariably associated with vagotomy.

SOURCE: National Center for Health Statistics, National Hospital Discharge Survey, Hyattsville, Md.

Thus, the sum of partial gastrectomies and vagotomies can serve as a reasonable proxy for the number of surgical operations done for peptic ulcer disease. Summing these two procedures may double count some patients who undergo surgery, because a patient who receives both partial gastrectomy and vagotomy is recorded under both procedures. Despite the possibility of some double counting, the trend over time in the total of these two procedures would remain a useful index.

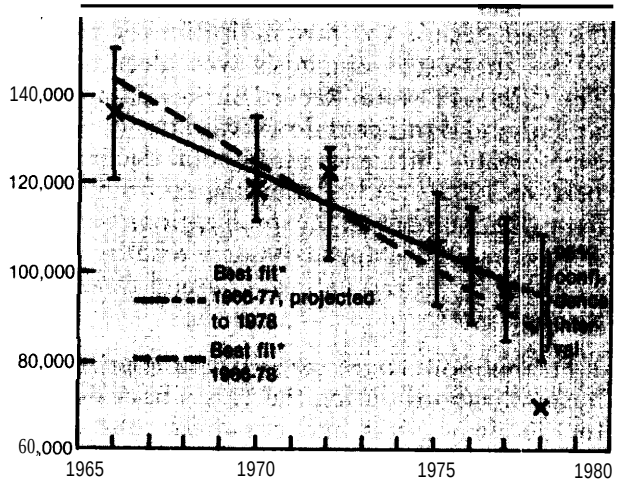
Estimates for the number of partial gastrectomies and vagotomies from NCHS tend to be higher than estimates from CPHA, but data from both sources show a distinct downward trend over time in the number of operations (see table **8,** p. 22). An acceleration (or deceleration) of this downward trend in surgery following the advent of cimetidine might be ascribable to the introduction of this new, widely used medication.

We tested whether the number of surgical procedures performed in **1978** was different from that which would be predicted by the previous trend in the following way. First, we fitted a least-squares, linear regression line to the surgical data available through 1977. The predicted number of procedures in **1978** is based on a direct extension of the regression line. This is shown in figures 5 and 6, respectively, for the NCHS and CPHA surgery data. The NCHS estimates of surgery are consistently higher than the CPHA estimates, but the rates of decline (slopes of the regression lines) are quite similar, within one standard error of each other .25 The plots also show the 95- percent confidence interval about this regression line for individual estimates in each year for which data are available.

According to the NCHS data (figure 5), the rate of surgery in **1978** is significantly ($p < 0.01$) below the rate that would have been predicted on the basis of the trend through 1977. The drop in **1978** is less striking in the CPHA data (figure **6),** but even here there is only about a **10-** percent chance that the estimated amount of

[25]The slope of the regression line for the NCHS data is 0.3361; that for the CPHA data is 0.3945.

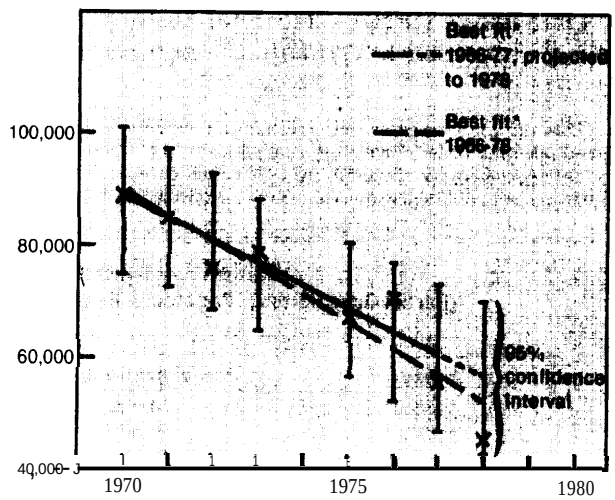
Figure 5.— NCHS Data on Number of Selected Surgical Procedures (Partial Gastrectomy and Vagotomy) in the United States, 1966.78



• Best fit computed by least-squares method. Confidence intervals shown for curve fit to years 1966-77,

SOURCE Based on data from the National Center for Health Statistics Hyattsville Md

Figure 6.—CPHA Data on Number of Selected Surgical Procedures (Partial Gastrectomy and Vagotomy) in the United States, 1966-78



• Best fit computed by least-squares method. Confidence Intervals shown for curve fit to years 1966-77.

SOURCE Based on data from the Commission on Professional and Hospital Activities compiled by J D Elashoff and M I Grossman 1981)(42)

surgery in 1978 is in line with the preceding trend. The number of surgical procedures in **1978** was approximately 11,000 fewer than the predicted number based on CPHA data, and **26,000** fewer than the predicted number based on NCHS data.

Further evidence for the apparent excessive drop in surgery in **1978** compared to earlier years comes from a comparison of the number of surgical procedures as a proportion of hospitalizations for ulcer disease for various years (see table 18). Each year from 1966 to 1977, the number of operations was between 25 and 29 percent of hospital admissions; in 1978, the number of operations for ulcer disease was 19 percent of hospitalizations. Roughly speaking, for the decade before 1978, more than one in four patients hospitalized for peptic ulcer received surgery; in **1978,** the proportion dropped below one in five.

If an unexpected decline in ulcer surgery did, in fact, occur in **1978,** the question is, why? Did cimetidine play any role in the apparent drop? Are there other plausible explanations? What sorts of data might be obtained that could answer these questions?

Table 19 shows numbers and rates of surgical procedures for all abdominal surgery and for selected abdominal surgical procedures for selected years from **1970** through **1978.** There was no general decline in abdominal surgery over these years. Only surgery for peptic ulcer disease shows a marked decline in **1978** compared with the rates in earlier years. Some surgery for peptic ulcer is elective, and one might imagine that part of the decline could be related to a newly emerging, more cautious attitude toward elective operations. This might occur, for example, **as a** result of more patients seeking second opinions or of greater cost-con-

Table 18.— Proportion of Patients With First-Listed Diagnosis of Ulcer Disease Having Surgery, 1966-78

Year	A Number of surgical procedures	B Number of patients discharged with diagnosis of ulcer[b]	A/B
1966	135,500	526,000	0.258
1970	118,600	438,000	0.271
1972	122,600	429,300	0.286
1975	106,100	411,700	0.258
1976	102,500	385,400	0.267
1977	96,600	385,400	0.251
1978	68,900	360,400	0.191

[a] Includes partial gastrectomy and vagotomy
[b] Includes gastric duodenal, gastrojejunal and peptic ulcer (site unspecified)

SOURCE National Center for Health Statistics, National Hospital Discharge Survey, Hyattsville, Md

Table 19.— Number and Rate of All and Selected Abdominal Surgical Procedures in the United States, 1970-78

	All abdominal surgery		Partial gastrectomy and vagotomy		Appendectomy		Cholecystectomy[a]		Herniorrhaphy[b]	
Year	Number	Rate[c]	Number	Rate[c]	Number	Rate[c]	Number	Rate[c]	Number	Rate[c]
1970	2,440,000	122	119,000	6	325,000	16	367,000	18	496,000	25
1975	2,894,000	138	106,000	5	319,000	15	442,000	21	549,000	26
1976	2,809,000	133	102,000	5	306,000	14	442,000	21	507,000	24
1977	2,937,000	139	97,000	4	342,000	16	446,000	21	533,000	25
1978	2,830,000	132	69,000	3	299,000	14	432,000	20	510,000	24

[a] Surgical removal of the gallbladder
[b] Surgical repair of a hernia
[c] Rates shown are per 10,000 population

SOURCE Based on data from the National Center for Health Statistics, National Hospital Discharge Survey, Hyattsville, Md

sciousness on the part of physicians. However, we find no parallel decline between 1977 and 1978 in other abdominal surgery, such as herniorrhaphy (surgical repair of a hernia), which is probably more frequently elective than is surgery for ulcer disease.

A dramatic change in the criteria used to decide on surgery or use of a different type of surgery for patients with ulcer disease might account for some decline. To our knowledge, however, neither the recognized indications for surgery nor the types of operations have changed dramatically in the past few years. Also we know of no changes in the standard coding for operative procedures in 1978 that might account for the observed decline. Diagnostic advances, such as fiberoptic endoscopy, may provide greater- assurance of benignity of a slowly healing gastric ulcer and thus avert some surgery that would have been performed previously. Even if present, however, such effects seem very unlikely to reach the proportions of the evident decline in 1978.

Results from at least one of the maintenance trials comparing cimetidine with placebo support the possibility that the decline in surgery in 1978 is related to the availability of cimetidine. In a year of maintenance treatment, Bodemar and Walan (16) found that 1 patient in 32 who received cimetidine and 15 in 36 who received placebo underwent surgery because they had two recurrences or because of severe symptoms at the first recurrence (difference significant, $p < 0.0005$).[26] Thus, one possible explanation for the decline in surgery for ulcer disease in 1978 is that the dramatic growth in the use of cimetidine enabled more patients to be treated successfully medically. If cimetidine were responsible, the effect could be temporary. Patients who were scheduled for an elective operation may have decided with their physicians to delay surgery in order to try the new drug. Since patients appear to relapse at the same rate following cessation of cimetidine, the decline in surgery might be followed by a compensatory rebound, especially if more reports (e. g., 121) suggest increased risks or adverse side effects with long-term use of cimetidine.

To date, only circumstantial evidence and argument by exclusion can make the case for the role of cimetidine in decreased rates of surgery. However, more direct evidence may be forthcoming from several sources. Murray Wylie of the University of Michigan is engaged in a detailed analysis of CPHA data on patients hospitalized with ulcer disease .27 Wylie has data on all patients discharged with a diagnosis of ulcer disease from a cohort of 790 hospitals that participated continuously in the CPHA data system from January 1974 through October 1978. Although the data do not specifically identify patients who did and did not receive cimetidine, he is able to examine surgical rates on a month-to-month basis. Thus, he can test the correspondence between any accelerated decline in surgery and the introduction of cimetidine in the United States in August 1977.

Wylie's preliminary impression is that the frequency of surgery began to drop even a few months before the release of cimetidine. He speculates that this might be attributable to a delay in elective surgery in anticipation of the new medication. It would be very informative to compare changes in rates of surgery separately for uncomplicated cases (presumably admitted because of pain) and for those with hemorrhage or perforation. If cimetidine is reducing surgery by effecting a medical remission after patients are hospitalized, the largest drop in surgery as a proportion of admissions should be for patients hospitalized because of pain.

Wylie will also be able to analyze his data separately for surgical and medical admissions, including length of stay. This is of particular interest to a cost-effectiveness assessment of the

[26] In a second maintenance study that reported surgical experience, possible effects of cimetidine on surgery are obscured by the practice of treating "placebo failures" with a course of cimetidine rather than surgery; the effected remission in most 'placebo failures" during the 6 months of the study (64) In this study, 30 patients were treated initially with maintenance placebo; 24 relapsed, all of whom were then treated with cimetidine, and 4 underwent surgery within the 6-month period of the study. Of the 26 patients in initially treated with maintenance cimetidine, 7 relapsed; 1 received surgery then and 6 received a second course of (higher dose) cimetidine; 2 of those 6 underwent surgery within the 6-month period of the study

"We are grateful to Professor Wylie to J sharing this description of his work in progress.

number of days of hospital care that might be saved by cimetidine. Presumably, some fraction of the reduction in surgery that might be attributable to cimetidine is due to patients not being hospitalized, and another fraction is due to hospitalized patients being treated medically only. (The large drop in surgery in 1978 compared with the drop in hospitalizations suggests that the latter fraction may be the larger.) On the average, surgical lengths of stay would be expected to be longer than medical, and a shift from surgical to medical care in a hospital should typically produce a reduction in hospital days. If a very large number of patients who are considered potential candidates for surgery are first treated medically, however, any failures on the medical regimen would then undergo surgery after a delay, and this could add to the average length of stay for patients. In addition, successful medical treatment with cimetidine might or might not take longer than a medical regimen without the drug. A few points of data would be preferable to a lot of speculation.

Another approach to assessing cimetidine's effects on the health system has been undertaken by Professors Burton Weisbrod and John Geweke at the University of Wisconsin .28 They are analyzing patient records developed for accounting purposes by the Texas medicaid program. Weisbrod and Geweke aim first to reconstruct medicaid expense records on a patient-by-patient basis for all patients with a diagnosis of ulcer disease. They have identified **1,206** patients with ulcers in a sample that begins in January **1976** and will extend to August **1979.** These investigators have conducted a pilot study with 81 patients randomly selected from this population, 36 with and 45 without a history of cimetidine use. Their intent is to compare the health and expenditure history (including nearly **50** categories of various expenses for hospitalization, physicians, drugs, nursing homes, etc.) for patients treated with and without cimetidine.

Weisbrod and Geweke recognize some inherent limitations in the available data. For example, approximately one-fifth of the medicaid claims do not include the patient's diagnosis; medicaid patients over **65** years old are also covered by medicare, about which the investigators have no information; and the data do not include information concerning patient status at discharge or work history. The major difficulty Weisbrod and Geweke face, however, is controlling for selectivity bias in those patients who do receive cimetidine. Their approach is to stratify patients according to demographic factors and clinical history. Although it will be impossible to overcome the aforementioned barriers completely, Weisbrod and Geweke's study promises to be the first large-scale, patient-based study providing data on the direct and induced health system effects of cimetidine. The data base can also be used to describe the diffusion of the drug in a given patient population and the pattern of present use by medical practitioners in one State.

We are aware of a few additional studies of the health system effects of cimetidine that are in more preliminary stages of development. At least one of these involves a health maintenance organization (HMO); if the HMO's population is sufficiently stable, it may be a particularly valuable setting for study. Ideally, one would seek results from a long-term, randomized, controlled study of patients with ulcer disease who are or are not treated with cimetidine, but for ethical and practical reasons, such a study is unlikely to materialize.

In summary, hospitalization and surgery for peptic ulcer disease have both declined significantly during the past decade. The decline in hospital admissions for **1978** is consistent with earlier trends. However, the fall in surgical procedures for ulcer disease in 1978 is unexpectedly large, amounting to 11,000 to 26,000 fewer procedures in **1978** than would be expected from the trend leading up to that year. The introduction and widespread use of cimetidine is one plausible explanation for this unexpected decline. More specific information from studies in progress, including a month-by-month tracing of surgical rates and a comparison of health resources used by patients who did and did not receive cimetidine, would help strengthen or refute this inference.

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[28] We are grateful to Professor Geweke for sharing information about their study for this report

Outcome

The outcome effects of cimetidine are consequences of its clinical and health system effects. We have already discussed how clinical and health system effects interest and lead to the two components of outcome: health status and resource costs. In this section, we present additional empirical evidence about cimetidine's possible effect on outcome.

The available empirical evidence plus methodologic and other considerations raised in a later section entitled "Guidelines for Review of Health Care Benefit-and-Cost Analyses" serve as a basis for our review of published analyses of cimetidine's benefits and costs in the next part of this case study.

Health Status

As we have already discussed, it is convenient and usual to think of health status in terms of mortality and morbidity.

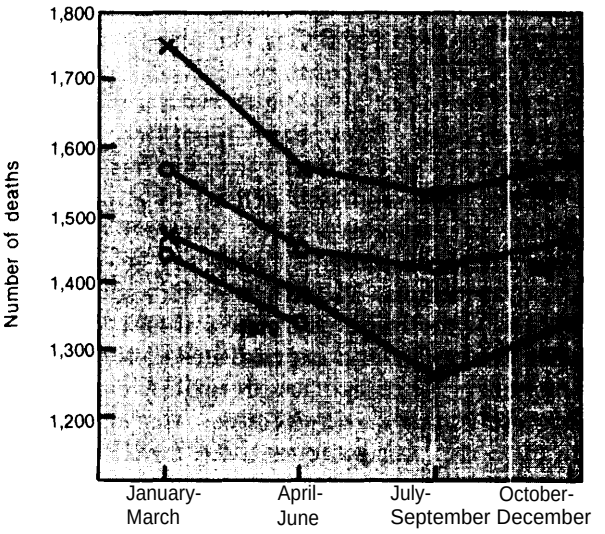
MORTALITY

We are aware of no empirical studies of the effects of cimetidine on mortality from peptic ulcer disease. This is not surprising, because mortality from this disease is relatively low. A controlled cohort study would require enormous numbers of patients, for reasons presented earlier in the discussion of possible effects of cimetidine on complication rates. One might argue that insofar as cimetidine delays or supplants surgical intervention and attendant surgical mortality and delays the development of complications, it will forestall some deaths. However, it is conceivable that patients who would naturally develop the more virulent complications of peptic ulcer might benefit less from cimetidine or that complications following cessation of the drug would be more severe than they might have been had cimetidine not been administered. Any of these circumstances would counter potential improvements in survival related to cimetidine. In addition, any severe and unanticipated side effects from long-term use would further compromise cimetidine's beneficial effects on mortality.

Table 3 (p. **16)** shows that mortality from ulcer disease has been declining steadily over the past 15 years. Figure **7** shows NCHS ulcer mortality statistics on a quarterly basis from **1976** to mid-1979. It shows both a continuing downward trend and a seasonal variation in mortality, No unexpected mortality reduction following the introduction of cimetidine in August 1977 is evident. If cimetidine has saved lives of ulcer patients, the lives saved are too few to have a substantial effect on overall mortality to date. Of course, these figures are mute on the question of whether even more widespread and consistent use of cimetidine might demonstrably delay or prevent deaths from ulcer disease in the future.

In summary, there are some reasons to believe cimetidine might have beneficial effects on ulcer mortality and other reasons to doubt it. If cimetidine did have a small beneficial effect on mortality, it would be very difficult to detect in controlled cohort studies or from national mortality trends.

Figure 7.— Number of Deaths in the United States From Ulcer Disease (Gastric, Duodenal, and Peptic—Site Unspecified), 1976-79



NOTE: 1978 and 1979 figures extrapolated from a 10-percent sample.

SOURCE Based on data from the National Center for Health Statistics, Division of Vital Statistics, Hyattsville, Md

MORBIDITY

From the perspective of BCA, in which there is an effort to translate morbidity into social resource costs, an important consideration is the effect of cimetidine on disability and days lost from work. Cimetidine produces more prompt and consistent relief from ulcer pain than does placebo. In the short-term treatment of peptic ulcers, it is reasonable to expect that faster healing and pain relief can mean earlier return to work. This potential benefit may be reduced insofar as doctors prescribe and patients follow "rest at home" for a set number of days or weeks following diagnosis of a new ulcer, irrespective of the promptness of symptom remission. That policy would be reasonable, for example, if clinicians believed that patients returning to the stress of work with unhealed ulcers would be more likely to develop bleeding or other complications of ulcer disease.

A number of the randomized clinical trials of cimetidine in the United States included a special protocol to assess time lost from work **(118).** A preliminary report presented results in **64** outpatients, **37** treated with cimetidine and **27** with placebo. (Many of the 217 potential subjects were disqualified because of uncertain employment status, a problem that is being rectified with a revised protocol.) Among the patients analyzed, there was a striking tendency to be absent full time or to work full time. Compared to the number of days lost from work during the week prior to treatment, the group receiving cimetidine averaged significantly more days of work in weeks one, two, and four ($p < 0.001$) and in week six ($P <$ **0.05) following** the initiation of treatment. This report is notable not only for its results, but because it represents an admirable effort to collect data pertinent to the economic consequences of a medical practice in the context of a controlled clinical trial.

One of the trials comparing maintenance cimetidine with placebo also reported on the work experience of patients (15). During the year of the study, 1 of **32** patients taking cimetidine did not report to work for **79** days, and **23** of **26** patients taking placebo did not report to work for a total of 1,405 days because of symptoms. Thus, the cimetidine-treated patients reported to work an average of approximately **36** more days per patient during the year of the study (difference significant, $p < 0.001$).

The effectiveness of cimetidine compared to other treatments, such as antacids, in enabling patients to return to work is not addressed in any of the controlled trials we have reviewed.

Resource Costs

The economic implications of an intervention such as cimetidine include the costs of the intervention itself, the resource costs and savings related to induced effects on the health care system, and indirect effects on productivity related to change in mortality and morbidity. In this section, we offer a few observations on the direct costs of cimetidine compared to alternatives. We defer consideration of the resource value attached to the induced and indirect effects of cimetidine until the next part of this study, in which we review some of the benefit-and-cost analyses that have been carried out.

The daily cost of cimetidine is less than the daily cost of antacid in doses that have been shown to be as effective in promoting the healing of newly discovered duodenal ulcers (80). The retail cost of cimetidine is approximately $0.25 to $0.30 per 300-mg tablet.[29] Assuming consumption of four tablets daily, the daily cost of cimetidine is $1.00 to $1.20.

Antacids vary in their compositions, neutralizing capacities, and costs (115). Two of the more popular blends of aluminum hydroxide and magnesium hydroxide are Maalox® and Mylanta II®.[30] The latter was the antacid used in the studies by Peterson, et al. **(116)** and Ippoliti, et al. **(80).** Mylanta II® has approximately 50-percent more neutralizing capacity than the same quantity of Maalox® and costs approximately $3.80 per 12-ounce bottle compared to $1.80 for Maalox®.[31]

[29] Based on information provided by four Boston-area drug stores and consistent with estimates of the manufacturer.

[30] Mylanta II contains, in addition to antacid, the defoaming silicone and antiflatulent simethicone.

[31] Cost estimates based on average charges at four Boston-area drug stores.

If we assume administration of the same amount of antacid as used in the studies cited above (seven daily doses, each with approximately **120** mEq of buffering capacity), the daily cost would be approximately $1.58 for Maalox® (seven 45-ml doses) and $2.22 for Mylanta® (seven 30-ml doses). If patients who are prescribed cimetidine consume three or four additional doses of antacid daily, their medication costs would still be comparable to those of patients who follow an intense antacid regimen. Thus, a typical patient can expect to pay no more, and possibly somewhat less, for cimetidine than for a therapeutically equivalent course of popular, brand-name antacids .32

Summary

Organized according to the benefit-and-cost model for medical interventions presented earlier, this part of our case study has described available information about the effects of cimetidine—its clinical effects, its health system effects, and its potential impact on outcome.

Numerous controlled studies of patients with duodenal ulcer confirm that cimetidine promotes healing and provides faster and more complete pain relief than placebo. Less conclusive evidence suggests the drug may be more effective than placebo for patients with gastric ulcer. An intense antacid program appears to be about as effective as cimetidine for patients with duodenal ulcer, but more evidence on this matter is needed. Clinical studies have also shown that relief of symptoms is not a reliable indicator of healing. In general, European studies have found more favorable results with cimetidine than have' U.S. trials.

Cimetidine used for up to 2 months appears to be a relatively safe drug. Most known side effects are minor or reversible, but recently reported changes in gastric flora and endocrinologic effects are disturbing. Available studies of maintenance cimetidine do not alter this assessment. As with any new drug, uncertainty exists as to possible long-term consequences of the drug's use.

Compared to an intense course of antacids, cimetidine is comparably effective, more risky, and less troublesome to the patient with duodenal ulcer. Cimetidine plus a moderate amount of antacids costs no more than a therapeutically equivalent course of intense antacid therapy, Experts now differ in their recommendations for initial therapy of duodenal ulcer, some favoring cimetidine and others antacids. A reasonable approach is to select therapy based on each patient's preferences and personality.

Compared to placebo, maintenance treatment with cimetidine as long as 1 year significantly reduces the chance of ulcer recurrence. Once cimetidine is discontinued, patients appear to relapse at the same rate as they would have without maintenance treatment. We are aware of no controlled trials comparing maintenance cimetidine to treatments other than placebo. There is little empirical evidence either that cimetidine prevents future complications of ulcer disease or that cessation of cimetidine promotes complications. At present, FDA is considering approval of cimetidine for use longer than **8** weeks in patients with duodenal ulcers who are at high risk for surgery.

In European trials, but not in U.S. studies, cimetidine-treated patients tend to consume less antacid than placebo-treated patients. Very limited empirical data are currently available on the possible effects of cimetidine on use of other medication, on diagnostic tests, or on physician visits. Several studies are underway that may shed light on these matters.

Data we have compiled from NCHS show an unexpectedly sharp decline in the rates of surgery for ulcer disease in **1978,** the first full calendar year after the introduction of cimetidine. This drop occurred against a background of falling rates of surgery and hospitalization for ulcer disease over the previous decade. Other explanations are possible, but the widespread use of cimetidine may have contributed to the mag-

[12] It may be possible to find less expensive, generic brands of antacids with equivalent neutralizing capacity, but the costs of Maalox ® and Mylanta ® are no more than those of most other brands of aluminum-magnesium antacids (63). Antacids are available without a prescription, and their use does not necessarily entail the cost of a physician visit, but in this discussion we have assumed that a high-dose antacid regimen or cimetidine would be consumed only following a physician's advice.