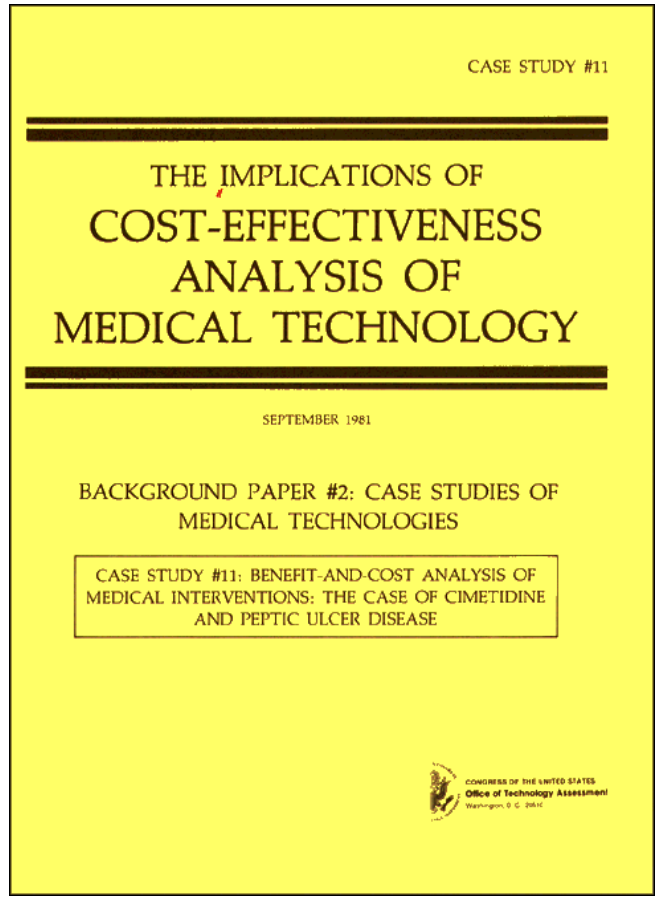
Benefit-And-Cost Analysis of Medical Interventions: The Case of Cimetidine and Peptic Ulcer Disease

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CASE STUDY #11

THE IMPLICATIONS OF COST-EFFECTIVENESS ANALYSIS OF MEDICAL TECHNOLOGY

SEPTEMBER 1981

BACKGROUND PAPER #2: CASE STUDIES OF MEDICAL TECHNOLOGIES

CASE STUDY #n: BENEFIT-AND-COST ANALYSIS OF MEDICAL INTERVENTIONS: THE CASE OF CIMETIDINE AND PEPTIC ULCER DISEASE

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OTA Background Papers are documents that contain information believed to be useful to various parties. The information under-girds formal OTA assessments or is an outcome of internal exploratory planning and evaluation. The material is usually not of immediate policy interest such as is contained in an OTA Report or Technical Memorandum, nor does it present options for Congress to consider.

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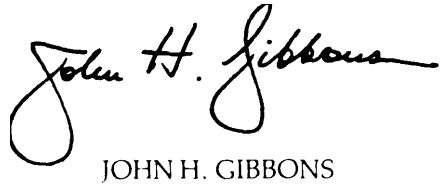
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Foreword

This case study is one of 17 studies comprising Background Paper #2 for OTA's assessment, *The implications of* Cost-Effectiveness *A Analysis* of *Medical* Technology. That assessment analyzes the feasibility, implications, and value of using cost-effectiveness and cost-benefit analysis (CEA/CBA) in health care decisionmaking. The major, policy-oriented report of the assessment was published in August 1980. In addition to Background Paper #2, there are four other background papers being published in conjunction with the assessment: 1) a document which addresses methodological issues and reviews the CEA/CBA literature, published in September 1980; 2) a case study of the efficacy and cost-effectiveness of psychotherapy, published in October 1980; 3) a case study of four-common diagnostic X-ray procedures, to be published in summer 198 1; and 4) a review of international experience in managing medical technology, published in October 1980. Another related report was published in September of 1979: A Review of *Selected Federal Vaccine and Immunization Policies.*

The case studies in *Background Paper* #2: Case Studies of Medical *Technologies* a r-e being published individually. They were commissioned by OTA both to provide information on the specific technologies and to gain lessons that could be applied to the broader policy aspects of the use of CEA/CBA. Several of the studies were specifically requested by the Senate Committee on Finance.

Drafts of each case study were reviewed by OTA staff; by members of the advisory panel to the overall assessment, chaired by Dr. John Hogness; by members of the Health Program Advisory Committee, chaired by Dr. Frederick Robbins; and by numerous other experts i n clinical medicine, health policy, Government, and economics. We are grateful for their assistance. However, responsibility for the case studies remains with the authors.



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Preface

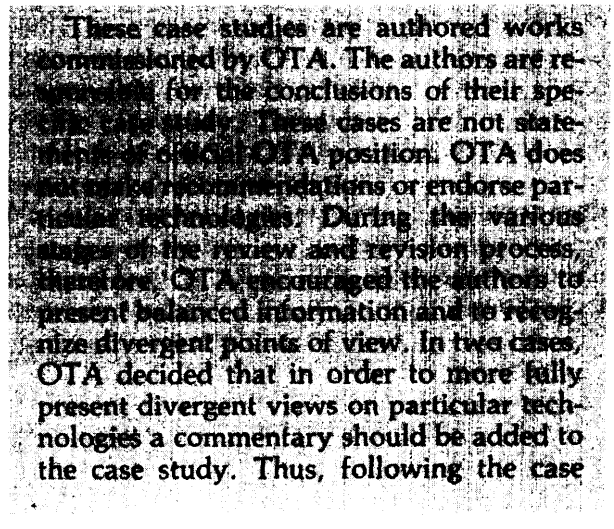
This case study is one of 17 that comprise Background Paper #2 to the OTA project on the *lmplications of Cost-Effectiveness Analysis of Medical Technology*.* The overall project was requested by the Senate Committee on Labor and Human Resources. In all, 19 case studies of technological applications were commissioned as part of that project. Three of the 19 were specifically requested by the Senate Committee on Finance: psychotherapy, which was issued separately as Background Paper #3; diagnostic X-ray, which will be issued as Background Paper #.5; and respiratory therapies, which will be included as part of this series. The other 16 case studies were selected by OTA staff.

In order to select those 16 case studies, OTA, in consultation with the advisory panel to the overall project, developed a set of selection criteria. Those criteria were designed to ensure that as a group the case studies would provide:

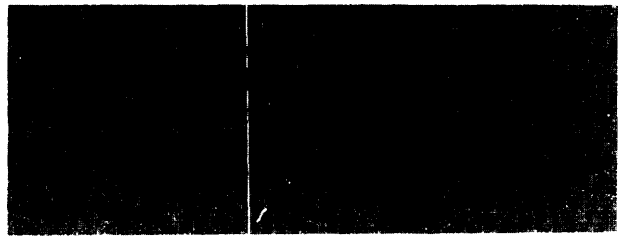
- examples of types of technologies by function (preventive, diagnostic, therapeutic, and rehabilitative);
- examples of types of technologies by physical nature (drugs, devices, and procedures);
- examples of technologies in different stages of development and diffusion (new, emerging, and established);
- examples from different areas of medicine (such as general medical practice, pediatrics, radiology, and surgery);
- examples addressing medical problems that are important because of their high frequency or significant impacts (such as Cost);
- examples of technologies with associated high costs either because of high volume (for low-cost technologies) or high individual costs;
- examples that could provide informative material relating to the broader policy and methodological issues of cost-effectiveness or cost-benefit analysis (CEA/CBA); and
- examples with sufficient evaluable literature.

On the basis of these criteria and recommendations by panel members and other experts, OTA staff selected the other case studies. These 16 plus the respiratory therapy case study requested by the Finance Committee make up the 17 studies in this background paper.

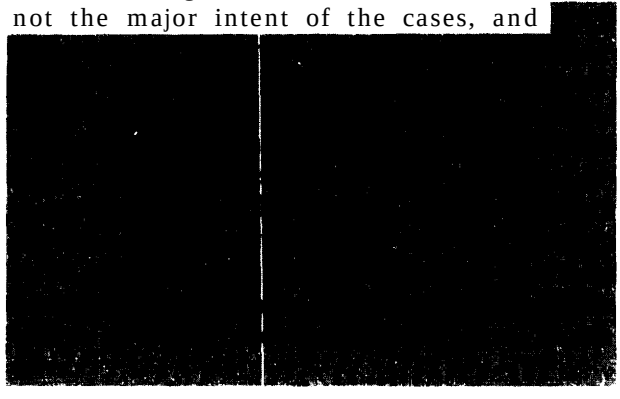
All case studies were commissioned by OTA and performed under contract by experts in academia. They are authored studies. OTA subjected each case study to an extensive review process. Initial drafts of cases were reviewed by OTA staff and by members of the advisory panel to the project. Comments were provided to authors, along with OTA's suggestions for revisions. Subsequent drafts were sent by OTA to numerous experts for review and comment. Each case was seen by at least 20, and some by 40 or more, outside reviewers. These reviewers were from relevant Government agencies, professional societies, consumer and public interest groups, medical practice, and academic medicine. Academicians such as economists and decision analysts also reviewed the cases. In all, over 400 separate individuals or organizations reviewed one or more case studies. Although all these reviewers cannot be acknowledged individually, OTA is very grateful for their comments and advice. In addition, the authors of the case studies themselves often sent drafts to reviewers and incorporated their comments.



*Office of Technology Assessment, U.S. Congress, *The Implications of Cost-Effectiveness Analysis of Medical Technology*, GPO stock No. 052-003-00765-7 (Washington, D.C.: U.S. Government Printing Office, August 1980).



The case studies were selected and designed to fulfill two functions. The first, and primary, purpose was to provide OTA with specific information that could be used in formulating general conclusions regarding the feasibility and implications of applying CEA/CBA in health care. By examining the 19 cases as a group and looking for common problems or strengths in the techniques of CEA/CBA, OTA was able to better analyze the potential contribution that these techniques might make to the management of medical technologies and health care costs and quality. The second function of the cases was to provide useful information on the specific technologies covered. However, this was not the major intent of the cases, and



Some of the case studies are formal CEAS or CBAs; most are not. Some are primarily concerned with analysis of costs; others are more concerned with analysis of efficacy or effectiveness. Some, such as the study on end-stage renal disease, examine the role that formal analysis of costs and benefits can play in policy formulation. Others, such as the one on breast cancer surgery, illustrate how influences other than costs can determine the patterns of use of a technology. In other words, each looks at evaluation of the costs and the benefits of medical technologies from a slightly different perspective. The reader is encouraged to read this study in the context of the overall assessment's objectives in order to gain a feeling for the potential role that CEA/CBA can or cannot play in health care and to better understand the difficulties and complexities involved in applying CEA/CBA to specific medical technologies.

The 17 case studies comprising *Background Paper #2* (short titles) and their authors are:

Artificial Heart: Deborah P. Lubeck and John P. Bunker
Automated Multichannel Chemistry Analyzers: Milton C. Weinstein and Laurie A. Pearlman
Bone Marrow Transplants: Stuart O. Schweitzer and C. C. Scalzi
Breast Cancer Surgery: Karen Schachter and Duncan Neuhauser
Cardiac Radionuclide Imaging: William B. Stason and Eric Fortess
Cervical Cancer Screening: Bryan R. Luce



Colon Cancer Screening: David M. Eddy"'
CT Scanning: Judith L. Wagner
Elective Hysterectomy: Carol Korenbrot, Ann B. Flood, Michael Higgins," Noralou ROOS, and John P. Bunker
End-Stage Renal Disease: Richard A. Rettig
Gastrointestinal Endoscopy: Jonathan A. Showstack and Steven A. Schroeder
Neonatal Intensive Care: Peter Budetti, Peggy McManus, Nancy Barrand, and Lu Ann Heinen
Nurse Practitioners: Lauren LeRoy and Sharon Solkowitz
Orthopedic Joint Prosthetic Implants: Judith D. Bentkover and Philip G. Drew
Periodontal Disease Interventions: Richard M. Scheffler and Sheldon Rovin
Selected Respiratory Therapies: Richard M. Scheffler and Morgan Delaney

These studies will be available for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Call OTA's Publishing Office (224-8996) for availability and ordering information.

Case Study #11

Benefit-and-Cost Analysis of Medical Interventions: The Case of Cimetidine and Peptic Ulcer Disease

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AUTHORS' ACKNOWLEDGMENTS

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We also appreciate the cooperation of Mr. Charles Dennison, Mr. Donald Greenberg, and Ms. Ethel Black of the National Center for Health Statistics, who promptly responded to our numerous requests for information. Dr. Joan Standard of the Food and Drug Administration was also very helpful.

By naming people who have advised and assisted us, we do not mean to shift responsibility for any errors or misinterpretations that may appear in this case study.

Contents

Page

Summary . . . 3
Introduction . . . 3
The Benefit-and-Cost Model for Medical Interventions. . . . 3
Peptic Ulcer Disease. . . . 4
Cimetidine. . . . 4
The Benefit-and-Cost Model Applied to Cimetidine. . . . 5
Review of Benefit-and-Cost Analyses of Cimetidine. . . . 6
Suggestions for Further Research . . . 6
Introduction . . . 6
The Benefit-and-Cost Model for Medical Interventions . . . 7
Peptic Ulcer Disease . . . 10
Definition and Etiology . . . 10
Symptoms and Diagnosis . . . 11
Treatment and Natural History . . . 11
Epidemiologic Patterns . . . 13
Cost of Illness . . . 18
Summary . . . 22
Cimetidine . . . 23
Physiologic Rationale and Development . . . 23
Diffusion . . . 24
The Benefit-and-Cost Model Applied to Cimetidine . . . 25
Elements in the Analysis . . . 25
Clinical Effects . . . 26
Health System Effects . . . 39
Outcome . . . 46
Summary . . . 48
Review of Benefit-and-CostAnalyses of Cimetidine . . . 49
Available Analyses . . . 49
The Study by Robinson Associates, Inc. . . . 49
Guidelines for Review of Health Care Cost Analyses . . . 57
Suggestions for Further Research. . . . 58
References . . . 59

LIST OF TABLES

Table No. Page

1. Selected Contemporary Interventions Used in Peptic Ulcer Disease . . . 7
2. Number of Deaths in the United States With Ulcer Disease as the Primary Cause, 1960-79. 15
3. Mortality Rates in the United States for Deaths Due to Ulcer Disease, 1953-78 . . . 16
4. Number of U.S. Hospital Discharges With Ulcer Disease Diagnoses, 1966-78 . . . 16
5. Ulcer Disease in the United States According to the Health Interview Survey, NCHS . . . 17
6. Costs of Ulcer Disease in 1975 as Estimated by NCDD and SRI . . . 19
7. Costs of Ulcer Disease in 1975 and 1977 as Estimated by SRI. . . . 22
8. NCHS and CPHA Data on Number of Selected Surgical Procedures in the United States, 1966-78. . . . 22
9. Components and Measures of Components in a Benefit-and-Cost Analysis of Cimetidine. 26
10. Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Duodenal Ulcer Healing . . . 29
11. Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Gastric Ulcer Healing . . . 31
12. Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Duodenal Ulcer Pain Relief . . . 32
13. Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Gastric Ulcer Pain Relief. . . . 33
14. Controlled Trials of Maintenance Cimetidine in Peptic Ulcer. . . . 36
15. Results of Treatment With Two Hypothetical Subpopulations of Ulcer Patients: Type A More Resistant to Treatment and Prone to Relapse Than Type B. . . . 37
16. Short-Term, Double-Blind, Placebo-Controlled Studies of Cimetidine: Effect on Antacid Consumption. . . . 40
17. Number of Selected Surgical Procedures in the United States, 1966-78 . . . 41
18. Proportion of Patients With First-Listed Diagnosis of Ulcer Disease Having Surgery, 1966-78 . . . 43
19. Number and Rate of All and Selected Abdominal Surgical Procedures in the United States, 1970-78. . . . 43
20. Percentage Cost Savings Estimated From Robinson Associates Study . . . 56

LIST OF FIGURES

Figure No. Page

1. Benefit-and-Cost Model for Medical Interventions . . . 8
2. Number of Deaths in the United States With Ulcer Disease as the Primary Cause, 1966-79. . 15
3. U.S. Hospital Discharges With Ulcer Disease Diagnoses, All Sites, 1966-78 . . . 17
4. Paradigm Decision Tree: Cimetidine and Alternative lntervention Strategies . . . 26
5. NCHS Data on Number of Selected Surgical Procedures in the United States, 1966-78. . . . 42
6. CPHA Data on Number of Selected Surgical Procedures in the United States, 1966-78. . . . 42
7. Number of Deaths in the United States From Ulcer Disease, 1976-79 . . . 46

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Benefit= and-Cost Analysis of Medical Interventions: The Case of Cimetidine and Peptic Ulcer Disease

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SUMMARY

Introduction

This case study presents a conceptual model for assessing the benefits and costs of medical technology, and uses this model as a framework for analyzing the benefits and costs of cimetidine in the treatment of peptic ulcer disease.

The body of the study is organized into three major parts: 1) a description of the benefit-and-cost model; 2) a selective description of clinical features, epidemiologic patterns, and costs of peptic ulcer disease; and 3) a review of the development, dissemination, health benefits, and resource costs of cimetidine. The study ends with a critique of one major analysis of cimetidine's costs and benefits and some suggestions for further research.

The Benefit-and-Cost Model for Medical Interventions

The benefit-and-cost model stresses that an evaluation of medical technology must apply to an identifiable patient population and a specific health intervention. An intervention may have a diagnostic or a therapeutic purpose. A patient population may be defined in terms of diagnostic category, a clinical sign or symptom, a risk factor, or a complication of disease.

The model posits two principal classes of effects: clinical effects and health system effects. The specific components of each depend on the population and intervention of interest. Clinical effects and health system effects interact and lead to an outcome, expressed in terms of health status and resource costs.

The components of the model apply to both cost-effectiveness analyses (CEAs) and benefit-cost analyses (BCAs), but the two analytic approaches have distinct purposes and measure some components in different ways. The model can also serve as a basis for identifying the structural components of a decision analysis that compares alternative medical interventions.

The model and a set of guidelines for review of health care benefit-and-cost analyses are used to organize and guide our discussion of the costs and benefits of cimetidine in peptic ulcer disease.

Peptic Ulcer Disease

Ulcers probably have multiple causes, but gastric acid and pepsin appear to be necessary ingredients. Epigastric pain (pain in the upper middle abdomen) is often a prominent symptom of peptic ulcers, but the clinical presentation is variable. Furthermore, typical ulcer symptoms may be caused by conditions other than ulcers. A definite diagnosis requires direct visualization by endoscopy or radiographic imaging of the ulcer. Specific treatments of ulcer disease are directed at reducing the presence or effects of gastric acid.

Ulcer disease is a chronic condition with spontaneous remissions and recurrences. Rates of complications and mortality from ulcers are relatively low, Excessive mortality appears to be present only in the first year or so following diagnosis. Little reliable information exists about the natural history of ulcer disease in the general population.

Peptic ulcer is a common condition that affects millions of Americans at some time during their lives. The best available epidemiologic evidence suggests that about 250,000 Americans develop new peptic ulcers each year. New duodenal ulcers are more than four times as common as new gastric ulcers. Some studies have found that the incidence of duodenal ulcer rises gradually with age; others have found that it remains fairly constant above age 35. Above age 40, the incidence of gastric ulcer appears to rise more dramatically than the incidence of duodenal ulcer. Duodenal and gastric ulcers are epidemiologically distinct. Several lines of clinical and epidemiologic evidence suggest that over the past 20 years the occurrence of new ulcers has declined, or ulcer disease is generally less severe than it was at one time, or both.

The basis for some estimates of the costs of ulcer disease and the benefits of treatment is the Health Interview Survey of the National Center for Health Statistics (NCHS). Results of the Health Interview Survey, based on self-reported conditions in a household survey, however, appear to overestimate the occurrence and consequences of ulcer disease.

We estimate that the costs of ulcer disease in 1975 were approximately $2 billion. Just under half of this total was due to health care expenditures (direct costs), and the remainder was due to productivity losses from morbidity and mortality (indirect costs). Our estimate is based on a review of two independent analyses of the costs of ulcer disease, one by the National Commission on Digestive Diseases (NCDD) and the other by the Stanford Research Institute (SRI). The NCDD and SRI estimates of the total costs of ulcer disease in 1975, $1.3 billion and $2.6 billion, respectively, differ by approximately $1.3 billion. The NCDD and SRI estimates of direct costs differ by approximately $400 million, a difference that reflects differences in the two studies' methods and differences in their detailed assumptions and procedures. Their indirect cost estimates differ by approximately $900 million, a difference that reflects differences in the studies' projected morbidity losses. SRI'S indirect cost estimate, the higher one, is based on data from the Health Interview Survey, which is an inflated indicator of disease-specific morbidity. In both the NCDD and SRI studies, estimated indirect costs are based on a rather low discount rate—2.5 percent. Use of a smaller discount rate increases the present value of future earnings, thereby increasing apparent costs of illness due to morbidity and premature death.

In addition to estimating costs for 1975, SRI projected an estimate of peptic ulcer costs in 1977. Because of unwarranted assumptions of growth in the morbidity of ulcer disease and use of more expensive resources, the problem of overestimated costs is compounded for 1977.

Cimetidine

Cimetidine represents a new class of histamine antagonists, called H_2-receptor antagonists, which block stimulation of gastric acid secretion. The product was developed after extensive research by the Smith Kline & French pharmaceutical firm and is marketed under the registered brand name Tagamet®.

The Food and Drug Administration (FDA) approved the use of cimetidine for up to 8 weeks by patients with duodenal ulcer disease or hy-

persecretory conditions such as Zollinger-Ellison syndrome in August 1977. Use of cimetidine spread rapidly. Since March of 1978, the drug has been prescribed in approximately 60 percent of ambulatory visits for ulcer disease each month. In 1978, a conservatively estimated 1.5 million to 2 million U.S. ambulatory patients with ulcers and other symptoms of gastric acidity were treated with cimetidine. Worldwide sales to hospitals and pharmacies in 1979 probably exceeded $400 million.

The Benefit- and-Cost Model Applied to Cimetidine

Organized according to the benefit-and-cost model presented earlier, this part of the case study describes available information about the effects of cimetidine. It deals separately with cimetidine's 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 ulcers, but more evidence of this is still 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; however, recently reported changes in the bacterial flora of the stomach and endocrinologic effects may be more significant. Available studies of maintenance cimetidine for periods up to 1 year do not alter the current assessment of the drug's relative safety. As is the case with any new drug, possible long-term consequences of cimetidine's use are not known.

Compared to an intense course of antacids, cimetidine is about equally effective and more risky, but less troublesome to patients with duodenal ulcer. Cimetidine plus a moderate amount of antacid. 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 individual patient's preferences and personality.

Compared to placebo, maintenance treatment with cimetidine for as long as 1 year significantly reduces the chance of ulcer recurrence during the treatment period. Once cimetidine treatment 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, and on physician visits. There are several studies under way that may shed light on these matters.

Data from NCHS show that in 1978, the first full calendar year after cimetidine was introduced in the United States, there was an unexpectedly sharp decline in the rates of surgery for ulcer disease. This drop occurred against a background of falling rates of surgery and hospitalization for ulcer disease over the previous decade. Although other explanations of the large drop in surgery for ulcer disease in 1978 are possible, the widespread use of cimetidine may have been a contributing factor.

There is little evidence of any effect of cimetidine on mortality from ulcer disease. In one short-term trial and one maintenance study, patients treated with cimetidine lost significantly

fewer days of work than patients taking placebo, but no controlled study has compared work loss among patients receiving different effective treatments.

Review of Benefit- and-Cost Analyses of Cimetidine

Several analyses of the resource cost implications of cimetidine have been undertaken in the past few years. One major study, by Robinson Associates, Inc., estimated that if cimetidine had been used in 80 percent of duodenal ulcer patients, 1977 cost; for duodenal ulcer disease in the United States would have been reduced by $645 million. This conclusion rests on subjective estimates provided by selected physician experts of the clinical and health system effects of cimetidine, and on independent estimates of the costs of duodenal ulcer disease based in part on the costs of peptic ulcer disease in 1977 projected by SRI.

Our critical review of the Robinson Associates study focuses on the following five areas: 1) the accuracy of the clinical and health system effects projected by their physician experts, 2) the relation between a percentage reduction in health services devoted to ulcer disease and savings in health resources, 3) the accuracy of the estimated total costs of all duodenal ulcer disease used as a baseline for percentage savings, 4) the applicability of projected percentage effects to the total population of patients with duodenal ulcer disease, and 5) the validity of the methods used to compute average percentage effects due to cimetidine. We question some of the assumptions and methods used in each of these areas. Aside from the fundamental issue of possible inaccuracy in the physician estimates, we believe the Robinson Associates study overstates expected savings by twofold to threefold. Potential bias introduced by the selection of physician informants would increase the magnitude of the overestimate.

Despite our criticisms of the study by Robinson Associates, available data and analyses support the belief that cimetidine currently saves more health resources than it costs. Whether further studies will affirm this conclusion or new developments will alter cimetidine's cost effectiveness are empirical questions for the future.

Suggestions for Further Research

If the object of analysis is to help inform clinicians and health policy decisionmakers about the efficient use of resources in the care of patients with ulcer disease, then the most helpful approach would be to do a CEA of alternative interventions oriented to particular groups of patients, comparing incremental clinical benefits to marginal resource costs. Rather than enumerate the resource and health implications for a cross-section of the population in a single year, the analysis might equally or more usefully focus on a cohort of patients and project effects over their lifetimes.

INTRODUCTION

This case study has both a specific and a general objective. The specific objective is to assess available evidence about the benefits and costs of cimetidine, a recently introduced pharmaceutical agent, in the treatment of peptic ulcer disease. The general objective is to present an approach to the evaluation of medical technology that emphasize:; salient features of both the patient population and the medical intervention of interest. The specific purpose serves the general one—we present our analysis of cimetidine and ulcer disease as an application of the general model for benefit-and-cost evaluation. [1]

Peptic ulcer is a logical choice for this kind of evaluation for several reasons. As a diagnostic category, it comprises several anatomically and epidemiologically distinct entities, but these are sufficiently related to make peptic ulcer a valid diagnosis. This common medical problem has a

[1] We use the term "benefit-and-cost analysis" to encom pass both cost-effectiveness and cost-bend it (or bend it-cost) analyses.

highly variable clinical course and an evolving pattern of clinical expression and occurrence. These features help demonstrate that a careful assessment of a disease can be as important to the evaluation of technology as is a comprehensive understanding of the technology itself.

Our selection of cimetidine emerged gradually. Initially, we wanted to use an assessment of peptic ulcer disease as a backdrop for reviewing the costs and benefits of a number of diagnostic tests and therapeutic interventions such as those listed in table 1. (In addition to these contemporary interventions, the variety of clinical approaches to ulcer disease over the past century constitutes a rich history for anyone interested in the progress and byways of medical science (85).) It soon became evident that we could either review several interventions superficially or analyze one in detail. We elected the latter course, believing it would produce a more coherent exposition of the general model.

Table 1.—Selected Contemporary Interventions Used in Peptic Ulcer Disease[a]

Diagnostic interventions
Imaging
• Air-barium, double-contrast radiographic studies
• Fiberoptic endoscopy
Physiologic function tests
• Gastric secretory testing
Therapeutic interventions
Medical
• Antacids
• Anticholinergics
• Cimetidine
Surgical
• Partial gastrectomy
• Truncal vagotomy, with antrectomy or drainage procedure
• Highly selective vagotomy

[a]Descriptions of some of these interventions are provided later in this study

We selected cimetidine for several reasons. First, it is a recent innovation that was disseminated rapidly. Second, as a chemical entity, the drug cimetidine does not evolve technically (unlike, for example, endoscopy) and its effects are relatively independent of the skill of the clinician (unlike, for example, surgery's). Since there are fewer such complications related to the technology, we can appreciate more readily the complexity introduced by features of the disease. Finally, the clinical effects of cimetidine have been studied extensively, and its costs and benefits have been and continue to be formally assessed.

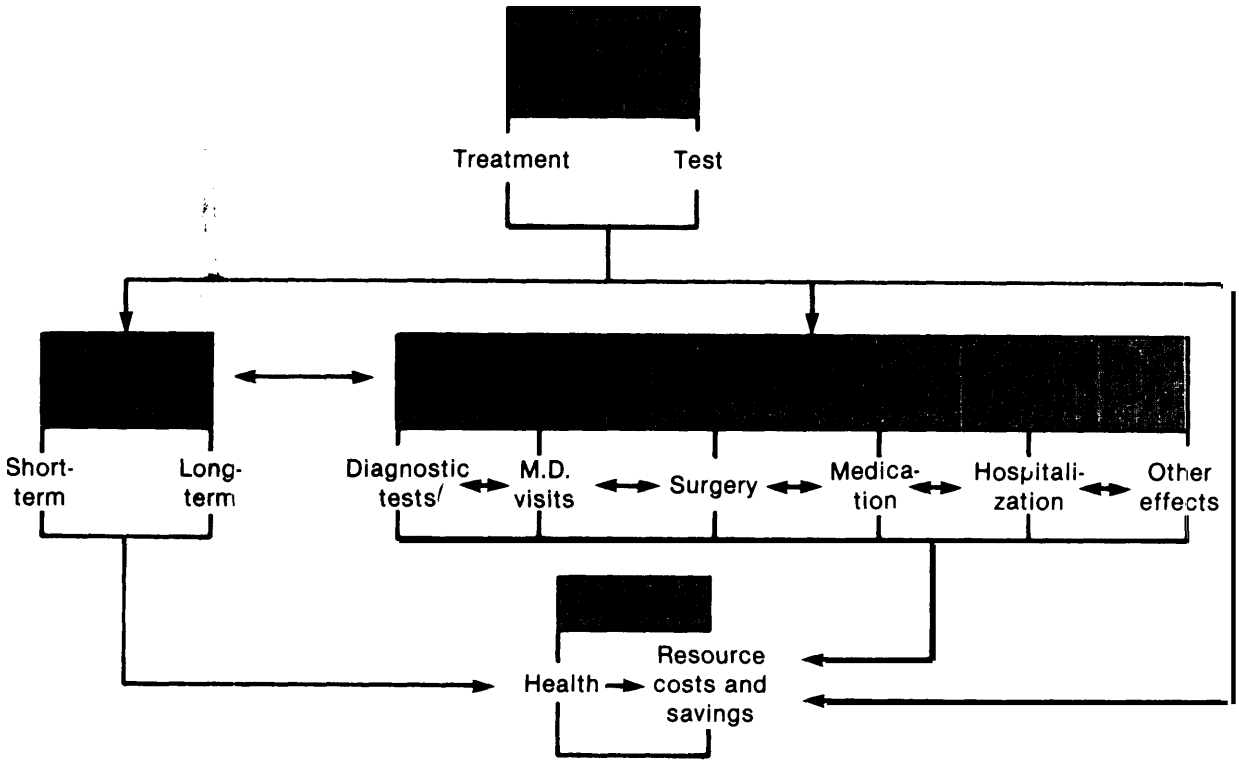
The body of this case study is organized into three main parts. First, we present a brief description of a general benefit-and-cost model for evaluating medical interventions. Second, we describe pertinent clinical and epidemiologic features of peptic ulcer disease, and summarize several cost-of-illness studies of the disease. Third, we review the development, dissemination, health benefits, and resource costs of cimetidine. As a framework for the analysis of cimetidine, we use the general benefit-and-cost model for evaluating medical interventions and a set of questions provided in a section of this case study entitled "Guidelines for Review of Health Care Benefit-and-Cost Analyses." We offer a critique of one major analysis of cimetidine's costs and benefits and end with suggestions for further research.

THE BENEFIT-AND-COST MODEL FOR MEDICAL INTERVENTIONS

Every assessment of the benefits and costs of medical care should apply to an identifiable patient population and a specific health intervention. The ultimate objective of a benefit-and-cost assessment is to measure the effects that a specific intervention has on the health outcome of those patients and on resource consumption. Implicit in this objective is a societal perspective. The health and resource outcomes result from the intervention's direct and induced effects on the clinical well-being of patients and on other components of the health system. These relations and interactions are summarized in the benefit-and-cost model shown in figure 1.

The principal components of the model are as follows: 1) population, 2) intervention, 3) clinical effects, 4) health system effects, and 5) outcome. The population may be delineated in terms of a particular diagnosis or pathologic en-

Figure 1.—Benefit-and-Cost Model for Medical Interventions



tity (e.g., peptic ulcer), a risk factor (e.g., cigarette smoking), a clinical sign or symptom (e.g., dyspepsia), or a complication of disease (e.g., gastrointestinal hemorrhage). Interventions are of two broad types: tests, which are meant to produce information about the clinical status of the patient; and treatments, which are intended to alter the development or course of disease.[2] Clinical effects include any physical or psychological changes that may alter the health status of the patient; these effects may be short or long term. Health system effects include all changes in the methods and means of medical care that are consequent to the initial intervention. The health outcome is reflected in mortality and morbidity, i.e., in the length and quality of life. The resource outcome, resource costs and savings, pertains to net effects on social resource consumption.

[2]The distinction between tests and treatments is useful analytically, but not absolute, since, albeit rarely, a therapeutic trial may also have a diagnostic intent.

The general framework of the model applies to any intervention and patient population. The detailed components under clinical and health system effects, however, will vary with the particular disease and intervention being considered. Thus, for example, if we were analyzing an intervention that might affect chronic disease in the elderly (e.g., a prevention or treatment for senile dementia), we would want to consider nursing home use explicitly under health system effects. In general, the components identified for clinical effects and for health system effects should be: pertinent to the disease and intervention; complete, in that all important effects are considered; and mutually exclusive, so that a single effect is not counted twice. They should also be components for which readily available and accurate measures can be obtained. The validity and feasibility of a cost-effectiveness or a benefit-cost evaluation depend on the extent to which the analytic components conform to these criteria.

According to the model, an intervention itself may alter a patient's clinical status, effect changes in the health system, and consume resources. Clinical effects include both the advantages and risks of care. The direct clinical effects of a test are typically limited to side effects and complications, but a test can also alter clinical status by inducing changes in the health system, primarily by altering the choice of therapy. A treatment is intended to have direct clinical effects, but can also alter subsequent use of diagnostic procedures (a health system effect) by changing the course of the disease.

Clinical effects and health system effects can interact in both directions. As illustrated in the model, interactions among the various health system components may also occur. Changes in a patient's clinical status are likely to alter the future course of medical care for the patient; and shifts in the medication, hospitalization, surgery, or other care given to the patient are likely to affect clinical status.

Although the model is premised on the application of a particular intervention for a particular disease, health system effects may not be limited to the target disease entity. For example, if an intervention reduces the number of physician visits for a particular disease, it could alter the number of diagnostic tests and amount of medication employed for other disease problems.

Health outcome typically includes mortality measures, such as number of deaths, age-adjusted death rates, or years of life lost. It also includes morbidity measures, such as quality-of-life or health-status indexes. Morbidity and mortality may also be combined into a unitary measure, such as quality-adjusted life years (152) or another multiattribute utility scale (87). As indicated in the model, morbidity and mortality also have direct implications for productivity and hence for social resource consumption.

The benefit-and-cost model for a particular population and intervention suggests the complexity of undertaking a comprehensive assessment of either all uses of a single intervention or all interventions for a particular population. Consider two interventions, endoscopy and cimetidine, and the population of patients with duodenal ulcer. Both interventions are used in some patients with duodenal ulcer; each is used independently of the other in some patients with duodenal ulcer; and both interventions are also used, singly or together, in some patients without duodenal ulcer. Moreover, neither intervention is used in some patients with duodenal ulcer. Compound these partial overlaps with additional interventions, add variations in the particular populations for which data are available, and the magnitude of the problem begins to become apparent.

The benefit-and-cost framework outlined here is applicable to both BCA, or cost-benefit analysis (CBA), and CEA. A BCA assesses the net value of an intervention by summing all effects on a common scale. Typically, both resource expenditures and health outcome effects are assigned monetary values. A variety of means to measure the resource value of health benefits have been proposed; the most widely used is expected productivity loss based on discounted future earnings at the age of death or disability (31,89). Thus, a BCA converts decreased deaths and disabilities into increases in productivity, and treats them as the indirect benefits of a health intervention. These indirect benefits are added to any direct savings in health resource consumption (the direct benefits) to yield a net value.

In the cost-effectiveness approach, the aim is to measure the efficiency with which an intervention achieves health benefits. The questions addressed in CEA are: 1) What is the most efficient way to achieve a particular health benefit? or 2) Given specified available resources, what intervention strategy offers the greatest gain in health benefit? Answering these questions requires the commensuration of different types of benefits, such as morbidity and mortality, but permits benefits to be measured in their own, nonmonetary terms. A cost-effectiveness approach is more likely than a benefit-cost approach to preserve a sense of intangible health care benefits, which in the latter are typically noted and left unassessed. Although CEA may be more suitable for comparing alternative in-

terventions for a particular disease, however, BCA is necessary for comparing health care with other socially desirable uses of resources.

If one chooses to develop a decision analysis comparing the use of a particular intervention with its alternatives, the benefit-and-cost model can serve as a useful basis for identifying pertinent structural components: chance events (e.g., important results of the principal and subsequent interventions), choices (e.g., use of other health system components), and outcomes (e.g., net benefits and costs). The decision-analytic approach is a prescriptive model for choosing among alternative treatment strategies. Even if technically correct in all assumptions and computations, a decision analysis does not necessarily predict the management strategies employed by physicians. In estimating the cost effectiveness of a given intervention, it is equally, if not more, important to apply a descriptive model (i. e., to base estimates on changes in management strategy that occur in practice). The distinction between prescriptive and descriptive assessment is analogous to the differentiation between efficacy (effects under ideal conditions) and effectiveness (effects under average conditions) noted in reports from OTA (112).

Any benefit-and-cost analysis encounters numerous conceptual and practical difficulties. These range from the presence of uncertainty and the lack of reliable information to questions of measurement and methods of aggregation over persons and time, to value judgments. Systematic reviews of methodologic issues in CEA and BCA in health have been presented by other authors (149,151).

Following descriptions of peptic ulcer disease and cimetidine in the next two parts of this case study, we present an analysis of the costs and benefits of cimetidine in peptic ulcer disease, using the general benefit-and-cost model described above. Later in the case study, we present a set of guidelines in the form of questions to be used in reviewing benefit-and-cost analyses in health care. These guidelines presume familiarity with the basic assumptions and approaches in BCA and CEA. We believe they are helpful for review of benefit-and-cost analyses of cimetidine such as that presented in the next to the last part of this case study.

PEPTIC ULCER DISEASE

Definition and Etiology

A peptic ulcer is a crater that extends through the full thickness of the mucosa (mucous membrane) of the stomach or duodenum (the first or proximal portion of the small intestine). The pathologic appearance of benign gastric (stomach) and duodenal ulcers is similar; both are believed to be related to too much stomach acid and pepsin for the level of mucosal resistance (82) .[3] Although the presence of stomach acid is necessary for ulcers to develop, the level of acid is often normal in patients with ulcer disease; these patients presumably have impaired tissue resistance. Sturdevant and Walsh (140) list 17 factors other than excessive gastric acidity that may predict increased likelihood of developing duodenal ulcer. These factors include sex, age, blood type, a few diseases, and habits such as smoking and drinking coffee. Despite the popular notion of the "high anxiety, ulcer-prone person, " psychological stress and personality factors have not been shown conclusively to be related to the development of ulcers,

The gastrointestinal tract is a continuous organ, and there is a continuum in the anatomic location of ulcers in the stomach and duodenum. For unknown reasons, peptic ulcers show a predilection for areas at or near rnucosal junctions (81). Since gastric and duodenal ulcers appear to differ in generic and other features, there are reasons to consider them separately in clinical and epidemiologic studies. Often, however, they are considered together, and the situation is further complicated by the frequent oc-

[3] Pepsins are digestive enzymes that are active only in the presence of acid Hence, it is difficult to separate the roles of acid and pepsin in the pathogenesis of ulcer.

currence of new duodenal ulcer in patients who previously had gastric ulcer (17).

Symptoms and Diagnosis

Both duodenal and gastric ulcers produce abdominal pain in the patient, typically in the epigastric region (upper middle abdomen). Less often, they produce nausea and vomiting. Usually, the pain is relieved by food, but in some patients, food may exacerbate pain. Most patients with epigastric pain do not have ulcers; a Danish study found that 68 percent of men and 83 percent of women with epigastric pain did not have ulcers (cited by 140). Some patients develop painless ulcers and have bleeding or perforation as the first manifestation of ulcer disease (119,140).

The specific diagnosis of peptic ulcer depends primarily on imaging examinations, with either barium X-rays or more direct fiberoptic endoscopy. Fully flexible fiberoptic gastroscopes were introduced in 1958 (77). Numerous technical improvements made since have enhanced the flexibility, ease of control, and clinical usefulness of these instruments (10). Endoscopists have formed their own professional society (the American Society for Gastrointestinal Endoscopy), and the endoscopic procedure is widely used. Radiographic examination of the stomach has been improved in recent years by the use of an air-barium, double-contrast technique involving high-density barium sulfate, effervescent tablets to distend the stomach and simethicone to break up small air bubbles (96).

Acid secretion and other tests play a secondary role in diagnosis, except in occasional patients, such as those whose ulcer is caused by gastrinoma (a gastrin-secreting tumor that produces the Zollinger-Ellison syndrome of severe ulcers, intractable pain, and diarrhea).

Treatment and Natural History

The treatment of peptic ulcer disease is intended to relieve symptoms, promote healing, and prevent recurrences and complications (140). Gastric acid is the focus of contemporary specific treatment for peptic ulcer—reducing acid secretion by pharmacologic or surgical means, neutralizing acid with antacids, or increasing tissue defenses against acid.[4] Some physicians begin treatment on the basis of clinical symptoms without pursuing a definitive **diagnosis** (140). A U.S. patient who is diagnosed as having a new peptic ulcer will typically be told to eat a regular, nutritious diet and to avoid aspirin, alcohol, cigarettes, and coffee. Specific medication might include antacids or cimetidine and possibly anticholinergic drugs (drugs that block the passage of impulses through the parasympathetic nerves).

Surgery is normally reserved for patients with recalcitrant symptoms, frequent relapse, or complications such as bleeding, perforation, or obstruction. A large variety of surgical procedures has been advanced over the past century, and there is considerable difference of opinion about the optimal timing and selection of an elective surgical procedure for patients with peptic ulcer disease (44,73,111,124). Highly selective vagotomy has been advocated recently (78). This procedure entails transection of only those nerve fibers that supply the lower esophagus and body of the stomach; the nerve supply to the remainder of the stomach and to other abdominal organs is left intact. Proponents of highly selective vagotomy believe that this procedure obviates some unpleasant side effects of standard vagotomy (cutting of the vagus nerve). The surgical procedure is technically demanding, however, and its comparative effectiveness in the hands of many different surgeons remains to be shown. Cochran, et al. (30) have described the complexity of evaluation and requirements for adequate assessment of any surgical treatment for ulcer disease.

Over the years, an enormous variety of nonsurgical therapeutic regimens has been employed to treat peptic ulcers. An example is diet: Leube introduced a starvation regimen in 1876; Lenhartz recommended frequent small feedings in 1906; and Sippy proposed a bland diet in 1915, variations of which remained popular for-

[4]Improved resistance of cells lining the stomach and duodenum is the presumed mechanism of action of the drug carbenoxolone. Carbenoxolone is a licorice derivative, first used clinically more than 15 years ago. Although prescribed in more than 40 countries, it is not currently available in the United States (86).

many years (84, 119). Now dietary restrictions are believed to play no role in the management of peptic ulcers (119,140), Despite the demonstrated ineffectiveness of diet in the treatment of ulcers, special diets are still widely prescribed (153). The plethora of unsubstantiated, but traditional and trusted, treatments led one authority to exclaim in the late 1960's: "Few conditions provide such a splendid opportunity for practicing 19th century medicine in the second half of the 20th century as gastric ulcer" (37). The 1960's witnessed the introduction, spread, and decline of gastric freezing, a nonsurgical treatment intended to reduce stomach acid and promote healing. Such treatment was eventually proven to be ineffective and occasionally harmful. Some clinicians have also used X-ray therapy to treat ulcer disease in selected patients, and renal failure has been reported as one late complication of such therapy (143).

The reasons for such diverse treatments, and particularly, for the extended use of some ineffective approaches, rest partly in the expression and natural history of ulcer disease. First, as mentioned earlier, the cardinal symptom of ulcer disease is stomach pain; so subjective an expression of illness as stomach pain may respond to suggestion or placebo. Second, ulcers often heal spontaneously; thus, any apparent success with treatment should be compared to the natural rate of healing. Finally, ulcer disease tends to be chronic, with recurrences and remissions; effective short-term treatment may or may not alter the long-term outlook.

The subjective nature of ulcer disease and its variable course suggest that evaluations of treatment must be controlled carefully for bias, preferably with double-blind randomization, On this score, the state of clinical assessments of peptic ulcer disease appears to be improving. Chalmers, et al. (25) reviewed studies of peptic ulcer treatments published in a leading gastroenterology journal and found that more than so percent of the therapeutic trials published after 1976 had a randomized, controlled design, compared to 30 percent or fewer of those published between 1970 and 1974. In addition, improved endoscopic methods now permit a more definitive diagnosis to be established in patients included in clinical trials.

Assessment of long-term results of any intervention in ulcer disease requires comparison to the natural history of the disease. Ideally, the natural history of peptic ulcer disease would be defined through long-term followup of a representative sample of patients with ulcer disease. As discussed below, however, available information about the natural course of ulcer disease is fragmentary.

Fry (57) reported a 5- to 15-year followup of 212 patients with ulcer disease diagnosed between 1948 and 1957 in his general practice in London. He found that symptoms tended to recur and worsen for the first 5 to 10 years, and then usually diminished, irrespective of treatment. Sixteen percent of patients with duodenal ulcer and 18 percent with gastric ulcer required surgery. Complications of bleeding occurred in 14 percent and complications of perforation in 6 percent. Only one patient died from causes related to ulcer.

Krause (91) found similarly low mortality from ulcer in 371 Swedish patients with duodenal ulcer followed for 25 to 35 years. In a study based on a 50-percent random sample of all patients with duodenal ulcer diagnosed between 1963 and 1968 in the population of 500,000 persons living in Copenhagen County, Denmark, Bonnevie (20) found a significant additional mortality risk in the first year following diagnosis of ulcer, but not thereafter. Griebe, et al. (66) interviewed 154 patients living; in Copenhagen in 1976 who had developed duodenal ulcer disease in 1963. One hundred and twenty patients (78 percent) had been treated medically; nearly half of these patients were asymptomatic, and approximately 16 percent still had severe symptoms. Thirty-four patients had been treated surgically, but their clinical status is not described further.

A Veterans Administration (VA) study followed more than 600 patients with gastric ulcer diagnosed in 16 hospitals during a 7-year period (69). More than 75 percent of the patients experienced ulcer healing with medical treatment

within 12 weeks, but 42 percent of these patients had one or more recurrences in the following 2 years. Patients who failed to heal initially were assigned randomly to further medical or surgical treatment. Two years later, a higher proportion of patients in the the surgical group were alive and free of symptoms and recurrence, but the differences between the surgical and medical groups were not statistically significant. Expressed as a proportion of incidence per year among all patients, complications of hemorrhage occurred in 2.5 percent, obstruction in 1.2 percent, and perforation in 0.6 percent.

For several reasons, the available data on the natural history of ulcer disease are unsatisfying. The data come from different geographic 1ocations and cover different time periods and different mixes of patients with duodenal and gastric ulcer. Patients received various treatments (and differing proportions were offered surgery), and results reflect the history under varied treatments rather than a natural history of the disease. Rates of complication and death due to ulcer are low and difficult to assess in relatively small cohort studies; Bonnevie's analysis (20) is exceptional in specifying the attributable mortality risk from newly developed ulcer disease. Finally, such studies of the clinical course of disease are necessarily dated. If the course of ulcer disease is changing over time, data from previous patient cohorts may not apply today.

Epidemiologic Patterns

Ulcer disease is a common medical problem, but has apparently become less common over the past 20 years. Here we summarize estimates of the present incidence and prevalence of ulcer disease and describe the basis for the conclusion that ulcer disease is occurring less frequently. We conclude this section with comments directed specifically to the Health Interview Survey conducted by NCHS, since although its results are used in several estimates of the costs of ulcer disease and the benefits of intervention, we believe the Health Interview Survey overestimates the prevalence of ulcer disease.

Several aspects of the definition of disease and of data collection limit our ability to compare results from different studies of the occurrence of ulcer disease in the United States today. Any effort to assess the incidence and prevalence of ulcer disease is necessarily restricted to a particular place and time. Insofar as there are geographic variations and shifts in the disease over time, projections to other countries and to the present data are uncertain.

In addition, different studies define the prevalence and incidence of this chronic and recurrent disease differently. Some (e.g., 35,36,57) define prevalence to mean the "period prevalence, " or the number of patients who suffer from ulcer disease during a given time period; others (e. g., 105) use prevalence to mean the "lifetime prevalence, " or the proportion of patients who have ever had an ulcer. Incidence may be taken to mean the proportion of a population at risk that first develops ulcers in a given time period (e.g., 18,19) or the percentage that develops either a new or recurrent active ulcer crater during a given time period (e. g., 147). The methods employed in different studies to detect disease also vary, ranging from the use of autopsy results, through review of clinical records, to the use of questionnaire surveys.

On the basis of a number of epidemiologic studies, some experts estimate that the current incidence of new cases of duodenal ulcer in the United States is about 200,000 per year and that the incidence of new cases of gastric ulcer is about one-fourth that (140).

Bonnevie (17, 18, 19) reported several comprehensive surveys of duodenal and gastric ulcer disease occurring between 1963 and 1968 in Copenhagen County, Denmark (an area with 500,000 inhabitants). Defining incidence as new ulcer disease and basing the diagnosis on review of hospital records, he estimated the annual incidence of duodenal ulcer per 1,000 persons age 15 and over to be about 1.8 for men, 0.8 for women, and 1.3 overall (18). The annual incidence of gastric ulcer alone per 1,000 inhabitants age 15 and over he estimated to be approximately 0.3 for both men and women (19). He also found that duodenal and gastric ulcers occur in the same patient much more often than would be expected by chance if the two types occurred independently (17). Bonnevie (18,19)

cites earlier population surveys conducted in England, Scotland, Norway, and Denmark that found incidence of duodenal ulcer ranging from 0.38 to 2.70 per 1,000 inhabitants age 15 and over and incidence of gastric ulcer ranging from 0.1 to 1.14 per 1,000 inhabitants age 15 and over.

A mail survey of Massachusetts physicians conducted in 1967 and 1968 found the incidence rates of reported duodenal ulcer of 1,000 persons age 25 and over to be approximately 2.9 per year for men and 1.5 per year for women (105). In the same study, physicians reported the incidence of gastric ulcer per 1,000 persons age 25 and over to be approximately 0.35 per year.

Different epidemiologic studies have found varying patterns of age-specific incidence of duodenal and gastric ulcer. In general, the incidence of duodenal ulcer appears to rise gradually with age or to remain essentially constant above age 35, and the incidence of gastric ulcer appears to rise more dramatically above age 40. Bonnevie (18) found the age-specific incidence rate of duodenal ulcer to increase gradually in both sexes to a maximum of 3 per 1,000 inhabitants between age 75 to 79. Gastric ulcer showed a more dramatic rise in incidence above age 40, peaking at a level of about 1 per 1,000 for men age 60 to 64 and for women above age 70 (19). Among Massachusetts physicians surveyed in the late 1960's, the incidence of duodenal ulcer in both sexes appeared to increase up to age 25 to 34, and then to remain fairly constant; gastric ulcer in male physicians continued rising to a peak at age 65 to 74 (105). Fry's review of his patient experience showed duodenal ulcers reaching their peak incidence in both sexes in the decade 1930-39 and gastric ulcers reaching their peak some 20 years later in the decade 1950-59 (57).

The aforementioned incidence figures are substantially lower than the rates found in recent household interview surveys conducted by NCHS (35,36). After we review evidence concerning the prevalence and changes in the occurrence of ulcer disease during the past 20 years, we will discuss NCHS's Health Interview Survey (which is based on household interviews) in more detail.

According to traditional medical lore, 1 U.S. male in 10 will develop a duodenal ulcer by age 55. As pointed out by Mendeloff (104), this easily remembered figure is based on projections made by Ivy in 1946 (84). A number of autopsy studies in Britain and elsewhere (cited by 104) confirmed this figure. It may be argued that insofar as the stress of illness can provoke ulceration, autopsy results may be misleading for the population at large. However, the previously cited survey of Massachusetts physicians (105) also found that approximately 10 percent of male physicians age 65 through 74 at some time had duodenal ulcer. The current level is a matter of conjecture, because the lifelong prevalence rate of ulcers ultimately depends on age-specific incidence rates, and these rates appear to be declining,

Ulcer disease appears to have been occurring less frequently or less severely, or both, over the past 20 years. This conclusion derives from several lines of clinical and epidemiologic evidence. These include overall declines in rates of mortality and hospitalization due to ulcer disease, and, especially, several age-cohort analyses of the incidence and mortality of ulcer disease.

Susser (141,142) deduced from age-specific mortality rates between 1900 and 1960 that there was a decrease in risk of ulcer disease in each successive age cohort, producing a rise in the mean age of patients. This decline was corroborated by a cohort analysis conducted by Monson and MacMahon in their survey of Massachusetts physicians (105). Monson and MacMahon found the age-specific risk of developing ulcer disease among physicians born between 1922 and 1932 to be much lower than the rate for those born in the preceding 20 years. A study of British physicians found a 40-percent decrease in the incidence of duodenal ulcer disease between 1947 and 1965 (103).

U.S. mortality from ulcer disease has declined steadily since the early 1960's (see table 2 and fig. 2). The age-adjusted mortality rate dropped by two-thirds in 1977 from its 1962 peak level

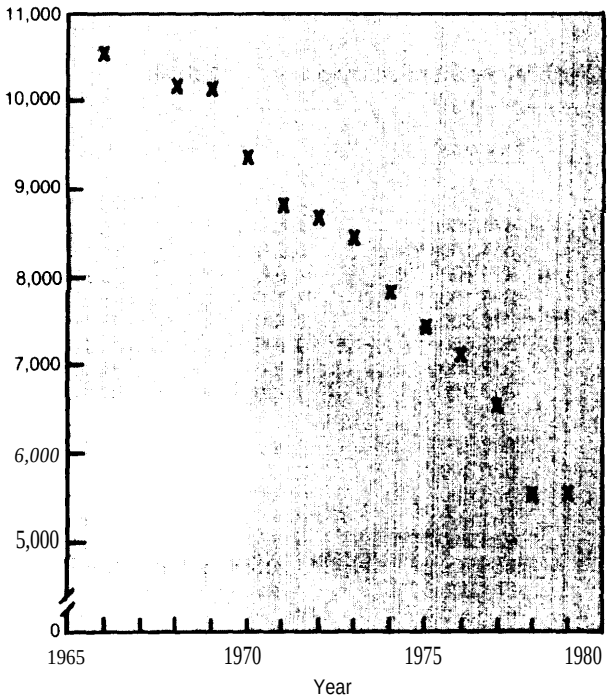
Table 2.–Number of Deaths in the United States With Ulcer Disease as the Primary Cause, 1960-79

Year	Gastric	Duodenal	Peptic, site unspecified	Gastrojejunal	Total
1960	5,707	5,653	—	322	11,682
1963	6,330	5,831	—	244	12,405
1966	5,599	4,722	—	197	10,518
1968	3,829	4,413	1,218	721	10,181
1969	3,719	4,381	1,212	798	10,110
1970	3,502	3,916	1,189	739	9,346
1971	3,385	3,680	1,055	700	8,820
1972	3,274	3,510	1,132	756	8,672
1973	3,289	3,385	1,014	765	8,453
1974	3,050	3,048	971	751	7,820
1975	2,900	2,920	923	710	7,453
1976	2,834	2,686	908	698	7,126
1977	2,669	2,452	779	662	6,562
1978	—	—	—	—	5,550[a]
1979	—	—	—	—	5,560[b]

[a]Preliminary figures, extrapolated from a 10-percent sample
[b]Preliminary figures extrapolated from a IO percent sample over the first 6 months of 1979

SOURCE National Center for Health Statistics, Division of Vital Statistics, Hyattsville, Md

Figure 2.— Deaths in the United States With Ulcer Disease as the Primary Cause, 1966-79



Note: 1978 and 1979 figures are preliminary.

SOURCE Based on data from the National Center for Health Stat{ stics, Division of Vital Statistics Hyatt sville Md

(see table 3), Hospitalizations for ulcer disease have also declined steadily in both the United States (see table 4 and fig. 3) and Great Britain (21). The drop in U.S. hospitalizations appears mainly due to a fall in admissions for duodenal ulcer, whereas the drop in Great Britain is due more to declining admissions for gastric ulcer. Mendeloff (104) reported a sO- percent decline in the number of diagnoses of duodenal ulcer between 1960 and 1972 among an apparently constant population in the U.S. armed forces. Data from a large U.S. manufacturing company showed a 56-percent drop in episodes of disability due to duodenal ulcer and a 68-percent drop in episodes of disability due to gastric ulcer between 1960 and 1970 among male employees (3).

Some of these trends might be explained by the advent of a dramatic and continuing improvement in the prevention and care for ulcer disease during the past 20 years, but no likely candidate representing this can be found (21). The data are consistent with a shift in the spectrum of ulcer disease toward less severe forms, a possibility posited by Mendeloff (104). Such a shift may accompany what appears to be the simplest explanation: Ulcers are occurring less frequently than they did previously. The rea-

Table 3.—Mortality Rates in the United States for Deaths Due to Ulcer Disease 1953-78

Year	Age-ad lusted rate per 100,000 populatation[b]	Crude rate
1953	5.1	
1958	5.3	—
1960	5.2	—
1961	5.2	—
1962	5.4	—
1963	5.2	—
1964	4.6	—
1965	4.3	—
1966	4.2	—
1967	3.9	—
1968	3.7	—
1969	3.6	—
1970	3.2	—
1971	3.0	—
1972	2.9	—
1973	2.7	—
1974	2.4	—
1975	2.2	3.2
1976	2.1	2.7
1977	1.8	2.7
1978	—	2.6

[a]Rates shown include gastric, duodenal, and peptic ulcer (site unspecified)
[b]Adjusted to 1940 population, the standard population used by the National Center for Health Statistics

SOURCE National Center for Health Statistics, Division of Vital Statistics, Hyattsville, Md

sons for the apparently declining incidence and severity of ulcers are matters for speculation,

The data on ulcer disease from the Health Interview Survey of NCHS warrant separate consideration for three reasons. First, the Health lnterview Survey data are gathered in a unique manner; they are based on self-reported conditions in household interviews. Second, estimates of disease incidence and consequences obtained from Health Interview Survey data are substantially greater than those obtained from other sources, including other NCHS sources and epidemiologic studies such as those described above; also, estimates from the Health Interview Survey show little change between the years 1968 and 1975. Finally, the survey data deserve special attention, because they are used to estimate some of the costs and benefits of treatment for ulcer disease that we review later in this case study.

Household surveys of chronic digestive diseases in the United States were conducted in

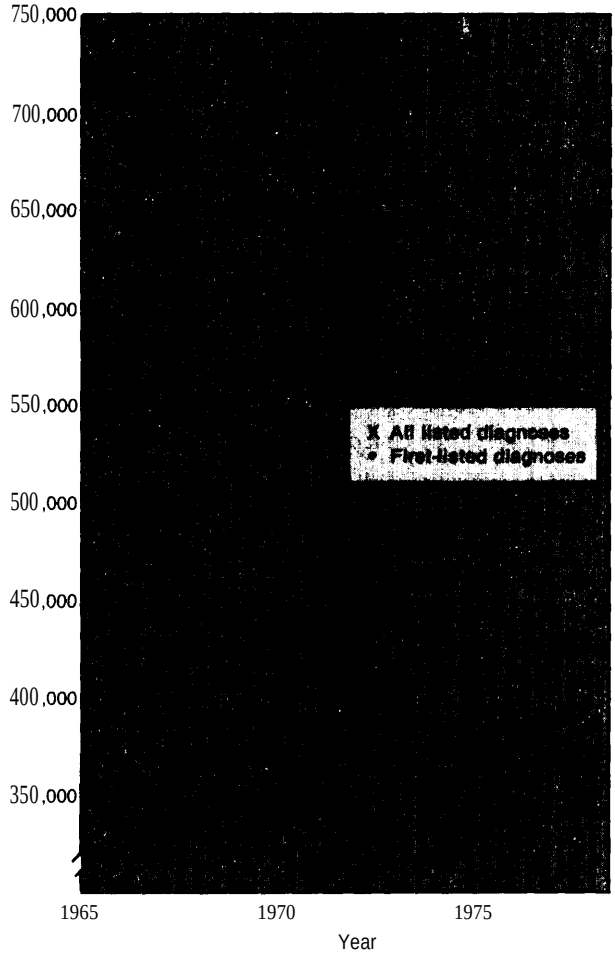
Table 4.—Number of U.S. Hospital Discharges With Ulcer Disease Diagnoses, 1966-78

Year	Gastric	Duodenal	Peptic, site unspecified	Subtotal[a]	Gastrojejunal	Total[b]
Ulcer as first-listed diagnosis						
1966	166,100	345,200	—	511,300	14,700	526,000
1970	89,200	273,500	68,300	431,000	7,400	438,400
1971	94,100	251,400	68,600	414,100	6,600	420,700
1972	99,300	241,400	81,200	421,900	7,400	429,300
1973	102,900	227,100	68,100	398,100	7,200	405,300
1974	101,500	239,800	75,300	416,600	8,700	425,300
1975	101,500	224,100	77,000	402,600	9,100	411,700
1976	103,400	194,000	81,100	378,500	6,900	385,400
1978	105,100	166,300	81,900	353,300	7,200	360,500
Ulcer as a listed diagnosis						
1966	223,800	464,300	—	688,100	17,500	705,600
1970	127,200	384,200	108,900	620,300	9,100	629,400
1971	137,200	358,600	110,800	606,600	9,100	615,700
1972	147,300	362,300	131,800	631,400	9,500	640,900
1973	149,800	339,900	123,700	613,400	9,600	623,000
1974	156,400	360,200	136,100	652,700	11,200	663,900
1975	158,400	336,200	150,300	644,900	12,400	657,300
1976	160,700	302,300	158,300	621,300	10,700	632,000
1977	173,000	285,900	159,300	618,200	8,700	626,900
1978	165,400	279,400	184,600	629,400	10,800	640,200

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

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

Figure 3.—U.S. Hospital Discharges With Ulcer Disease Diagnoses, All Sites, 1966.78



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

Table 5.—Ulcer Disease in the United States According to the Health Interview Survey, NCHS[a]

Measure	1968	1975	1978
Number of conditions (in 000's)	3,360	3,955	3,778
Prevalence per 1,000 persons[b]	17.2	18.9	17.7
Incidence per 1,000 persons[c]	3.0	2.9	–
Ever hospitalized for ulcer disease	40.60/0	38.30/0	—
Ever had surgery for ulcer disease	6.90/o	8.1%	–
Currently under M.D. care	61.1 0/0	65.40/o	—
M.D. visits in past 12 months:			
0	32.4%	36.1%	–
1	17.1%	17.8%	—
2 to 4	23.70/o	26.30/0	—
5 or more	18.20/o	15.80/o	—
Unknown	4.60/0	4.00/0	—
Number of bed-disability days[d]:			
0	74.5	74.5	—
1 to 3	—	7.4	–
4 to 7	—	5.2	–
8 to 14	4.9	4.4	—
15 to 30	3.6	3.6	–
31 or more	3.4	2.2	–

[a] Includes gastric, duodenal, peptic (site unspecified), and gastrojejunal ulcer
[b] Condition reported as having been present at some time during the Year Prior to Interview
con set reported as within year prior to interview
[d] A bed-disability day is a day in which a person stays in bed for all or most of the day because of ulcer

SOURCE National Center for Health Statistics, Division of Health Interview Statistics, Hyattsville, Md

by NCHS 1968 and 1975 (35,36). The surveys consisted of questions asked at a sample of households designed to represent the civilian, noninstitutionalized U.S. population. Selected Health Interview Survey results pertaining to ulcer disease are summarized in table 5. The projected incidence of new ulcers based on the Health Interview Survey, approximately 600,000 cases per year, is more than double that based on other epidemiologic evidence described earlier. People interviewed at home reported approximately 7 million physician visits for ulcers in 1975, nearly triple the 2.5 million physician visits for ulcer disease that year reported in the NCHS National Ambulatory Medical Care Survey (34). In contrast to other epidemiologic evidence for the declining incidence of ulcers, the Health Interview Survey results show little change, with even a slightly increased prevalence between 1968 and 1975.

These discrepancies may derive from several sources. Most likely, more people report having ulcers in the Health Interview Survey than actually have them. Some individuals without medical training may think of any stomach trouble as "ulcers" and use the specific medical term more broadly than is clinically correct. In 1975, more than 36 percent of the people who reported having ulcers in the previous year did not see a doctor for that reason. (The proportion with newly reported ulcers who were self-diagnosed is not given.) Many of those who did see a doctor may have been treated on the basis of symptoms without a definite diagnosis. The Health Interview Survey may be an accurate summary of what the noninstitutionalized public reports, but that is not the same as an ac-

curate epidemiologic assessment of a disease problem.

Cost of Illness

Studies of the cost of peptic ulcer disease are among the earliest efforts by economists to assess the costs of individual diseases (14). Beginning with the very first studies, a basic distinction was drawn between direct costs (health system expenditures to prevent, diagnose, and treat the disease) and indirect costs (economic losses due to morbidity and mortality). Most economic studies measure the indirect costs of illness in terms of loss of productivity due to disability from disease and loss of future productivity due to premature death.

The same basic categories of direct and indirect costs continue to be used in contemporary economic analyses of the cost of illness (31,114). Most researchers take an aggregate approach to measuring direct costs of disease, using data from third-party payers, NCHS, and other hospital and physician surveys, and estimating total expenditures for a given disease population in a given time period, usually 1 year; we will return to these methods shortly. First, however, we will mention patient-specific alternatives to measuring direct costs of illness.

One alternative is to trace over time expenditures for a cohort of patients with a particular disease. As far as we know, no such studies of ulcer disease have been published, but at least one study now under way at the University of Wisconsin may produce useful information of this sort (58). We comment on this study by Weisbrod and Geweke in our discussion of cimetidine. Such cohort studies have the advantage of being patient-specific and may show relationships between interventions and expenditures at one point in time and subsequent clinical courses and health expenditures. Cohort cost studies thus could complement other research, possibly as a part of longitudinal studies of the clinical course of disease.

A second patient-specific approach is to study the cost of treating episodes of illness. Duodenal ulcer disease was one of eight medical conditions studied in this way by Scitovsky and McCall (128), These investigators defined an episode of duodenal ulcer illness as a 6-month period beginning with the date of diagnosis of duodenal ulcer. They assessed the cost of treating episodes of duodenal ulcer disease for nonhospitalized patients treated at the Palo Alto Medical Clinic in 1964 (35 patients) and in 1971 (27 patients). In constant dollar terms, the overall cost of treating ambulatory patients with duodenal ulcer declined slightly (but not significantly) between 1964 and 1971. The average number of physician visits per patient during the defined 6-month episode of illness fell from 4.7 in 1964 to 3.8 in 1971. The average number of X-rays also declined slightly. These decreases were nearly offset by increased expenditures for drugs.

Patient-specific studies are very useful for many purposes, but they are not intended to provide a cross-sectional view of all costs for all patients with ulcer disease in a given time period. Providing such a view is the aim of studies that take an aggregate approach to estimating direct costs of disease.

In two recent studies of the cost of ulcer disease discussed below, the indirect costs of ulcer disease were measured by using the "human capital" approach of estimating losses in productivity attributable to the disease. A number of philosophical objections have been raised to the "human capital/lost productivity" approach to valuing lives, e.g., productivity measures omit consideration of pain and suffering. Alternative methods for valuing life, such as a "willingness-to-pay" approach, have been used (1), but not as often as the human capital approach. Over the past 20 years, the sophistication of lost productivity estimates has increased considerably, and now may include the discounting of future earnings, the adjustment of future earnings for productivity gains, adjustments for labor force participating rates, and calculation of productivity loss for people performing unpaid housework (31), In addition to the sophistication of analysis, a second major difference between recent studies of the cost of ulcer disease and the earliest studies 20 years ago is the greater amount of information now available about the prevalence, distribution,

and health consequences of the disease. As discussed in the previous section of this case study, however, uncertainty about the evolving epidemiology of ulcer disease is a major source of discrepancies in contemporary estimates of the cost of the disease.

One of the two recent analyses of the cost of ulcer disease that we will now discuss was undertaken as part of the NCDD assessment of the socioeconomic impact of digestive diseases (4). The other analysis was prepared at SRI under contract with Smith Kline & French Laboratories by Von Haunalter and Chandler (146). Both the NCDD and SRI studies estimated the cost of ulcer disease in 1975, and we focus primarily on those figures. In addition, the SRI study projected estimates for 1977; these served as the basis for a major cost-effectiveness study of cimetidine (the study by Robinson Associates (121)) that is reviewed in another part of this case study.

The costs of peptic ulcer disease in 1975, as estimated by NCDD and SRI, are summarized in table 6. The total cost (direct and indirect) estimated by NCDD is approximately $1.3 billion; the estimate by SRI is approximately $2.6 billion.[6] Table 6 also shows a "midpoint estimate" of approximately $2 billion. We believe $2 billion to be a defensible overall cost estimate, for reasons we shall explain. Peptic ulcers accounted for less than 1 percent of total costs of all illness in 1975 (114), and, according to NCDD figures, health system expenditures for ulcer were approximately 9 percent of health expenditures for all digestive diseases in 1975. Of the total $2 billion costs for ulcer disease, just under half are attributed to health system costs (direct costs); the rest are attributed to lost productivity due to premature mortality and to morbidity (indirect costs).

A comparison of the NCDD and SRI estimates by cost category reveals that the discrepancy between them is largely due to differences in the indirect costs attributed to morbidity (see table 6). In addition, SRI's estimates of direct costs for hospital and physician services are notably higher than NCDD's (see table 6). Closer examination of the sources of these discrepanices in direct cost estimates reveals variation in the two studies' analytic methods, as well as shortcomings in data needed for such cost estimates.

Table 6.—Costs of Ulcer Disease in 1975 as Estimated by NCDD and SRI (millions of dollars)

	NCDD estimates	SRI estimates	Approximate midpoint estimates
Direct costs			
Hospitalization	$501	$ 803	$652
Physician visits	123	240	182
Drugs		100	
Nursing home care	102[a]	11	108a
Other professional	1	3	}
Subtotal	$726	$1,157	$942
Indirect costs[b]			
Mortality	$369	$ 357	$ 369c
Morbidity	179d	1,116	648
Subtotal	548	1,473	1,017
Total	$1,274	$2,630	$1,959

[a]This sum represents the total for drugs, nursing homes, and other professional costs Figures were not broken down further
[b]Future earnings discounted at 25 Percent
[c]The higher NCDD figure is adopted for reasons explained in the text
[d]This figure is imputed from Information supplied in the NCDD report

SOURCES **NCDD estimates:** T P Almy, et al , "Report of the Workgroup on the Socioeconomic Impact of Digestive Diseases of the Subcommittee on Epidemiology and Impact. " in *Report to the Congress of the United States of the National Commission on Digestive Diseases,* 1979 (4)
SRI estimates: G Von Haunalter and V V Chandler, Cost *of Ulcer Disease in the United States,* 1977 (146)

Medical care costs attributable to a particular disease may be estimated in two ways: 1) by a "top-down" approach that begins with total expenses for all disease and imputes to a particular disease the proportion of costs equal to the proportion of total units of service used by patients who have the disease; or 2) by a "bottom-up" approach that prices and sums the units of service consumed by patients who have a particular disease. Each approach has its strong points, and ideally, the two would corroborate each other. In general, the top-down approach is simpler; by definition, the sum of all top-down estimates for each disease equals the total expenditures for all disease. Theoretically, the same would be true for bottom-up calculations, but such calculations are typically undertaken

'Smith Kline & French markets cimetidine.
*Peptic ulcer disease was only one 01 n umerous digestive diseases for which NCDD developed cost estimates. The authors of the NCDD report (4) state clea r] v that they consi der thei r esti ma tes to be conserva t ive.

for a single disease only, and potential inconsistencies between known total expenditures for all disease and the sum of disease-by-disease expenditures bottom-up calculations remain untested in typical bottom-up calculations.

NCDD and SRI both used a bottom-up approach to estimate hospital costs due to ulcer disease, but differed in the detailed assumptions they employed. NCDD began with the number of hospital days for each ulcer diagnosis obtained by the Hospital Discharge Survey of NCHS, and multiplied that number by the average charge per hospital day, The average was obtained from Blue Cross/Blue Shield figures for Federal workers and from medicare data for patients over 65 years of age. SRI also began with NCHS figures on numbers of discharges, but it used a more complicated calculation that involved an estimated proportion of surgical and nonsurgical cases from the Commission on Professional and Hospital Activities (CPHA), an allocation to hospitals of different sizes based in part on American Hospital Association data, and estimated daily costs based on information from disparate sources combined in an unspecified manner. The end result of SRI'S calculation was an estimate of hospital costs ($803 million) that is approximately 60 percent larger than NCDD's estimate ($501 million). Further exploration of the discrepancy between the two figures would require more details about the calculation:; than was provided in either report. Interestingly, and usefully, SRI also applied a top-down cross-check using estimated hospital expenditures for 1975 and the proportion of ulcer hospital days to total hospital days, and came up with an estimated cost of $738 million, reasonably close to our $652 mill ion midpoint estimate for this cost component.

To estimate the cost of physician services, NCDD used a top-down approach, multiplying the cost of all physician services for fiscal year 1975 by the proportion of total visits attributable to ulcer. SRI used a bottom-up approach, multiplying units of service (computed separately for initial and followup visits) by unit costs, estimated on the basis of multiple sources. SRI's estimate for physician visits for ulcer disease ($240 million) is approximately double that obtained by NCDD ($123 million) and, if correct, would imply that a physician visit for ulcer disease is twice as expensive as a typical physician visit. Although this seems unlikely, it is impossible to judge the difference in the cost of physician visits without a more comprehensive analysis. We settled on a $182 million midpoint estimate of the cost of physicians' services as a reasonable compromise.

Estimates for remaining direct costs are comparable in the NCDD and SRI studies. We have imputed the NCDD figure of $102 million from a more global estimate for selected digestive diseases that included ulcer disease and was adopted by NCDD (113). Summing the above components for each report, we find that the estimated direct costs presented in the two reports differ by more than $400 million: NCDD, $726 million; SRI, $1,157 million. Our final midpoint estimate is $942 million.

Indirect cost estimates for ulcer mortality loss are straightforward. NCDD and SRI used identical methods to estimate lost future earnings from death due to ulcer. The small difference in the two studies' figures for mortality loss (NCDD, $369 million; SRI, $357 million) is presumably due to the fact that SRI used smaller, preliminary mortality figures (6,840 deaths) rather than the final NCHS figures (7,245 deaths) that NCDD used. We have adopted NCDD's $369 million estimate.

The very large difference in the NCDD and SRI studies' estimated ulcer morbidity costs (NCDD, $179 million; SRI, $1,116 million) stems from several sources. Most important, SRI attributed to ulcer disease morbidity as estimated in the Health Interview Survey conducted by NCHS in 1975. As discussed earlier, the Health Interview Survey estimates are based on the responses of people interviewed at home who say they have had an ulcer at some time during the past year. These estimates are inconsistent with other evidence for the declining prevalence of ulcer disease, and they almost surely overestimate morbidity due to the disease. Furthermore, SRI assumed that the economic effects of work loss are distributed by age

in the same way the disease is distributed. Since older patients tend to lose more days of work and earn less per day, the assumption of uniform effects inflates the actual productivity loss. This flaw is acknowledged in SRI's report, but no correction or sensitivity analysis is offered. Ulcer patients who continue to work might have lower productivity, and this effect, also omitted from SRI's calculations, would increase the actual loss of productivity due to ulcer disease and tend to offset the effect of the assumption about age distribution.

NCDD considered and expressly rejected using data from the Health Interview Survey, because "there were also serious questions raised by experts in digestive diseases about the validity of the self-reported diagnosis-specific morbidity information" (4). Instead, NCDD accepted a more global estimate of morbidity loss due to 15 different digestive diseases, including liver disease, gallbladder disease, and hernia (113). The NCDD figure for morbidity loss due to ulcer disease shown in table 6 is approximately 6 percent of that total, a percentage equal to the ratio of the mortality cost for ulcer compared to that for all 15 diseases.[7] The NCDD report also refers to data collected for an earlier review of the medical and socioeconomic importance of digestive disease, published by Almy and his coworkers (3). That earlier publication included data on absenteeism due to digestive disease at a large northeastern U.S. manufacturing company during the 13-year period from 1959 to 1972. In persons who missed 3 or more days of work during that period due to 1 of the 15 digestive diseases covered by the NCDD morbidity estimate, more than 20 percent of days lost were attributed to ulcer. We do not propose translating such figures, obtained over a 13-year period from one large firm, to a national estimate of days of work lost in a later year. However, if ulcer disease does account for 20 percent of the total morbidity costs assigned to the 15 digestive diseases in the NCDD report, the NCDD morbidity figure would be very close to our midpoint estimate of $648 million.

The magnitude of indirect cost estimates is very sensitive to the rate at which future costs are discounted. Both NCDD and SRI discounted future earnings at 2.5 percent, although NCDD also presents some alternative calculations at a 10-percent discount rate. Economists agree more on the appropriateness of discounting than on the appropriate rate to employ, but 2.5 percent is at the very low, end of the spectrum. The smaller the discount rate, the higher the present value of future earnings and the higher the apparent indirect cost of illness. For example, the "present" value of lifetime earnings for a 32-year-old man in 1975 was $148,195 at a 2.5-percent discount rate and $176,882 at a IO-percent discount rate (4). This is not a differential point between the NCDD and SRI analyses, since they both used the same low discount rate, but the reader should be aware of the large difference a change in the discount rate can make and be wary of unadjusted comparisons between these and other cost-of-illness studies that may use different discount rates. In addition, "present" values are usually expressed in terms of dollars in the base year. Estimates discounted to different base years will differ in part because of inflation and are directly comparable in resource cost terms only if adjusted into constant dollars.

In the SRI analysis, Von Haunalter and Chandler extrapolated their estimated costs to 1977 (expressed in 1977 dollars) by assuming variably inflated rates for different unit costs of medical care and a 2-percent annual increase in the number of persons with ulcer disease (see table 7). The presumed 2-percent annual increase, based on responses to the Health Interview Survey in 1968 and 1975, is contrary to all other indicators of the changing epidemiology of ulcer disease; it is also contradicted by subsequent preliminary data obtained in the 1978 Health Interview Survey (see table 5, p. 17). The presumed growing population with ulcers is also treated by Von Haunalter and Chandler as having the identical age distribution and spectrum of disease severity as assumed for the population in 1975. Their assumptions about

[7] This imputation brings the total costs NCDD would assign to peptic ulcer to $1.3 billion, which is consistent with their stated overall economic loss due to peptic ulcer of $1 billion to $1.6 billion (4).

Table 7.—Costs of Ulcer Disease in 1975 and 1977 as Estimated by SRI (millions of dollars)[a]

	1975		1977	
Direct **costs**				
Hospital care	$ 803	—	$1,072	—
Physicians	240	—	283	–
Drugs	"loo	—	113	—
Nursing home care	11	—	15	—
Other professional	3	—	3	–
Subtotal	$1,157	440/o	$1,486	460/0
Indirect costs[b]				
Mortality	357	—	408	—
Morbidity	1,116	—	1,330	—
Subtotal	1,473	56%	1,738	54%
Total	$2,630	**1000/0**	$3,224	1000/0

[a]Figures for 1975 and 1977 are expressed in terms of dollars in the respective base years, not in constant dollars

SOURCE Adapted from G VonHaunalter and V V Chandler, *Cost of Ulcer Disease in the United Stales*, 1977(1 46)

these characteristics of the presumed growing ulcer population are questionable for reasons discussed in the section of this case study above on epidemiologic patterns of peptic ulcer disease. Von Haunalter and Chandler's projection of the population with ulcers to 1977 thus compounds the problem of overestimation of the costs of ulcer disease, particularly indirect costs. Some specific estimates that feed into direct costs are also Inappropriately projected upward. For example, the percentage of hospitalized patients undergoing surgery for ulcer disease is presumed in the analysis to increase between 1975 and 1977. According to data from both NCHS and CPHA (42), however, the percentage actually decreased (see table 8).

Summary

We may summarize the salient clinical and epidemiologic features of peptic ulcer disease as follows,

Ulcers probably have multiple causes, but gastric acid and pepsin appear to be necessary ingredients. Epigastric pain is often **a** prominent symptom of peptic ulcers, but the clinical presentation is variable. Furthermore, typical ulcer symptoms may be caused by conditions other than ulcers. A definite diagnosis requires direct visualization by endoscopy or radiographic imaging of the ulcer. Specific treatment of ulcer disease is directed at reducing the presence or effects of gastric acid.

Ulcer disease is a chronic condition with spontaneous remissions and recurrences. Rates of complication and mortality from ulcers are relatively low. Excessive mortality appears to be present only in the first year or so following diagnosis. Little reliable information exists about the natural history of ulcer disease in the general population.

Peptic ulcer is a common condition that affects millions of Americans at some time during their lives. The best available epidemiologic evidence suggests that about 250,000 Americans develop new peptic ulcers each year. New duodenal ulcers are more than four times as common as new gastic ulcers. Some studies have found that the incidence of duodenal ulcer rises gradually with age, others have found that it remains fairly constant after age 35. After age 40,

Table 8.—NCHS and CPHA Data on Number of Selected Surgical Procedures (partial Gastrectomy, Vagotomy) **in the United States, 1966-78**

	Partial gastrectomy		Vagotomy		Total	
Year	NCHS	CPHA	NCHS	CPHA	NCHS	C P H A
1966	74,500	—	61,200	—	135,500	—
1970	55,800	59,000	62,800	30,000	118,600	89,000
1971	—	57,000	—	28,000	—	85,000
1972	63,300	52,000	59,300	24,000	122,600	76,000
1973	—	52,000	—	27,000	—	79,000
1975	53,300	45,000	52,800	23,000	106,100	68,000
1976	54,200	45,000	48,300	16,000	102,500	71,000
1977	51,100	37,000	45,500	19,000	96,600	56,000
1978	39,700	29,200	29,200	17,000	68,900	46,000

SOURCES ***NCHS data:*** National Center for Health Statistics, National Hospital Discharge Survey, Hyattsville, Md
CPHA data: Commission 01 Professional and Hospital Activities data compiled by J D Elashoff and M I Grossman, 1960 (42)

the incidence of gastric ulcer appears to rise more dramatically than the incidence of duodenal ulcer. Duodenal and gastric ulcers are epidemiologically distinct. Several lines of clinical and epidemiologic evidence suggest that over the past 20 years the occurrence of new ulcers has declined, or ulcer disease has become generally less severe than it was at one time, or both.

The basis for some estimates of the costs of ulcer disease and benefits of treatment is the Health Interview Survey of NCHS. Results of the survey, based on self-reported conditions in a household survey, however, appear to overestimate the occurrence and consequences of ulcer disease.

We estimate that the costs of ulcer disease in 1975 were approximately $2 billion (see table 6, p. 19). Just under half of this total was due to health care expenditures (direct costs), and the remainder was due to productivity losses from morbidity and mortality (indirect costs). our estimate is based on a review of two independent analyses of the costs of ulcer disease, one prepared by NCDD (4) and the other by SRI (146). The NCDD and SRI studies estimates Of the total costs of ulcer disease in 1975, $1.3 billion and $2.6 billion, respectively, differ by approximately $1.3 billion. The approximately $400 million difference between the two studies' direct cost estimates (NCDD, $726 million; SRI, $1,157 million) arises in part from differences in the studies' methodologies (top-down v. bottom-up calculations) and in part from differences in their more detailed assumptions and procedures. The approximately $900 million difference in the two studies' indirect cost estimates (NCDD, $548 million; SRI, $1,473 million) reflects differences in the two studies' projected morbidity losses. The higher estimate is based on data from the Health Interview Survey, which is an inflated indicator of disease-specific morbidity. In both the NCDD and SRI studies, estimates of indirect costs are based on the relatively low discount rate of 2.5 percent, although the NCDD report also supplied estimates based on a lo-percent discount rate. SRI also projected an estimate of peptic ulcer costs in 1977. Because of unwarranted assumptions of growth in the morbidity of ulcer disease and the use of more expensive resources, the problem of overestimated costs is compounded for 1977.

We have briefly noted alternatives to cross-sectional expenditure assessments of the direct costs of illness, including tracking patient cohorts over time and measuring costs of treating episodes of illness. Results of a study of the latter type in one setting found that an episode of duodenal ulcer disease cost approximately the same to treat in 1971 as in 1964, in constant dollar terms.

The human capita] approach is the principal method used to assess indirect costs of illness. In general, lost productivity is measured as the present value of discounted stream of future earnings. Use of a smaller discount rate increases the present value of future earnings, thereby increasing apparent costs of illness due to morbidity and premature death.

The next four parts of this case study deal with the evaluation of cimetidine in peptic ulcer disease. We begin with background on the development and dissemination of cimetidine. Then we explore current understanding of the costs and benefits of this drug in the treatment of peptic ulcers, using the general benefit-and-cost model as a framework. Finally, we critique a major report on the costs and benefits of cimetidine and offer a few suggestions for further research.

CIMETI DINE

Physiologic Rationale and Development

The major physiologic stimulant to acid secretions in humans is the ingestion of food, but three chemical substances in the body are also known to stimulate acid secretion in the stomach: acetylcholine, gastrin, and histamine. The first two are clearly involved in the physiologic release of acid; histamine appears to

potentate the action of other acid stimulants (136). Even before the physiologic role of histamine was well understood, some researchers believed that a drug that would block histamine stimulation of gastric acid would be of great value in the treatment of ulcer disease. Conventional antihistamines have no effect on histamine receptors in the stomach.

By the mid-1960's, J. W. Black and his colleagues at the British laboratory of Smith Kline & French Laboratories (the pharmaceutical division of SmithKline Corp.) had set up a research program to develop new kinds of histamine blockers. Their strategy in this effort was similar to that which had led to their successful development of beta-adrenergic blockers, namely, systematic chemical manipulation to create nullifiers of the parent drug's effects (136). They reported their first successful effort in 1972 (12).

This work demonstrated the existence of a new class of histamine receptors, designated H_2-receptors, which were distinct from the classic H_1-receptors. The new histamine antagonist, called burimamide, was very effective in suppressing stomach acid production, not only in response to histamine, but from other stimuli as well, Burimamide had to be injected to be effective, and it was supplanted by an orally active Hz-receptor antagonist, metiamide. This drug was used in human trials in 1974, but was abandoned when it was found to cause granulocytopenia and agranulocytosis (growth of fewer white blood cells than normal) and at least one fatality (24,45). The chemical metiamide possessed a thiourea side chain that was believed to be the offending component, and it was replaced by a cyanoguanidine chain. The result of this chemical manipulation was the third H_1-receptor antagonist, cimetidine (SKF Tagamet®).[8] Along the way to the discovery of cimetidine, Black and his colleagues developed, tested, and rejected more than 700 different compounds (135).

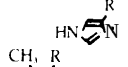
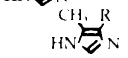
Cimetidine powerfully inhibits all phases of gastric acid production. The drug not only interferes with histamine-stimulated acid output, but also inhibits the effects of gastric and acetylcholine. Preliminary studies found that a 300 mg oral dose of cimetidine reduced nocturnal and basal acid secretion by 90 to 95 percent (74,97). Cimetidine also lowers the acid response to food by 70 percent, a reduction twice that achieved by anticholinergic agents (46,120).

Diffusion

After preliminary trials, cimetidine was released for use in Great Britain in November 1976. FDA recognized the clinical promise of cimetidine and rated it 1A, FDA's highest classification, meaning the drug is a new molecular entity believed to represent a major therapeutic advance over other drugs (47). FDA approved cimetidine on August 16, 1977 (50), for up to 8 weeks use in patients with duodenal ulcer disease and in patients with hypersecretory conditions such as Zollinger-Ellison syndrome, systematic mastocytosis, and multiple endocrine adenomas. Although cimetidine is not yet officially approved in the United States for longer term use, some physicians use it for more than 8 weeks in patients with duodenal ulcer (7).

The use of cimetidine spread rapidly in U.S. clinical practice. By the beginning of 1978, private practitioners prescribed cimetidine in approximately 40 percent of ambulatory visits made by patients with duodenal ulcers, By March 1978, the proportion of such visits resulting in a prescription for cimetidine reached approximately 60 percent, where it has remained since that time. A substantial fraction of total ambulatory use of the drug, perhaps as much as half, is for patients with acid reflux, gastritis, gastric ulcer, or problems other than duodenal ulcer.[9]

"The structural similarities of histamine and H, antagonists are evident from their chemical structures.

Compound name	Structure: Imidazole ring	Structure: Side Chain (R)
Histamine		-C H_2 CH_2 NH_2
Burimamide		-$CH_2CH_2CH_2CH_2CH_2CH_2CH_2NHCNHCH_3$
Meteamide		-$CH_2SCH_2CH_2NHCNCH_3$
Cimetidine		-$CH_2SCH_2CH_2NHCNHCH_3$, N-C = N

"Estimates based on figures published by the National Disease Therapeutic Index, which obtains reports of clinical practices from a sample of private practitioners.

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

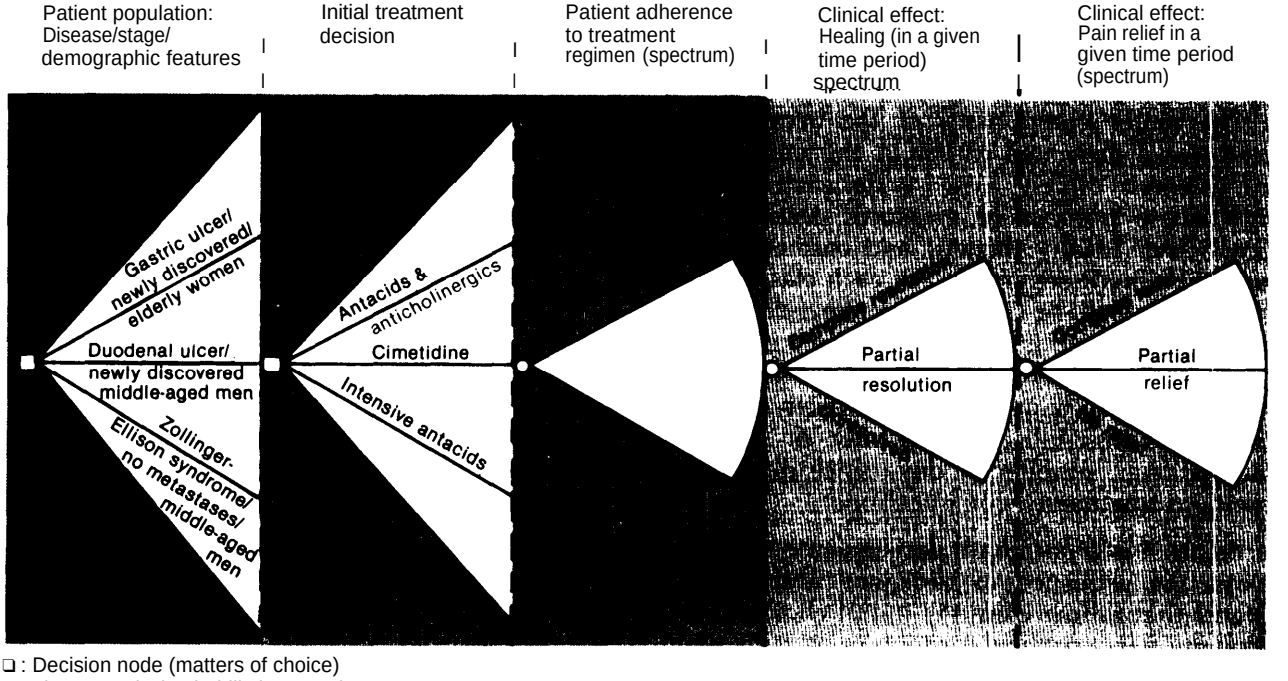
Clinical *effects*	• Number/time period
Short-term	Hospitalization
• Healing	• Number/time period
• Relief of symptoms	• Duration
• Side effects and adherence	Surgery
• Complications	• Number/time period
• Recurrence	• Type
Long-term	Other
. Recurrence	• Non-M. D. provider visits
• Side effects and adherence	• 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

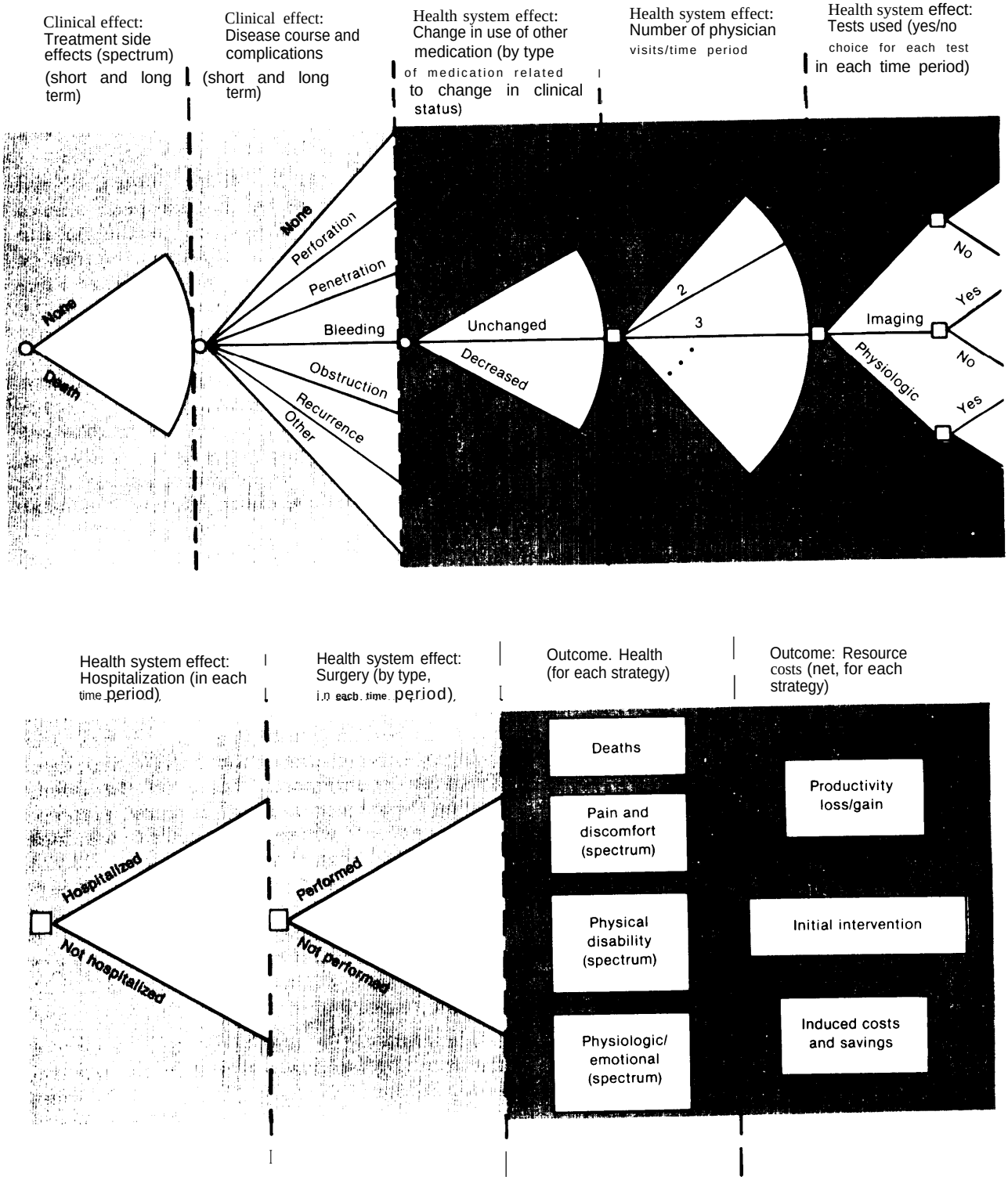
No treatment for duodenal ulcer has been subjected to as many randomized, controlled, double-blind studies as cimetidine has (68). These studies of cimetidine vary in their methodological stringency and completeness. In a review of the quality of 10 published, randomized, controlled trials of H_2 antagonists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

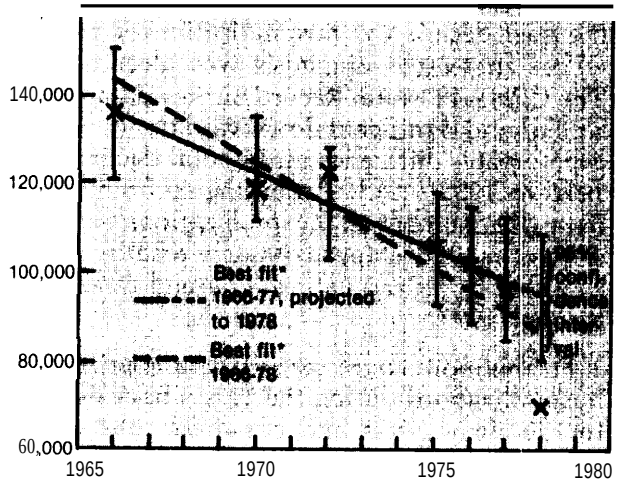
Estimates for the number of partial gastrectomies and vagotomies from NCHS tend to be higher than estimates from CPHA, but data from both sources show a distinct downward trend over time in the number of operations (see table **8,** p. 22). An acceleration (or deceleration) of this downward trend in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

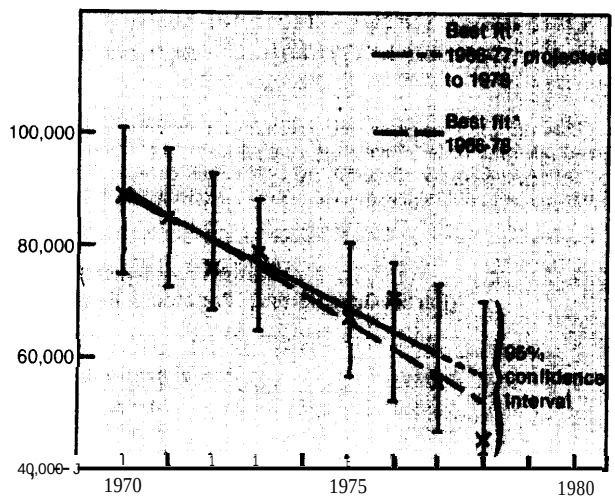
Figure 5.— NCHS Data on Number of Selected Surgical Procedures (Partial Gastrectomy and Vagotomy) in the United States, 1966.78



• 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.

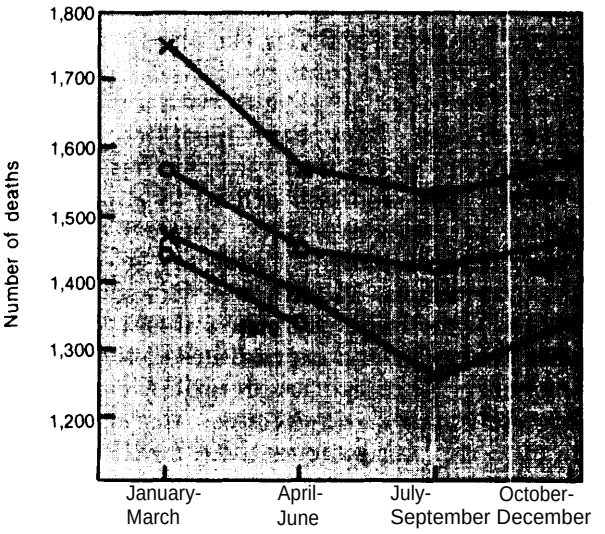
MORTALITY

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.

nitude of the **1978** decline in surgery for ulcer disease.

There is little evidence of any effect on cimetidine on mortality from ulcer disease. In several studies, patients treated with cimetidine lost significantly fewer days of work than patients taking placebo, but no controlled study compares work loss among patients on different, effective treatments.

REVIEW OF BENEFIT-AND-COST ANALYSES OF CIMETIDINE

Available Analyses

We are aware of two analyses of the social resource implications of cimetidine (109, 121). Both were sponsored by Smith Kline & French Laboratories, through their office of cost-benefit studies. One study, published by the Netherlands Economic Institute in February 1977 (109), analyzed the possible effect of cimetidine on the Dutch economy. That analysis estimated that if cimetidine had been used by half of all ulcer patients in the Netherlands, the potential savings would have been **$23** million, or **21** percent of the estimated $111 million total costs of ulcer disease in 1975, We will not comment on this study, because most of the issues it raises are also raised in the second study, and the latter is a more recent analysis which focuses on the United States.

The second study, entitled *The lmpact of Cimetidine on the National Cost of Duodenal Ulcers* **(121),** was conducted by Robinson Associates, Inc., a marketing research and management consulting organization located in Pennsylvania. A summary of the methods and conelusions of the Robinson Associates study, along with our critique of the study, are presented in the section below.

The Study by Robinson Associates, Inc.

Summary of Methods and Conclusions

The Robinson Associates study **(121)** estimated that if cimetidine had been used in **80** percent of duodenal ulcer patients in the United States, 1977 national health care costs for duodenal ulcer disease would have been reduced by **$645** million **(29** percent of that study's estimated total expenditures for duodenal ulcer). An estimated **$271** million would have been saved in medical care costs. The estimated **$271** million savings is the net result of a $34 million increase in drug costs, offset ninefold by $305 million in savings in other expense categories; the bulk of the $305 million medical care savings is from estimated reductions in hospital care ($258 million) and surgeons' fees ($30 million). In addition to the **$271** million net savings in medical expenditures, the study estimated that $373 million would have been gained from increased productivity—$329 million (88 percent) from decreased morbidity, and the remainder from decreased mortality.

The Robinson Associates analysis was based on two types of estimates. First, physician experts were asked in late 1977 to estimate the likely clinical and health system effects of cimetidine compared to traditional therapy for duodenal ulcer patients. Then, applying cost figures derived principally from SRI's assessment of the costs of ulcer disease in the United States **(146),**[33] Robinson Associates estimated the potential savings in 1977 due to the average predicted changes in health status and medical care. Summing the results for each cost category, the analysis yielded the conclusions summarized in the preceding paragraph.

A detailed reconstruction of the Robinson Associates analysis is beyond the scope of this review. Below we provide a description of certain methodologic features of the analysis as a basis for our comments in the critique that follows. First, we consider the expert estimates of the clinical and health system effects of cimetidine; then, we consider the conversion of these estimates into projected annual savings.

[33] SRI's assessment was discussed in some detail in the section of this case study on the cost of illness.

Twenty-three physicians who were familiar with cimetidine served as expert consultants for the Robinson Associates analysis. Each was asked in an interview about five specified ulcer-patient types—ranging from a patient with typical symptoms and newly diagnosed ulcer to a patient hospitalized with the complication of bleeding but not requiring immediate surgery—which were intended to represent a spectrum of severity of illness in patients with duodenal ulcer. The 23 physicians first estimated the proportion of all ulcer patients represented by each type. Then they described what they believed to be the usual treatment for each patient type and any changes in that treatment that would be made in a program that would include cimetidine. Finally, they estimated clinical and health system effects (including such elements as recurrence, physician visits, hospitalizations, surgery, diagnostic tests, missed work, complications, and mortality) for each type of patient treated without cimetidine and with up to 8 weeks of cimetidine. The physicians were not asked to estimate dollar costs for any postulated effects.

The methods that were used in the Robinson Associates study to convert estimated clinical and health system effects into dollar savings were as follows. As a baseline for estimating the costs of duodenal ulcers, Robinson Associates used estimates of the costs of peptic ulcer disease in 1977 developed by SRI **(146).** Within each direct and indirect cost category, the analysts estimated from secondary sources the fraction of peptic ulcer costs attributable to duodenal ulcer disease (with the remainder attributable to gastric ulcer).

To estimate the proportion of costs that would be saved by cimetidine, the analysts then proceeded as follows. First, they assigned prices to each component of each cost category. For example, in the category of hospital costs, they established the cost per hospital day for patients who do not have surgery and the cost per hospitalization for patients who do undergo surgery. Next, the analysts combined these cost components with physician estimates of the management and course of patients with and without cimetidine. For example, the hospital costs for each type of patient were calculated as the sum of costs for the proportion of those patients given surgery plus costs for those not given surgery, as follows:

proportion of patients of this type who are hospitalized
x [(proportion of patients hospitalized without surgery
x number of nonsurgical hospitalizations per year
x average length of stay for nonsurgical patients
x cost per day)
+ (proportion of patients hospitalized with surgery
x cost per surgical admission)]
= total annual hospital cost per patient of this type

Similar calculations yielded an estimate of the annual costs in each cost category for each type of patient with and without cimetidine.

Next, the percentage difference in costs in each cost category due to cimetidine was calculated for each type of patient. The percentage change for each type of patient was then weighted by the proportion of all ulcer patients estimated by the physicians to be represented by that type. This yielded the percentage change in a given cost category for an "average" patient treated with cimetidine rather than traditional therapy.

The percentage change in cost per "average" patient was further adjusted to reflect: the posited extent of use of cimetidine. The physician consultants predicted that an average of 80 percent of the five patient types would be treated with cimetidine 2 to 3 years after the time of the interviews. This figure, used as the basis for dollar projections in Robinson Associates study's conclusion, is a composite of the estimated extent of use (ranging from 73 to 93 percent) for each of the five types of patients.

Next, the percentage change in cost for each cost category, as adjusted for the proportion of patients using cimetidine, was multiplied by the costs of duodenal ulcer disease assigned to that category. This provided a dollar estimate of savings in each category. Summing the dollar estimates over all cost categories yielded the total projected savings attributable to the use of cimetidine by a given proportion of patients.

In short, the Robinson Associates analysis used prices of the components of medical care only as a basis for estimating the percentage

change in cost due to cimetidine. Once derived, these percentages were applied to independent assessments of the cost burden of all duodenal ulcer disease to estimate dollar savings.

Critique

The cost-and-benefit analysis that Robinson Associates prepared for Smith Kline & French has many positive attributes. First, the study represents the kind of serious analysis of the economic effects of a new drug that is important and valuable. If society is to attend to both the economic and clinical implications of medical interventions, careful analyses of costs and benefits are essential. Second, we believe the analysts selected appropriate categories of resource costs to assess. Their direct cost components correspond roughly to the **health** system effects outlined in the benefit-and-cost model we presented earlier in this case study. Their translation of mortality and morbidity components into indirect costs is appropriate for a resource cost analysis. Third, their approach of comparing estimated net resource effects of cimetidine to resource use without cimetidine is a reasonable one. Fourth, their method of obtaining physician estimates of clinical and health system effects was an imaginative one, and it required no guesses about costs from clinicians. Finally, the report provides sufficient detail about its methods and assumptions to allow the reader to reach independent conclusions.

We believe this report deserves scrutiny, because, to our knowledge, it is the most comprehensive analysis of the resource implications of cimetidine in the United States. As a thorough economic assessment of a recently introduced drug, the study may serve as a model for future evaluations of other emerging medical practices. In the discussion of the study that follows, we have attempted to examine the analysis carefully in light of the benefit-and-cost model and data presented earlier and the guidelines for review of benefit-and-cost analyses that are presented in the next section of this case study.

We believe the Robinson Associates study substantially overestimates expected savings from cimetidine. The accuracy of the estimated savings attributable to cimetidine in the Robinson Associates study depends on at least five features: 1) the accuracy of the clinical and health system effects projected by their physician experts; 2) the relation between a percentage reduction in health services devoted to ulcer disease and savings in health resources; 3) the accuracy of the estimated total costs of all duodenal ulcer disease used as a baseline for percentage savings; 4) the applicability of projected percentage effects to the total population of patients with duodenal ulcer disease; and 5) the validity of the methods used to compute average percentage effects due to cimetidine. We question some of the assumptions and methods used in each of these five areas.

Let us consider first the physician experts' opinions of the clinical courses of patients with and without cimetidine. The mean of these estimates is intended to represent an unbiased estimate of the course of duodenal ulcer disease using conventional treatment, and an unbiased estimate of the effects of cimetidine. An unbiased estimate of the former is best achieved by physicians of varied specialty backgrounds who together treat the full range of patients with ulcer disease, An unbiased estimate of the latter requires both knowledge of cimetidine's clinical effects and a neutral attitude toward the drug.

The 23 physicians whose opinions form the basis of the Robinson Associates study were **all** gastroenterologist-researchers who had participated in early clinical trials of cimetidine and whose participation in this study was solicited by Smith Kline & French (121). This selection, the authors state, ensured informed opinion about the potential effects of cimetidine—but it does not ensure individual objectivity or a balanced range of views. Of 32 physicians contacted by Smith Kline & French to participate in the study, 4 refused either because they were too busy or for unknown reasons.[34] It is possible

[34]Four others were disqualified or unavailable because of extensive travel. One of the 24 physicians who agreed to participate was not interviewed because of illness (121).

that researchers who were less enthusiastic about the drug were less eager to express their views when contacted by the manufacturer.

To enhance the credibility of subjective physician estimates, Robinson Associates cite a Danish study (66) that compared observed experience in 154 patients over 13 years with physician estimates of some of the long-term consequences of ulcer disease (proportion treated surgically and proportion of medically treated patients with varying degrees of symptoms). The Danish study found that the mean estimates of 143 physicians corresponded fairly closely to patient experience. The Danish investigators interviewed a wide range of general practitioners, medical specialists, and surgeons to obtain their mean estimates. These investigators also noted that there were some systematic biases that tended to balance one another. For example, the **65** general practitioners in the Danish study estimated that 15 percent of patients would undergo operations for ulcers, and the **50** surgeons predicted 27 percent; the observed proportion was 22 percent. Thus, this study suggests the importance of using a broadly based sample to achieve unbiased mean estimates. Just as surgeons' estimates alone might not accurately represent surgery experience, a group of research gastroenterologists seems unlikely to represent a fair cross-section of physician experience with and expectations for patients who have ulcer disease.

The effects estimated by the physician consultants in the Robinson Associates study varied widely. The projected cost consequences of using cimetidine in **100** percent of duodenal ulcer patients ranged from a savings of **67** percent based on one physician's estimates to an increased expenditure of 40 percent based on another's estimates. Seven of the physicians projected effects that yielded net losses or small savings (of less than 10 percent), while eight physicians projected effects that led to savings of 40 percent or more. If the selection was biased in favor of physicians at the "optimistic" end of the spectrum of clinical and health system effects of cimetidine, the mean cost savings estimate will be similarly biased.

Cost savings in the Robinson Associates study are estimated as a proportion of the total costs of duodenal ulcer disease. Two aspects of the Robinson Associates calculations deserve comment, and we expand on these points below. First, a given percentage reduction in health services requirements for a particular disease probably does not convert directly to an equivalent proportion of health resource savings. Second, we believe that the baseline costs of duodenal ulcer disease employed by Robinson Associates are too large, primarily because of an inflated indirect cost estimate.

An implicit assumption in applying a percentage cost reduction to the health system expenditures for ulcer disease is that savings will be realized in direct proportion to the decreased use of medical services. For example, if hospital days decline by **10** percent, then 10 percent of resources devoted to hospital care are assumed to be saved. This calculation uses average costs per hospital day rather than marginal costs of the last 10 percent of hospital days. To the extent that fixed and semivariable costs contribute to the cost of a hospital day, the marginal savings from reducing a given fraction of hospital days will be less than the average cost of those days.[35] The remaining fixed cost components will simply be redistributed over the remaining hospitalized patients, Thus, the direct conversion of percentage reduction in hospital days to percentage savings in resource costs of hospital care may be questioned.[36] Short-term resource savings might even be less than the averted marginal costs, insofar as available supply of hospital resources induces other demand.[37] If hospital beds previously occupied by patients with ulcer disease are filled by other patients (without ulcer disease) who previously would not have been hospitalized, then potential savings would be eroded further.

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[35] Fixed costs are independent of the volume of services. Semivariable costs are a function of both time and volume of services.

[36] A related problem is the frequent use of charges as proxies for resource costs of care. Charges reflect average rather than marginal costs, and for a variety of reasons, charges for particular services may differ from their average resource costs.

[37] The notion of hospital bed supply creating demand for more hospital services, called Roemer's Law, was originally proposed 20 years ago (130).

The total costs of duodenal ulcer disease used by Robinson Associates are based on the estimated costs of peptic ulcer developed by SRI **(146).** SRI's estimate is substantially higher than another recent, independent estimate of the cost of ulcer disease by NCDD (4), and, as we discussed earlier, we believe a more correct figure lies between the two. If Robinson Associates had based their projected savings from cimetidine use on the costs of ulcer disease as estimated by NCDD, making no other changes in their analysis, the resulting estimated savings would have been over **50** percent less. Use of NCDD's cost figures, without altering any other assumption or calculation used in the Robinson Associates study, would have produced an estimated savings of only **$307** million, in contrast to the **$645** million savings projected on the basis of SRI's figures. Use of our midpoint calculation developed in the section of this case study on the cost of peptic ulcer disease yields estimated savings of only **$476** million.

Another important source of misestimation in the Robinson Associates study is the assumption that the five patient types represent the full range of patients with duodenal ulcer disease. The most severely ill type of patient included in the Robinson Associates study is one who is hospitalized and bleeding but not in need of immediate surgery. Thus, the study omits patients who have very severe bleeding or other life-threatening complications of ulcer disease such as perforation. According to CPHA data **(42),** nearly **6** percent of patients hospitalized for duodenal ulcer disease in 1977 had perforation, and **28** percent had bleeding. The number of excluded patients who require prompt surgery may be estimated conservatively to include 90 percent of patients with perforation (or 5 percent of hospitalized patients) and between 10 and 20 percent of patients admitted for bleeding (or an additional 4 percent of hospitalized patients). Thus, approximately 9 percent of hospitalized patients, all of whom receive surgery, are excluded from the range of patients in this study.

The omission of these patients from the Robinson Associates study has substantial consequences for the study's cost estimates. For example, consider the area of hospital costs alone. Assuming traditional therapy, Robinson Associates estimate total hospital costs to be $732 million. At 80-percent cimetidine use, they estimate savings in hospital costs to be **$258** million, a 35-percent reduction from hospital costs with traditional therapy. According to the SRI figures that served as a baseline for the Robinson Associates estimates, nearly **72** percent of hospital costs for ulcer patients in 1977 were due to the estimated 20 percent of hospitalized patients who underwent surgery (146). Assuming the excluded patients, who are most severely ill, were responsible only for a proportionate share of costs for surgical cases, the proportion of total hospital costs for duodenal ulcer disease devoted to these patients would be approximately **32** percent, and the dollar amount devoted to their care would be **$237** million .[38]

Although the expert consultants were not asked about this group of most severely ill patients, we think that cimetidine would not have been expected to alter the acute management of more than a small fraction of them. Assuming that 80-percent cimetidine use would have been estimated to save as much as 15 percent (approximately **$36** million) of the hospital costs for these patients, and then applying the proportion of savings estimated for "all" duodenal ulcer patients in the Robinson Associates study to the hospital costs attributable only to the included patients, we compute the savings in hospital care to be **$209** million rather than **$258** million. [39]

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[38] Proportion of hospital costs due to surgical care of excluded patients = proportion of surgical cases excluded x proportion of total costs due to surgical cases: 0.324 = (0.09 0.20) x 0,72. Dollar amount devoted to hospital care of excluded patients = proportion of hospital costs due to excluded patients x total hospita] costs: $237 million = 0.324 X $732 million.

[39] Let :

$C \equiv$ estimated hospital costs due to all patients with traditional therapy

$C_E \equiv$ estimated hospital costs due to excluded patients with traditional therapy

$C_I \equiv$ estimated hospital costs due to included patients with traditional therapy

$S \equiv$ estimated hospital savings from all patients with 80-percent cimetidine use

$P_{SE} \equiv$ estimated proportion of costs saved by 80-percent cimetidine use attributable to excluded patients

$P_{SI} \equiv$ estimated proportion of costs saved by 80-percent cimetidine use attributable to included patients

Thus, the incomplete spectrum of patients included in the study produces an overestimate in savings of nearly **$50** million in the area of hospital costs alone. The exclusion of the most severely ill patients also incurs additional, if smaller, overestimates of savings in other cost areas. If cimetidine reduces the fraction of patients who reach the most severely ill category, however, then this source of overestimation would be reduced proportionately. The authors of the Robinson Associates report repeatedly point out that their projected percentage savings are unaffected by changes in estimated baseline costs for ulcer disease. As we have just seen above, however, the percentage savings calculated in the study are quite sensitive to the inclusion or exclusion of different types of patients with duodenal ulcer.

Two other sets of assumptions in the Robinson Associates study also affect the calculated savings. The first of these is the relative dollar values assigned to the components of each cost category (e.g., how much less expensive is a hospital stay for nonsurgical than for surgical patients?). The second set of assumptions is the estimated proportion of all included patients in each of the five patient types. The data underlying these assumptions can be expected to vary over some range. To accommodate such variation, one could, for example, estimate a confidence interval about physician estimates of the proportion of patients of each type.[40] The Robinson Associates study would have been strengthened by explicit sensitivity analysis, testing the effect on the conclusions of systematic alteration of key assumptions.

(continued from p. 53)

Given:

- C - $732 million (from Robinson Associates study)
- C_E - $237 million (from preceding footnote)
- C_I - $C - C_E = \$(732 - 237 \text{ million}) = \$495$ million (by definition, $C = C_I + C_E$)
- P_{SE} - 0.15 (assumption; see text)
- P_{SI} - 0.35 (from Robinson Associates study)

Then:

S - $C_E \times P_{SE} + C_I \times P_{SI}$

- ($237 million) (0.15) + ($495 million) (0.35)
- $209 million.

[40] This is separate from the question of bias in the mean estimate, i.e., whether a group of gastroenterologist-researchers would perceive the world of ulcer patients to be made up of as high a proportion of "initial diagnosis patients" (type 1) as would a group of general practitioners or less specialized internists.

The method used by Robinson Associates to compute the expected reduction in costs caused by cimetidine use has another subtle, but potent, effect on their estimate. Assume for the moment that the interviewed physicians did constitute a representative sample of informed opinion about the effects of cimetidine. It would be desirable, then, for the overall estimated percentage reduction in costs to be a statistically unbiased measure of individually perceived percentage reductions. Take a simplified case. If physician A provides estimates of cimetidine's effects that produce a 70-percent decrease in resource consumption, and physician B provides estimates that produce a 50-percent decrease, we would like the overall estimated reduction to be midway between the two, or **60** percent. Since we presumably trust each physician's judgment equally, each perceived percentage reduction should contribute equally to the overall estimate of percentage reduction. However, the method used by Robinson Associates to compute percentage reduction in costs has the effect of placing greater weight on the percentage reduction estimates of physicians who perceive ulcer disease as more severe and requiring higher levels of resources.

Mathematically speaking, this distortion occurs because the ratio of estimated means is not the same **as** the mean of estimated ratios. To see how this distortion can arise, again consider two simplified examples. First, physician A and physician B are asked about the consequences of ulcer disease with and without cimetidine for a given type of patient. The effects are translated into various categories of resource cost, such as hospital care. Physician A estimates effects that lead to a total annual cost of **$1,000** without cimetidine and **$500** with cimetidine use. Physician B estimates effects that lead to a cost of $100 without cimetidine and **$50** with the drug. In each case, the estimated percentage reduction is 50 percent. Proceeding as Robinson Associates did, we can compute an average cost without cimetidine and an average cost with cimetidine.

$$\text{average cost without cimetidine} = \frac{\$1,000 + \$100}{2} = \$550$$

$$\text{average cost with cimetidine} = \frac{\$500 + \$50}{2} = \$275$$

Then the "average" percentage reduction attributed to cimetidine, as computed by Robinson Associates, would be the difference between these average costs divided by the cost without cimetidine, or:

$$\frac{\$550 - \$275}{\$550} = 0.50$$

In this case, both physicians projected the same percentage reduction, and the calculated percentage reduction agrees with both of them. So far, this approach appears sound.

Now consider the following variation. Physician A estimates effects that cost **$1,000** without cimetidine and $400 with cimetidine, a 60-percent reduction in costs. Physician B estimates effects that lead to a cost of **$100** without cimetidine and **$60** with the drug, a 40-percent reduction. The average estimated reduction is:

$$\frac{0.60 + 0.40}{2} = 0.50$$

or **50** percent. Calculated by the method of Robinson Associates, the percentage reduction IS:

$$\frac{(51{,}000 + \$100) - (\$400 + \$60)}{\$1{,}000 + \$100}$$

$$= \frac{\$1{,}100 - \$460}{\$1{,}100}$$

$$= \frac{\$640}{\$1{,}100} = 0.58$$

Thus, the calculated reduction of 58 percent is much closer to the perceived reduction of physician A, who viewed ulcer disease in this type of patient as more severe and costly than did physician B.[41]

The estimation method used by Robinson Associates confounds the estimate of perceived effects of cimetidine, on the one hand, with variability in the perceived severity and overall management of ulcer disease, on the other. If the Robinson Associates study had taken the mean of physician estimates with traditional therapy as the baseline from which percentage reductions were calculated, there might be a stronger case for an approach like that used. However, the calculated percentage reductions were applied to an independently determined baseline cost. This reinforces the argument for seeking an unbiased measure of expected percentage reduction, namely the mean of the physicians' percentage estimates.

The practical consequences of this distortion are substantial. A series of bar graphs provided in the Robinson Associates report (their tables **34** through **43,** pp. **54-63)** shows percentage changes in cost based on the estimates of each of the **23** physician informants. A separate figure in the report depicts the distribution of physician percentage estimates for each of nine cost categories and overall costs. On the basis of the bar graph for the distribution of physician estimates of overall cost savings, we calculate that the mean of the estimated percentage reductions by the 23 physicians was approximately **24** percent (see table 20). By contrast, the "mean" shown in the Robinson Associates bar graph and used in the analysis was a percentage cost reduction of 34 percent (at 100-percent cimetidine use).

This suggests that the "average" percentage reduction used in the Robinson Associates

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[41] Symbolically the difference between the method in effect used by Robinson Associates to calculate a "mean" percentage cost reduction and the mean of the percentage reductions estimated by the physicians can be expressed as follows

n ≡ number of physician experts
TC_i ≡ cost calculated from physician i estimates of effects with traditional treatment (without cimetidine)
CC_i ≡ cost calculated from physician i estimates of effects with all patients receiving cimetidine treatment

Then:
$TC_i - CC_i$ ≡ cost savings calculated from physician i estimates
$\frac{TC_i - CC_i}{TC_i}$ ≡ percentage cost reduction calculated from physician i estimates

Robinson Associates estimates "mean" percentage cost savings as an "average of total costs":

$$\frac{\sum_{i=1}^{n} (TC_i - CC_i)}{\sum_{1=1}^{n} TC_i} \times 100 \qquad (1)$$

The mean of percentage savings estimated by physicians is:

$$\frac{\sum_{i=1}^{n} \left(\frac{TC_i - CC_i}{TC_i} \right)}{n} \times 100 \qquad (2)$$

In general, eqn. 1 # eqn. 2, although the two may give the same result in exceptional circumstances.

Table 20.—Percentage Cost Savings Estimated From Robinson Associates Study

Physician number	Percentage savings[a]
1	68%
2	62
3	62
4	55
5	50
6	48
7	47
8	42
9	36
10	35
11	28
12	27
13	19
14	13
15	12
16	11
17	8.5
18	8.5
19	3
20	0
21	– 9[b]
22	– 24[b]
23	– 40[b]
Total	562%
Mean percentage cost savings = 562/23=24.4%	

[a]Gauged from the height of the bar graph for each physician in Robinson Associates table 43
[b]Estimated cost increase

SOURCE Robinson Associates, Inc, *The Impact of Cimetidine on the National Cost of Duodenal Ulcers*, 1978(121)

analysis was approximately 42 percent larger than the mean of the estimated percentage reductions provided by the physician experts.[42] (Similar discrepancies of varying degree are found with each category of cost shown in the Robinson Associates bar graphs.) Basing overall percentage cost savings on the mean of percentage reductions estimated by the 23 physicians would reduce the projected savings at 80-percent cimetidine use by approximately $190 million, from **$645** million to approximately $455 million.

In summary, we believe the Robinson Associates analysis substantially overestimates expected savings from cimetidine. Considering the exaggerated baseline costs of ulcer disease assumed in the analysis, the incomplete spectrum of patients included, and the distortion introduced by the method of calculating mean percentage reduction in costs we believe the estimated $645 million savings are probably two to three times too large. Potential bias introduced by the selection of physician informants would increase the magnitude of that overestimate.

Despite our criticisms of the Robinson Associates study, we believe its basic thrust is probably correct. Cimetidine does appear to save more medical resources than it costs. The $305 million savings in medical costs that Robinson Associates estimates from the use of cimetidine are approximately nine times the estimated $34 million direct costs of the drug. Thus, even if the drug costs were tripled and the estimated savings reduced by two-thirds, use of cimetidine would still appear to be an economically sound investment. Also, the estimated savings in health resources omit potential gains in productivity from use of the drug.

The emerging empirical evidence cited in the section of this case study on health system effects supports the belief that use of cimetidine probably saves medical resources. In the coming years, more evidence will probably accumulate about the costs, risks, and benefits of cimetidine compared to alternatives. We may learn, for example, about newly recognized adverse effects of the drug or about rebound in the number of ulcer patients undergoing surgery or about the development of safer, equally effective and acceptable treatments. The comparative cost effectiveness of cimetidine for patients with ulcer disease in the long run is a matter of continuing empirical study,

Our discussion of the Robinson Associates study illustrates some of the difficulties of designing and conducting economic analyses of newly introduced medical practices. The work of the Robinson Associates analysts must be viewed in the context of the information available at the time it was done. The Robinson Associates study was undertaken before there was widespread clinical experience with cimetidine, and the analysts faced a dearth of empirical findings relating directly to resource costs. Given the information available at that time, the analysts might have considered the following procedure. First, define prototypical pa-

42 $\frac{0.34 - 0.24}{0.24} = 0.416$

tients that represent the full range of patients with ulcer disease, including the most severely ill. Second, obtain from a broad, representative group of physicians baseline estimates of the course of disease using traditional therapy. Third, check how closely these estimates correspond to other estimates of the total cost of duodenal ulcer disease, examine critically assumptions that underlie the estimates of the health system effects in each major cost category, and reach consensus estimates. Fourth, present to physicians familiar with cimetidine the consensus-estimated clinical courses for each patient type with traditional therapy; ask them to assume the consensus represents actual patient experience; and then ask them to estimate what changes, if any, would follow from the introduction of cimetidine. Finally, calculate the mean of the estimated percentage cost reductions and apply it to appropriately estimated costs of illness.

Guidelines for Review of Health Care Cost Analyses

Presented below are guidelines in the form of a series of questions that may aid in the design and review of cost-benefit and cost-effectiveness studies. These guidelines cover matters of definition and purpose, analytic methods, and conclusions. They are presented here in concise form and presume familiarity with the rationale and basic components of benefit-and-cost analyses in health care (see, e.g., 89).

Objectives of the Analysis

1. What is the purpose of the analysis? Is it a) to assess the optimal management of individual patients with a particular clinical condition; b) to measure the clinical and economic importance of particular clinical problems; c) to compare alternative strategies for addressing a particular health problem in a particular population; d) to compare alternative investments in health programs; or e) to compare health and other social resource investments?
2. Are the interests and potential biases of the analyst and client acknowledged? Are measures taken to guard against potential bias?

Specification of the Problem

1. Is the population of interest appropriately defined (e.g., a population with a particular diagnosis, or having a particular clinical symptom, or undergoing a particular test or treatment)? Is the population consistently defined throughout the analysis?
2. Does the analysis specify the interventions of interest and address them consistently throughout the analysis?
3. Are the conditions of use (e.g., ideal v. average) specified and consistently treated in the analysis?

Methods of Analysis

1. Are the analytic methods selected appropriate to the objectives of analysis? (e. g., CEA v. BCA, use of decision-analytic framework, etc.)
2. Is the time frame of analysis appropriate to the objectives (e. g., is patient lifetime a more suitable focus than a cross-section of patients for a limited time?)
3. Are clinical effects and other benefits appropriately specified? Are the methods of assessment explained? Are incremental benefits the basis for analysis?
4. Are cost estimates complete and appropriately categorized? Has double counting been avoided? Are induced costs and savings considered? Are marginal resources costs the basis for analysis? Are methods fully explained?
5. Are benefits and costs aggregated properly across the population and intervention of interest? Is the analysis restricted to a few uses of multipurpose intervention?
6. Are benefits and costs appropriately aggregated over time? Is discounting employed? Is the discount rate appropriate?
7. Are projected effects justified? Are the estimates based on empirical data or opinion? Are uncertainties recognized? Are the sources of all estimates clearly explained? Are estimates unbiased? Are assumptions acknowledged, fully exposed, and justified? Are estimates based on evidence from the same population and intervention that are the subjects of analysis? Are extrapolations and interpolations reasonable?

8. Are underlying trends in disease distribution and severity taken into account? Are other pertinent population trends assessed?
9. Are technological changes and evolution of practices taken into account?
10. Are the distributions of benefits and costs important and are they considered?

Conclusions

1. Are the conclusions consistent with the analysis and appropriately qualified?
2. Are conclusions robust? Have assumptions and key uncertainties been subjected to a sensitivity analysis?

SUGGESTIONS FOR FURTHER RESEARCH

Our suggestions for further research are cognizant of broadened clinical experience with cimetidine in recent years and newly emerging empirical evidence of health system effects of the drug. Any analysis must take account of the shifting epidemiologic pattern of ulcer disease. We believe that sound CEAs comparing effects of different strategies over an ulcer patient's lifetime would provide valuable guidance to medical decisions for patients with ulcer disease.

As discussed earlier in this case study, a number of well-controlled clinical trials have assessed the clinical effects of cimetidine in the past few years. These trials have not dealt with every important clinical comparison (e.g., maintenance antacids v. cimetidine), but they have provided a much sounder empirical base for projecting some of the clinical consequences of the drug. Since clinical use of cimetidine is so widespread, a broad group of clinicians could be consulted for subjective estimates of likely consequences in areas where clinical trials are lacking. It would be possible to begin by sending participating physicians a summary of empirical clinical findings with cimetidine. A systematic method, such as a Delphi process, could then be used to reach group consensus on key probabilities .4:

There is still little empirical information on health system effects of cimetidine to serve as a basis for estimating resource costs and savings. Any analysis of the health system effects of an intervention in ulcer disease must take as a baseline the epidemiologic trends in the disease discussed in this case study. As mentioned previously, the rate of surgery for ulcer disease shows a steeper decline in 1978 than would be predicted from the previous trend. Confirmation of this drop and additional evidence linking it to cimetidine would provide a sounder basis for projecting direct cost savings in one area, and for attributing such savings to the use of cimetidine. Additional evidence of health system effects of cimetidine may emerge from the ongoing research that we have described.

In further analyses of cimetidine, one fundamental concern must be the time frame of the analysis. Calculations based on a single year, for example, will overlook the important distinction between avoidance of surgery and delay in surgery. From the evidence we have cited in this case study, there is a good reason to believe that a year of maintenance cimetidine imparts a delay in inevitable surgery rather than a long-lasting cure of ulcer disease,

More generally, with diseases such as peptic ulcer, which are chronic, and with interventions such as cimetidine, whose long-term effects may be very important, a benefit-and-cost analysis might best focus on a cohort of patients, projecting effects over their lifetimes. Rather than attempt to enumerate all resource implications for a cross-section of the population in a single year, it might be more helpful to estimate the present-value lifetime resource costs and health effects for a given population of ulcer patients, Then, on the basis of available research evidence and subjective clinical judgments, one could estimate the consequences for a given type of patient of pursuing different management strategies. This approach would allow compari-

[43]The Delphi method is an iterative process for reaching group consensus that attempts to separate the reasons for an opinion from the authority of the opinionholder. It has been employed in the analysis of health care decisions to obtain estimates of probabilities from a group of medical experts (127).

son of marginal costs with incremental benefits for each shift in strategy. Focusing on each patient's lifetime rather than on a given calendar year would highlight, among other things, uncertainties in the long-term side effects of use of a relatively new agent such as cimetidine.

The prototype decision tree shown in figure 4 (PP. 26-27) could serve as a starting point for such an analysis. At least one group of researchers, in Switzerland, has begun to take a decision-analytic approach to the lifetime consequences of duodenal ulcer treatments **(137).** Their published analysis is restricted to a specific 50-year-old male patient, and one might fault their figures for not discounting future costs and benefits, but these researchers do approach the problem in an appropriate way.

If the object of analysis is to help inform clinicians and health policy decisionmakers about the efficient use of resources in the care of patients with ulcer disease, then the most helpful approach would be to do a CEA, oriented to particular groups of patients, comparing incremental clinical benefits, in terms of morbidity and mortality, to marginal resource costs. An assessment of the cost effectiveness of different management strategies in all patients with ulcer disease would be an enormous undertaking, but analyses do not have to be global to be valid and useful. As long as their limitations are understood and taken into account, such studies can aid both health policy formulation and medical decisionmaking.

REFERENCES

1. Acton, J. P., *Evaluating Public Programs To Save Lives–The Case of Heart Attacks,* Rand report R-950-RC (Santa Monica, Calif.: Rand Corp., **1973).**
2. Almy, T. P., Dartmouth Medical School, Hanover, N. H., personal communication, 1980.
3. Almy, T. P., et al., "Panel I: Prevalence and Significance of Digestive Disease, " *Gastroenty.* 68:1351, 1975.
4. _____ "Report of the Workgroup on the Socioeconomic Impact of Digestive Diseases of the Subcommittee on Epidemiology and Impact, " in *Report to the Congress of the United States of the National Commission on Digestive Diseases,* vol. 4, pt. 4, DHEW publication No. (NIH) 79-1885 (Bethesda, Md.: National Institutes of Health, 1979).
5. Bader, J. P., et al., "Treatment of Gastric Ulcer by Cimetidine: A Multicentre Trial, " in *Cimetidine—Proceedings of the Second International Symposium on Histamine Hz-Receptor Antagonists,* W. L. Burland and M. A. Simkins (eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
6. Bank, S., et al., "Histamine H,-Receptor Antagonists in the Treatment of Duodenal Ulcers, " S. *Afr. Med. J.* 50:1781, 1976.
7. Bardhan, K. D., "Cimetidine in Duodenal Ulaeration, " in *Cimetidine: The Westminster Hospital Symposium, 1978,* C. Wastell and P. Lance (eds.) (New York: Churchill Livingstone, 1978).
8. Bardhan, K. D., et al., "Comparison of Two Doses of Cimetidine and Placebo in the Treatment of Duodenal Ulcer: A Multicentre Trial, " *Gut* 20:68, 1979.
9. _____, "Double-Blind Comparison of Cimetidine and Placebo in the Maintenance of Healing of Chronic Duodenal Ulceration, " *Gut* 20:158, 1979.
10. Belber, J. P. "Gastroscopy and Duodenoscopy, " in *Gastrointestinal Disease,* vol. 1, 2d cd., M. H. Sleisenger and J. S. Fordtran (eds.) (Philadelphia: W. B. Saunders Co., 1978).
11. Binder, H. J., et al., "Cimetidine in the Treatment of Duodenal Ulcer: A Multicenter Double-Blind Study, " *Gastroenty.* 74:380, **1978.**
12. Black, J. W., et al., "Definition and Antagonism of Histamine Hz-Receptors, " *Nature,* 236:385, 1972.
13. Blackwood, W. S., et al., "Cimetidine in Duodenal Ulcer: Controlled Trial, " *Lancet* 2:174, 1976.
14. Blumenthal, I. S., *Research and the Ulcer Problem,* Rand report R-336-RC (Santa Monica, Calif.: Rand Corp., June 1959).
15. Bodemar, G., and Walan, A., "Cimetidine in the Treatment of Active Duodenal and Prepyloric Ulcers," *Lancet* 2:161, 1976.
16. _____, "Maintenance Treatment of Recurrent

Peptic Ulcer by Cimetidine," *Lancet* 1:403, 1978.
17. Bonnevie, O. E., "The Incidence in Copenhagen County of Gastric and Duodenal Ulcers in the Same Patient," *Sc. J. Gastr.* 10:529, 1975.
18. _____, "The Incidence of Duodenal Ulcer in Copenhagen County," *Sc. J. Gastr.* 10:385, 1975.
19. _____, "The Incidence of Gastric Ulcer in Copenhagen County," SC. *J. Gastr.* 10:231, 1975.
20. _____, "Survival in Peptic Ulcer," *Gastroenty.* 75:1055, 1978
21. Brown, R.C., et al., "HospitalA dmissionsfor Peptic Ulcer During 1958-1972," *Br.* Med. *J.* 1:35, 1976.
22. Burland, W. L., and Simkins, M. A. (eds.), *Cimetidine: Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists* (Amsterdam-Oxford: Excerpta Medica, 1977).
23. Burland, W. L., et al., "The Longer Term Treatment of Duodenal Ulcer With Cimetidine, " in *Cimetidine: The Westminster Hospital Symposium*, 1978, C. Wastell and P. Lance (eds.) (New York: Churchill Livingston, 1978) .
24. _____, "Reversal of Metiamide-Induced Agranulocytosis During Treatment With Cimetidine," *Lancet* 2:1085, 1975.
25. Chalmers, T. C., et al., "Randomized Controlled Trials in Gastroenterology With Particular Attention to Duodenal Ulcer, " *Report to the Congress of the United States of the National Commission on Digestive Diseases, vol.* 4, pt. 2B, DHEW publication No. (NIH) 79-1885 (Bethesda, Md.: National Institutes of Health, 1979).
26. Chang, H. K., and Morrison, S. L., "Bone-Marrow Suppression Associated With Cimetidine" (letter), *Ann, Int. Med.* 91:580, 1979.
27, Christensen, E., et al., "Treatment of Duodenal Ulcer: Randomized Clinical Trials of a Decade (1964 to 1974)," *Gastroenty.* 73:1170, 1977.
28. Ciclitira, P. J., et al., "A Controlled Trial of Cimetidine in the Treatment of Gastric Ulcer, " in *Cimetidine. Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists*, edited by W. L. Burland and M. A. Simkins (Amsterdam-Oxford: Excerpta Medica, 1977).
29. "Cimetidinefor Ever (and Ever and Ever. ..)?" (editorial), *Br Med. J.* 1:1435, 1978.
30. Cochran, W. G., et al., "Experiments in Surgical Treatmen t of Duodenal Ulcer, " in Costs, *Risks, and Benefits of Surgery*, J. P. Bunker, et al. (eds.) (New York: Oxford University Press, 1977).
31. Cooper, B. S., and Rice, D. P., "The Economic Cost of Illness Revisited, " Soc. Sec. *Buil.* 39:21, 1976.
32. DeGalocsy, C., and Van Ypersele de Strihou, c., "Pancytopenia With Cimetidine" (letter), *Ann. Int. Med.* 90:274, 1979.
33. Delaunois, L., "Hypersensitivity to Cimetidine" (letter), N. *Eng. J.* Med. 300:1216, 1979.
34. Department of Health, Education, and Welfare; Public Health Service, *The National Ambulatory Medical Care Survey:* 1975 *Summary, United States, January-December 1975*, Vital and Health Statistics Series 13, No. 33, DHEW publication No. (PHS) 78-1784 (Hyattsville, Md.: National Center for Health Statistics, January 1978).
35. _____, Health Services and Mental Health Administration, *Acute Conditions: Incidence and Associated Disability, United States, July 1970-June 2972*, Vital and Health Statistics Series 10, No. 82, DHEW publication No. (HSM) 73-1508 (Hyattsville, Md.: National Center for Health Statistics, April 1973).
36. _____, Office of Health Research, Statistics, and Technology, *Prevalence of Selected Chronic Digestive Conditions, United States, 1975*, Vital and Health Statistics Series 10, No. 123, DHEW publication No. (PHS) 79-1558 (Hyattsville, Md.: National Center for Health Statistics, July 1979).
37. Doll, R., "Introductory Remarks, " in *A Symposium on Carbenoxolone Sodium*, M. Robson and F. M. Sullivan (eds.) (London: Butterworths, 1968).
38. Drasar, B. S., et al., "Studies on the Intestinal Flora, I: The Bacterial Flora of the Gastrointestinal Tract in Healthy and Achlorhydric Persons, " *Gastroenty.* 56:71, *1969.*
39. Dunn, D. H., et al., "The Treatment of Hemorrhagic Gastritis With the Hz-Blocking Antihistamine, Cimetidine, " *Gastroenty.* 72:1053, *1977.*
40. Dyck, W. P., et al., "Cimetidine and Placebo in the Treatment of Benign Gastric Ulcer A Multicenter Double-Blind Study, " *Gastroenty.* 74:410, *1978.*
41. Dykes, P. W., et al., "Treatment of Upper Gastrointestinal Hemorrhage With Cimetidine, " in *Cimetidine: Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists*, W. L. Burland and M. A. Sim-

kins(eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
42. Elashoff, J. D., and Grossman, M. I., "Trends in Hospital Admissions and Death Rates for Peptic Ulcer in the United States From 1970 to 1978," *Gastroenty.* 78:280, 1980.
43. Englert, E., Jr., et al., "Cimetidine, Antacid, and Hospitalization in the Treatment of Benign Gastric Ulcer: A Multicenter Double-Blind Study," *Gastroenty.* 74:416, 1978.
44. Farris, J. M., and Greenburg, A. G., "Truncal Vagotomy With Drainage for the Elective Treatment of Duodenal Ulcer Disease," in Co) Z-*troversy in Surgery*, R. L. Varco and J. P. Delaney (eds.) (Philadelphia: W. B. Saunders Co., 1976).
45. Feldman, E. J., and Isenberg, J. I., "Effects of Metiamide on Gastric Acid Hypersecretion, Steatorrhea, and Bone-Marrow Function in a Patient With Systemic Mastocytosis," *N. Eng. J. Med.* 295:1178, 1976.
46. Feldman, M., et al., "Effect of Low-Dose Propantheline on Food-Stimulated Gastric Acid Secretion: Comparison With an 'Optimal Effective Dose' and Interaction With Cimetidine," N. *Eng. J. Med.* 297:1427, *1977.*
47. Finkel, M. J., "The FDA's Classification System for New Drugs: An Evaluation of Therapeutic Gain," *N. Eng. J. Med.* 302:181, *1980.*
48. Finkelstein, W., and Isselbacher, K. J., "Cimetidine," N. *Eng. J. Med.* 299:992, *1978.*
49. Fleiss, J. L., *Statistical Methods for Rates and Proportions* (New York: John Wiley & Sons, *1973).*
50. Food and Drug Administration, Rockville, Md., personal communication, 1979.
51. _____ Rockville, Md., personal communication, 1980.
52. Fordtran, J. S., and Grossman, M. I., "Third Symposium on Histamine H,-Receptor Antagonists: Clinical Results With Cimetidine," *Gastroenty.* 74:431, 1978.
53. Fordtran, J. S., et al., "Round Table Discussion on Gastric Ulcer," *Gastroenty.* 74:431, 1978.
54. Freiman, J. A., et al., "The Importance of Beta, Type II Error, and Sample Size in the Interpretation of the Randomized Control Trial," N. *Eng. J. Med.* 299:690, *1978.*
55. Freston, J. W., "Cimetidine in the Treatment of Gastric Ulcer: Review and Commentary," *Gastroenty.* 74:426, *1978.*
56. Frost, F., et al., "Cimetidine in Patients With Gastric Ulcer: A Multicentre Controlled Trial," *Br. Med. J.* 2:795, *1977.*
57. Fry, I., "Peptic Ulcer: A Profile," *Br. Med. J.* 2:809, *1964.*
58. Geweke, J. F., Department of Economics, University of Wisconsin, Madison, Wis., personal communication, 1979.
59. Gifford, L. M., et al., Medical Affairs Department, Smith Kline & French Laboratories, Philadelphia, "'Tagamet' Post-Market Outpatient Surveillance Program: Interim Report on Phase I," unpublished report.
60. Gill, M. J., and Saunders, J. B., "Perforation of Chronic Peptic Ulcers After Cimetidine" (letter), *Br. Med. J.* 2:1149, 1977.
61. Gillespie, G., et al., "Short-Term and Maintenance Cimetidine Treatment in Severe Duodenal Ulceration," in *Cimetidine: Proceedings of the Second International Symposium on Histamine Hz-Receptor Antagonists*, W. L. Burland and M. A. Simkins (eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
62. Gillies, R. R., et al., "Controlled Comparison of Two Dosage Regimens of Cimetidine in Duodenal Ulcer: A Multicenter Study," *Gastroenty.* 74:396, *1978.*
63. Gray, G. M., "Peptic Ulcer Disease," in *Medicine*, E. Rubenstein and D. D. Federman (eds.) (New York: Scientific American, October 1979).
64. Gray, G. R., et al., "Long-Term Cimetidine in the Management of Severe Duodenal Ulcer Dyspepsia," *Gastroenty.* 74:397, *1978.*
65. _____, "Oral Cimetidine in Severe Duodenal Ulceration," *Lancet* 1:4, *1977.*
66. Griebe, J., "Long-Term Prognosis of Duodenal Ulcer: Follow-Up Study and Survey of Doctors' Estimates," *Br. Med. J.* 2:1572, *1977.*
67. Grossman, M. I., Center for Ulcer Research and Education, Veterans Administration Center, Los Angeles, personal communication, 1980.
68. _____ "Closing Remarks (Cimetidine Sympodium')," *Gastroenty.* 74:487, *1978.*
69. _____ "Resume and Comment. Chapter 10, Veterans Administration Co-Operative Study on Gastric Ulcer," *Gastroenty. 61:635, 1971.*
70. Gudmand-Høyer, E., et al., "Prophylactic Effect of Cimetidine in Duodenal Ulcer Disease," *Br. Med. J.* 1:1095, *1978.*
71. Gugler, R., et al., "Cimetidine for Anastomotic Ulcers After Partial Gastrectomy: A Randomized Clinical Trial," N. *Eng. J. Med.* 301:1077, *1979.*
72. Hall, W. H., "Breast Changes in Males on Cimetidine," *N. Eng. J. Med.* 295:841, *1976.*

73. Hallenbeck, G. A., "Proximal Gastric Vagotomy Without Drainage for Duodenal Ulcer, " in Controversy *in* Surgery, R. L. Varco and J. P. Delaney (eds.) (Philadelphia: W. B. Saunders Co., 1976).
74. Henn, R. M., et al., "Inhibition of Gastric Acid Secretion by Cimetidine in Patients With Duodenal Ulcer," N. *Eng. J. Med.* 293:371, 1975.
75. Herbst, A. L., et al., "Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy With Tumor Appearance in Young Women, " N. *Eng. J. Med.* 284:878, *1971.*
76. Hetzel, D. J., et al., "Cimetidine Treatment of Duodenal Ulceration: Short-Term Clinical Trial and Maintenance Study, " *Gastroenty.* 74:389, **1978.**
77. Hirschowitz, B. I., et al., "Demonstration of a New Gastroscope, the 'Fiberscope', " *Gastroenty.* 35:50, 1958.
78. Hollender, L. F., and Marrie, A., *Highly* Selective *Vagotomy (New* York: Masson Publishing U. S. A., Inc., 1979).
79. Ippoliti, A. F., UCLA Center for Ulcer Research, Los Angeles, Calif., personal communication, **1980.**
80. Ippoliti, A. F., et al., "Cimetidine Versus Intensive Antacid Therapy for Duodenal Ulcer: A Multicenter Trial, " *Gastroenty.* 74:393, **1978.**
81. Isenberg, J. I., "Therapy of Peptic Ulcer, " *), A.M.A.* 233:540, **1975.**
82. _____, "Pathogenesis of Peptic Ulcer, " in *Gastrointestinal Diseases, vol. 1,* 2d cd., M. H. Sleisinger and J. S. Fordtran (eds.) (Philadelphia: W. B, Saunders Co., 1978).
83. _____, "Round Table Discussion on Duodenal Ulcer," *Gastroenty.* 74:407, 1978.
84. Ivy, A. C., "The Problem of Peptic Ulcer, " *J. A.M.A.* 1321053,1946.
85. _____ *Peptic Ulcer* (Philadelphia: Blakiston co., **1950).**
86. Jones, F. A., et al., *Peptic Ulcer Healing: Recent Studies on Carbenoxolone* (Baltimore, Md.: University Park Press, 1978).
87. Keeney, R. L., and Raiffa, H., *Decision With Multiple Objectives: Preferences and Value Tradeoffs (New* York: John Wiley and Sons, 1976).
88. Kennedy, T., and Spencer, A., "Cimetidine for Recurrent Ulcer After Vagotomy or Gastrectomy: A Randomised Controlled Trial, " *Br. Med. J.* 1:1242, 1978.
89. Klarman, H. E., "Application of Cost-Benefit Analysis to the Health Services and the Special **Case** of Technologic Innovation, " *Int. J. Hlth. Serv.* 4:325, **1974.**
90. Klotz, S. A., and Kay, B. F., "Cimetidine and Agranulocytosis" (letter), *Ann. Int. Med.* 88:579, **1978.**
91. Krause, U., "Long-Term Results of Medical and Surgical Treatments of Peptic Ulcer, " *Acta Chir. Sc.* suppl. 310, 1963.
92. Kruss, D. M., and Littman, A., "Safety of Cimetidine," *Gastroenty.* 74:478, **1978**
93. Lam, S. K., et al., "Treatment of Duodenal Ulcer With Antacid and Sulpiride: A Double-Blind Controlled Study, " *Gastroenty.* 76:315, 1979.
94. Lance, P., et al., "Non-Ulcer Dyspepsia, Duodenitis, and Cimetidine, " in *Cimetidine: The Westminster Hospital Symposium, 1978, C.* Wastell and P. Lance (eds.) (New York: Churchill Livingstone, 1978).
95. Landecker, K. D., et al., "Cimetidine and the Gastric Ulcer: A Double-Blind Controlled Trial, " *Med. J. Aust.* 2:43, 1979.
96. Laufer, I., "Assessment of the Accuracy of Double-Contrast Gastroduodenal Radiology, " *Gastroenty.* 74:874, *1976.*
97. Longstreth, G. F., et al., "Cimetidine Suppression of Nocturnal Gastric Secretion i n Active Duodenal Ulcer, " N. *Eng. J. Med.* 294:801, *1976.*
98. McCarthy, D. M., "Peptic Ulcer: Antacids or Cimetidine?" *Hospital Practice* 14:52, **1979.**
99. _____, "Report on the United States Experience With Cimetidine in Zollinger-Ellison Syndrome and Other Hypersecretory States, " *Gastroenty.* 74:453, 1978.
100. McDougall, B. R. D., et al., "Histamine H_1-Receptor Antagonists in the Prophylaxis and Control of Acute Gastrointestinal Haemorrhage in Liver Disease, " in *Cimetidine: Proceedings of the Second international Symposim on Histamine H_2-Receptor Antagonists,* W. L. Burland and M. A. Simkins (eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
101. McGuigan, J. E., "The Zollinger-Ellison Syndrome, " in *Gastrointestinal Disease,* vol. 1, 2d cd., M. H. Sleisenger and J. S. Fordtran (eds.) (Philadelphia: W. B. Saunders Co., 1978).
102. McMillen, M. A., et al., "Cimetidine and Mental Confusion, " N. *Eng. J.* Med. 293:284, 1978.
103. Meade, T. W., et al., "Recent History of Ischaemic Heart Disease and Duodenal Ulcer in Doctors, " *Br. Med. J.* 3:701, *1968.*
104. Mendeloff, A. I., "What Has Been Happening to Duodenal Ulcer?" *Gastroenty.* 67:1020, *1974.*
105. Monson, R. R., and MacMahon, B., "Peptic

Ulcer in Massachusetts Physicians, " N. *Eng. J. Med.* 281:11, *1969.*
106. Morris, T., and Rhodes, J., "Progress Report: Antacids and Peptic Ulcer, A Reappraisal, " *Gut* 20:538, *1979.*
107. Mosbech, J., and Videbaek, A., "Mortality From and Risk of Gastric Carcinoma Among Patients With Pernicious Anaemia," *Br. Med. J.* 2:390, *1950.*
108. Moshal, M. G., et al., "Treatment of Duodenal Ulcers With Cimetidine, " S. *Afr. J. Med.* 52:760, *1977.*
109. Netherlands Economic Institute, Present Cost of *Peptic Ulceration to the Dutch Economy and Possible Impact of Cimetidine on This Cost* (Rotterdam: Netherlands Economic Institute, 1977).
110. Northfield, T. C., and Blackwood, W. S., "Controlled Clinical Trial of Cimetidine for Duodenal Ulcer, " in *Cimetidine: Proceedings of the Second International Symposium on Histamine Hz-Receptor Antagonists,* W. L. Burland and M. A. Simkins (eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
111. Ochsner, A., "Treatment of Peptic Ulcer Disease, " in *Controversy in Surgery,* R. L. Varco and J. P. Delaney (eds.) (Philadelphia: W. B. Saunders Co., *1976).*
112. Office of Technology Assessment, U.S. Congress, *Assessing the Efficacy and Safety of Medical Technologies* (Washington, D. C.: U.S. Government Printing Office, 1978).
113. Paringer, L., and Berk, A., *Cost of illness and Disease, Fiscal Year 1975* (Washington, D. C.: Georgetown University, Public Services Laboratory, *1977).*
114. Paringer, L., et al., *Economic Cost of Illness, Fiscal Year 1975,* Report B1A (Washington, D. C.: Georgetown University, Public Services Laboratory, 1977).
115. Peterson, W. L., and Fordtran, J. S., "Reduction in Gastric Acidity, " in *Gastrointestinal Disease, vol.* 1, 2d cd., M. H. Sleisenger and J. S. Fordtran (eds.) (Philadelphia: W. B. Saunders Co., 1978).
116. Peterson, W. L., et al., "Healing of Duodenal Ulcer With an Antacid Regimen, " N. *Eng. J. Med.* 297:341, *1977.*
117. Priebe, H. J., et al., "Antacid Versus Cimetidine in Preventing Acute Gastrointestinal Bleeding: A Randomized Trial in *75* Critically Ill Patients, " N. *Eng. J. Med.* 302:426, *1980.*
118. Ricardo-Campbell, R., et al., "Preliminary Methodology for Controlled Cost-Benefit Studies of Drug Impact: The Effect of Cimetidine on Days of Work Lost in a Short-Term Trial in Duodenal Ulcer, " *J. Clin. Gastroenty.* 2:37, *1980.*
119. Richardson, C. T., "Gastric Ulcer, " in *Gastrointestinal Disease, vol. 1,* 2d ed., M. H. Sleisenger and J. S. Fordtran (eds.) (Philadelphia: W. B. Saunders Co., 1978).
120. Richardson, C. T., et al., "The Effect of Cimetidine, a New Histamine H,-Receptor Antagonist, on Meal-Stimulated Acid Secretion, Serum Gastrin, and Gastric Emptying in Patients With Duodenal Ulcer, " *Gastroenty.* 71:19, *1976.*
121. Robinson Associates, Inc., *The impact of Cimetidine on the National Cost of Duodenal Ulcers* (Bryn Mawr, Pa.: Robinson Associates, Inc., 1978).
122. Ruddell, W. S. J., et al., "Effect of Cimetidine on the Gastric Bacterial Flora, " *Lancet* 1:672, *1980.*
123. _____, "Pathogenesis of Gastric Cancer in Pernicious Anaemia," *Lancet* 2:521, *1978.*
124. Sawyers, J. L., "Truncal Vagotomy and Antrectomy as the Preferred Operation for Treatment of Duodenal Ulcer, " in *Controversy in Surgery,* R. L. Varco and J. P. Delaney (eds.) (Philadelphia: W. B. Saunders Co., 1976).
125. Scheurer, U., et al., "Gastric and Duodenal Ulcer Healing Under Placebo Treatment, " *Gastroenty.* 72:838, *1977.*
126. Schlippert, W., "Cimetidine: Hz-Receptor Blockage in Gastrointestinal Disease, " *Arch. Int. Med.* 138:1257, *1978.*
127. Schoenbaum, S. C., et al., "The Swine Influenza Decision," N. *Eng. J. Med.* 295:759, 1976.
128. Scitovsky, A. A. and McCall, N., "Changes in the Costs of Treatment of Selected Illnesses, 1951 -1964-1971," Palo Alto Medical Research Foundation, DHEW publication No. (HRA) 77-3161 (Rockville, Md.: National Center for Health Services Research, 1976).
129. Semb, L. S., et al., "A Double-Blind Multicenter Comparative Study of Cimetidine and Placebo in Short-Term Treatment of Active Duodenal Ulceration, " in *Cimetidine: Proceedings of the Second international Symposium on Histamine Hz-Receptor Antagonists,* W. L. Burland and M. A. Simkins (eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
130. Shain, M., and Roemer, M. I., "Hospital Costs Relate to the Supply of Beds, " *Mod. Hosp.* 92:71, **1959.**
131. Sharpe, P. C. and Hawkins, B. W., "Efficacy and Safety of Cimetidine: Long-Term Treatment With Cimetidine, " in *Cimetidine: Pro-*

ceedings of the Second International Symposium on Histamine Hz-Receptor Antagonists, W. L. Burland and M. A. Simkins (eds.) (Amsterdam-Oxford: Excerpta Medica, 1977).
132. SK&F Lab Co., *The History and Development of Hi-Receptor Antagonists* (Carolina, Puerto Rico: 1979).
133. Sleisenger, M. H., and Fordtran, J. S. (eds.), *Gastrointestinal Disease* (Philadelphia: W. B. Saunders Co., 1978).
134. Smith, M. P., ' Decline in Duodenal Ulcer Surgery, " *J. A.M.A.* 237:987, **1977.**
135. SmithKline Corp., 1O-K Reports filed with the U.S. Securities and Exchange Commission, Washington, DC., 1977 and 1978.
136. Soil, A. H., and Walsh, J. H., "Regulation of Gastric Acid Secretion, " *Ann. Rev. Physiol.* 41:35, 1979.
137. Sonnenberg, A. and Hefti, M., "The Costs of Postsurgical Syndromes (Based on the Example of Duodenal Ulcer Treatment)," *Clinics in Gastroenty.* 8:235, 1979.
138. Stadil, F., and Stage, J. G., "Cimetidine and the Zollinger-Ellison (Z-E) Syndrome, " in *Cimetidine: The Westminster Hospital Symposium, 1978, C.* Wastell and P. Lance (eds.) (New York: Churchill Livingstone, 1978).
139. Sturdevant, R. A. L., "How Should Results of Controlled Trials Affect Clinical Practice?" (editorial), *Gastroenty.* 73:1179, 1977.
140. Sturdevant, R. A. L., and Walsh, J. H., "Duodenal Ulcer, " in *Gastrointestinal Disease, vol.* 1, 2d cd., M. H. Sleisenger and J. S. Fordtran (eds.) (Philadelphia: W. B. Saunders Co., **1978).**
141. Susser, M., "Causes of Peptic Ulcer: A Selective Epidemiologic Review, *J. Chron. Dis.* 20:435, *1967.*
142. Susser, M., and Stein, Z., "Civilization and Peptic Ulcer, " *Lancet*, 1:115, 1962.
143. Thompson, P. L., et al., "Late Radiation Nephritis After Gastric X-Irradiation for Peptic Ulcer," Q. *J. Med.* 40:145, 1971.
144. Van Thiel, D. H., et al., "Hypothalamic-Pituitary-Gonadal Dysfunction in Men Using Cimetidine, " *N. Eng. J. Med.* 300:1012, 1979.
145. Villeneuve, J. P., and Warner, H. A., "Cimetidine Hepatitis, " *Gastroenty.* 77:143, 1979.
146. Von Haunalter, G., and Chandler, V. V., *Cost of Ulcer Disease in the United States* (Menlo Park, Calif.: Stanford Research Institute, 1977).
147, Walker, C. O., "Chronic Duodenal Ulcer," in *Gastrointestinal Disease*, M. H. Sleisenger and J. S. Fordtran (eds.) (Philadelphia: W. B Saunders Co., 1973).
148. Wallace, W. A., et al. "Perforation of Chronic Peptic Ulcers After Cimetidine, " *Br. Med. J.* 2:865, 1977.
149. Warner, K., et al., "Cost-Benefit and Cost-Effectiveness Analysis in Health Care: Methodology and Literature Review, " draft report submitted to the Office of Technology Assessment, U.S. Congress, Washington, D. C., October 1979.
150. Wastell, C., and Lance, P. (eds.), *Cimetidine: The West) ninster Hospital Symposium, 1978 (New* York: Churchill Livingstone, 1978).
151. Weinstein, M. C., "Economic Evaluation of Medical Procedures and Technologies: Progress, Problems, and Prospects, " in *Medical Technology*, NCHSR Research Proceedings Series, DHEW Publication No. (PHS) 79-3254 (Hyattsville, Md.: National Center for Health Statistics, *1979).*
152. Weinstein, M. C., and Stason, W. B., *Hypertension: A Policy Perspective* (Cambridge, Mass.: Harvard University Press, *1976).*
153. Welsh, J. D., "Diet Therapy of Peptic Ulcer Disease," *Gastroenty.* 72:740, *1977.*
154. Winship, D. H., "Cimetidine in the Treatment of Duodenal Ulcer, " *Gastroenty.* 74:402, 1978.
155. Wolfe, M. M., "Impotence on Cimetidine Treatment" (letter), *N. Eng. J. Med* 303:94, *1979.*
156. Wulff, H. R., and Rune, S. J., "A Comparison of Studies on the Treatment of Gastric Ulceration With Cimetidine, " in *Cimetidine: The Westminster Hospital Symposium, 1978, C.* Wastell and P. Lance (eds.) (New York: Churchill Livingstone, 1978).
157. Zeckhauser, R., and Shepard, D., "Where Now for Saving Lives?" *Law & Contemp. Prob.* 40:5, 1976.

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