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).

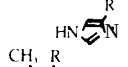
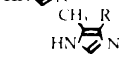
Cimetidine powerfully inhibits all phases of gastric acid production. The drug not only interferes with histamine-stimulated acid output, but also inhibits the effects of gastric and acetylcholine. Preliminary studies found that a 300 mg oral dose of cimetidine reduced nocturnal and basal acid secretion 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.