Ulcer Disease: New Aspects of Pathogenesis and Pharmacology

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PREFACE *

Ulcer is a defect caused by chemical, physical, or infectious agents in the epithelial lining (e.g., skin, mucous membranes). Gastric and duodenal ulcers as interpreted in this book refer to a complex group of disorders for which the only common element seems to be the mucosal defect resistant to healing.[1,2] It is, thus, appropriate to use the designation ulcer disease, since the pathogenesis of gastric and duodenal ulcers involves not only local alterations in the gut but central changes in brain and neuroendocrine system as well.

These nonspecific acute or chronic ulcers are preferentially localized in the acid-producing part of the stomach, antrum, and anterior or posterior wall of the duodenum. Nevertheless, their pathophysiology is poorly understood, and the lesions are often simplistically labeled "peptic ulcers". It is, however, unfortunate and misleading to label a disorder by only one, mostly historic pathogenetic factor, especially when gastric acid and pepsin hypersecretion, but especially peptic activity, play a more and more doubtful role in duodenal and gastric ulceration. Furthermore, only about 50% of duodenal ulcer patients secrete more than normal gastric acid, and a substantial number of gastric and duodenal ulcer patients are hyposecretors.[3] Until classification based on etiologic factors will be available for ulcer disease, it is more appropriate to rely on classification based on the well-elucidated localization of ulcers than to overemphasize a single and doubtful pathogenetic factor such as pepsin.

The incidence and prevalence of gastric and duodenal ulcers are different in various areas of the world, but it is generally estimated that about 10% of the population suffers from this disease at least once during their lifetime.[3] The etiology and pathogenesis of ulcer disease are complex and poorly elucidated. Drugs and stressors, such as burn, brain damage, and trauma, account for about 20 to 25% of all cases, while the etiology of ulcer disease is not known in about 70 to 80% of cases. If the plethora of descriptive studies on the pathogenesis and mostly empirical pharmacologic interventions are critically evaluated, one cannot escape from the surprising realization that we may not know more about the etiology and pathophysiology of ulcer disease than those of malignant tumors. Ulcer research is so confusing that doubts have been raised about whether we can equate etiology with pathogenesis.[4] Nevertheless, there is no successful treatment or prevention of a disease without pharmacology based on etiology. Furthermore, virtually everybody agrees that ulcer pathophysiology is a complex multifactorial or pluricausal disorder.[2,5-7]

Needless to say, to study the role of multiple etiologic and pathogenetic factors, animal models of ulcer disease are needed.[8,9] Clinical studies with ulcer patients are essential to determine the factors influencing the healing and recurrence of ulcers in the stomach and duodenum, but the early pre-ulcerogenic biochemical, functional, and structural alterations generally can be investigated only in animal models.[9-11] It is, thus, both from results of clinical studies and work with animal models that the major pathogenetic factors were recently reviewed and presented graphically in Figure 1.[2] Historically, most of the emphasis has been placed on "secretion"; i.e., neutralization or inhibition of secretion of gastric acid. In addition, new studies delineate the role of gastric and duodenal bicarbonate secretion. Elucidation of its regulation will yield important new therapeutic approaches to ulcer disease. Motility in the stomach has long been recognized as a possible pathogenetic factor in duodenal ulceration, but a recent review of the literature indicated that duodenal motor abnormality, contributing to abnormal acid emptying and a "misplaced mix" of duodenal bicarbonate and acid might be another factor in duodenal ulceration that can be pharmacologically modulated.[2] New results with models of duodenal ulceration are certainly promising in this respect.[12,13]

* Parts of this introductory overview originate from a foreword of a recently published book: Szabo, S. and Mózsik, Gy., Eds., *New Pharmacology of Ulcer Disease. Experimental and Therapeutic Approaches*, Elsevier, New York, 1987.

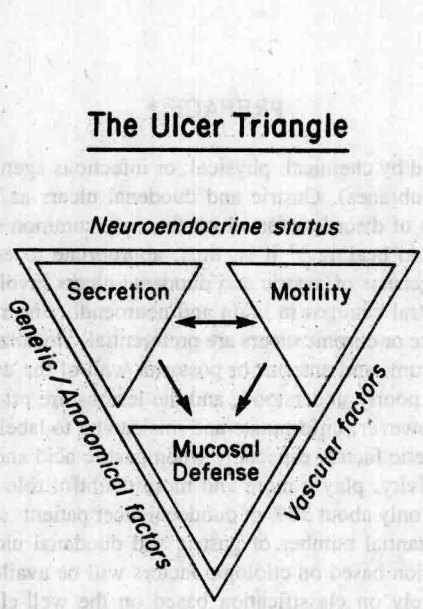

FIGURE 1. Major endogenous pathogenetic factors in ulcer disease. (Modified from Szabo, S., *Lab. Invest.*, 51, 121, 1984.)

Mucosal defense has been investigated with increasing vigor, especially after the introduction of the concept of gastric "cytoprotection".[14,15] Numerous publications and symposia have dealt with this new property of prostaglandins: to prevent at nonantisecretory doses the chemically induced and grossly visible hemorrhagic erosions in the rat stomach.[15] We now know that sulfhydryls, carotenoids, colloidal bismuth, and sucralfate also exhibit gastric mucosal protection without inhibiting gastric secretion. Thus, pharmacologic emphasis has been placed on strengthening "mucosal defense" despite the lack of agreement on a definition of mucosal defense.

Other new pathogenetic elements and new targets which can be pharmacologically modulated are being investigated, such as bicarbonate secretion, vascular factors, and neuroendocrine elements. These may replace the previous two factors as well as others (for example, acid secretion and motility). From the pathogenetic factors illustrated (Figure 1) only the genetic and anatomical determinants (e.g., position of the duodenum between certain ligaments, liver and pancreas that contribute to the drainage of gastric juice and localization of duodenal ulcers) cannot be influenced pharmacologically.[16] All the other etiologic and pathogenetic factors may be considered for new preventive or therapeutic targeting. If we accept that the pathophysiology of ulcer disease is pluricausal, why cannot its pharmacology be multifactorial? This does not mean that several drugs should automatically be prescribed for each patient but new drugs with multiple mechanisms of action (e.g., in addition to acid neutralization or decreased secretion, the drugs might stimulate bicarbonate secretion, stabilize motility and the vascular tree).

A revolution in ulcer pharmacology was created with the introduction of histamine H_2-receptor antagonists. These drugs, however, have side effects, some patients are resistant to them,[17] and certain factors such as cigarette smoking may neutralize the effect of at least some of the members of this class of drugs.[18] More disappointing, however, is the recognition that the effect of H_2-receptor antagonists is restricted: duodenal and gastric ulcer healing rate that, in placebo-treated patients varies from 30 to 60%, is only pushed up to 80 to 95% in most of the studies, and when the drug is discontinued the ulcer reappears in more than half of the patients within 1 year.[17,19] Similar temporary successes were seen in the pre-

penicillin era of antibiotics when the drugs were not strictly and causally designed for certain infectious diseases.

With such a need for additional information about the pathogenesis and pharmacology of ulcer disease, it is thus appropriate to present in a selected form the highlights of the new data presented at the 5th International Conference on Experimental Ulcer (Boston, MA, May 16 to 18, 1985). The abstracts of all the about 200 presentations were published in a journal,[20] and a critical evaluation of the results and concepts was also prepared and published.[21] Subsequently, we asked some of the invited speakers and authors of free communications to prepare a detailed and updated account of their work. The new information about the latest development in the pathogenesis and pharmacology of ulcer disease thus is derived from this material.

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He is one of the editors of the recently published *New Pharmacology of Ulcer Disease* (published by Elsevier, New York) and he published in 1988, as a guest editor, a series of six articles on *Seminars on Gastric Mucosal Injury in Digestive Disease and Sciences*. He is on the editorial board of *Archives of Gastroenterohepatology*. Presently, he is a member of the American Gastroenterological Association, American Society for Pharmacology in Experimental Therapeutics, American Association of Pathologists, the Endocrine Society, the Pharmacologic Society of Canada, Chemical Pathology and Toxicology Subdivision of the American Chemical Society, American Medical Association, and New York Academy of Sciences.

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