# advances in ulcer disease

editors:
K.-H. HOLTERMÜLLER
J.-R. MALAGELADA

# advances in ulcer disease

## Proceedings of a Symposium on the Pathogenesis and Therapy of Ulcer Disease

Munich,
March 13-14, 1980

editors:
K.-H. HOLTERMÜLLER
J.-R. MALAGELADA

EXCERPTA MEDICA 1980
AMSTERDAM-OXFORD-PRINCETON

International Congress Series No. 537
ISBN Excerpta Medica 90 219 9504 2
ISBN Elsevier North-Holland 0 444 90187 6

**Library of Congress Cataloging in Publication Data**

Symposium on the Pathogenesis and Therapy of Ulcer Disease, Munich, 1980.
Advances in ulcer disease.

(International congress series; no. 537)
Includes indexes.
1. Peptic ulcer--Congresses. 2. Peptic ulcer--Surgery--Congresses. I. Holtermüller, K.-H. II. Malagelada, J.-R. III. Title. IV. Series.
[DNLM: 1. Duodenal ulcer--Congresses. 2. Stomach ulcer--Congresses. W3 EX89 no. 537 1980 / WI 360 S9895a 1980]
RC821.S92 1980 616.3'43 80-25800

*Publisher:*
Excerpta Medica
305 Keizersgracht
1000 BC Amsterdam
P.O. Box 1126

*Sole Distributors for the USA and Canada:*
Elsevier North-Holland Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in The Netherlands by Casparie, Amsterdam

# Preface

Writing a book about ulcer disease in 1980 is a challenging task, for ulcer disease is in the midst of an explosion of new knowledge. Significant advances have occurred in both basic and clinical aspects of the disease. Concepts are being constantly revised, as new data become available. A traditional textbook approach would have almost surely produced a volume already outdated by the time it reached its potential readers. Instead, we invited key scientists around the world whose active programs and leadership in specific areas of research allowed them to give a detailed analysis of the currently available knowledge about ulcer disease. All participants assembled for 2 days of scientific presentations and open debate in Munich. We are deeply grateful to these colleagues for their generous help which produced thoughtful papers in particularly controversial and exciting areas. In many instances, the work contains not only an update on the topic, but also important hints about future research directions.

To spare our readers tedious transcriptions, we have summarized these discussions with the help of Drs. S. Bonfils, W. Dölle, W.P. Fritsch, W. Lorenz, G. Strohmeyer, and K.G. Wormsley. The latter also summarized and gave his personal viewpoints on the issues discussed during the round table on 'Future research directions in the medical therapy of ulcer disease'.

We also felt compelled to ask some friends to assist us in the task of reviewing, criticizing, and complementing selected areas that reached beyond our editorial expertise. Drs. A.J. Cameron, T.P. Dousa, R.A. Levine, M.I. Samloff, W. Schreiber and V. Schumpelick, performed this important task. Some of them also contributed with critical overviews, printed at the end of each section. Dr. Grossman honored us by contributing his overview of the topic, that closed the meeting and the book. Mr. Aart Brouwer of Smith Kline Dauelsberg, Germany, provided encouragement and generous support to make all of this possible.

The result of all this effort is the volume we now present to our readers for them to judge. We hope they will not be disappointed. This volume should provide a solid base of information both of practical value and as a point of departure for further discoveries. If we manage to capture the interest and approval of our readers we, and the rest of the contributors, will feel that our work has been worthwhile.

Professor Dr. Karl-Hans Holtermüller
I. Medizinische Klinik und Poliklinik
Langenbeckstraße 1
6500 Mainz
Federal Republic of Germany

Dr. Juan-Ramon Malagelada
Mayo Clinic and Mayo Foundation
Gastroenterology Research Unit
Rochester, MN 55901
U.S.A.

# Contents

Introductory remarks 1
*L. Demling*

**Chapter I: Heterogeneity of ulcer disease**

Genetic aspects of ulcer disease 7
*J.I. Rotter and M.I. Grossman*

Environmental aspects of ulcer disease 27
*A.R. Cooke*

Animal models of ulcer disease 37
*H.M. Jennewein and R. Hammer*

Discussion 49

**Chapter II: Pathogenesis of ulcer disease**

Gastric mucus and mucosal resistance to injury 57
*W. Domschke*

Prostaglandins as cytoprotective factors 72
*A. Robert*

Experimental studies on gastric cytoprotection by prostaglandins, antisecretory agents and epidermal growth factor 78
*S.J. Konturek, T. Radecki, T. Brzozowski, I. Piastucki, A. Dembińska-Kieć and A. Zmuda*

Lysosomal stability and mucosal resistance to injury 87
*D. Waldron-Edward and L. Greenberg*

Gastric mucosal blood flow and resistance to injury 101
*P.H. Guth*

Morphological phases in the development and healing of ulcers 110
*T. Miyake*

Discussion 124

Pathogenesis of ulcer disease: comments and perspectives 128
*T.P. Dousa*

**Chapter III: Regulation of gastric secretory function: relevance to ulcer disease**

Intracellular mechanisms of acid secretion 139
*G. Sachs, T. Berglindh, E. Rabon and G. Saccomani*

Parietal cell receptors of acid secretion 147
*M.J.M. Lewin*

Regulation of parietal cell function 164
*A.H. Soll and M.I. Grossman*

Intramucosal mechanisms: relevance of the mast cell concept 176
*W. Lorenz, K. Mohri, H.-J. Reimann, H. Troidl, H. Rohde and H. Barth*

Neural regulation of gastric acid secretion 195
*L. Olbe*

Hormones and their role in ulcer disease 207
*R. Arnold, H. Koop and W. Creutzfeldt*

Discussion 225

Regulation of gastric secretory functions: a critical overview 229
*R.A. Levine*

**Chapter IV: Pathophysiology and diagnosis of ulcer disease**

Gastric secretion in ulcer disease 243
*J.I. Isenberg*

Gastric motor function in ulcer disease 255
*J.-R. Malagelada and J.-R. Larach*

Current views on symptomatology of ulcer disease 273
*W.L. Peterson*

Endoscopy in the diagnosis of duodenal ulcer 282
*M. Classen, H. Dancygier and H.F. Fuchs*

Endoscopy in the diagnosis of gastric ulcer 287
*K. Ewe*

Discussion 296

**Chapter V: Medical treatment of ulcer disease**

Goals of medical therapy in ulcer disease 303
*K.-H. Holtermüller*

Pharmacologic requirements of the 'ideal' ulcer drug 315
*K.-F. Sewing*

Histamine $H_2$-receptor antagonists in short- and long-term treatment of duodenal ulcer 318
*J.J. Misiewicz*

Histamine $H_2$-receptor antagonists in short- and long-term treatment of gastric ulcer 330
*W. Dölle*

Comparison of the acid inhibitory effects of ranitidine and cimetidine 336
*S.J. Konturek, W. Obtułowicz, N. Kwiecień, E. Sito and J. Oleksy*

Medical therapy of ulcer disease after gastric resection 347
*K.-H. Holtermüller, H. Weis, P. Herzog, M. Rothmund and J. Gröninger*

Management of Zollinger-Ellison Syndrome 357
*S. Bonfils and M. Mignon*

Side effects of the histamine $H_2$-receptor antagonists and their implication for ulcer therapy 366
*H. Goebell and J. Hotz*

Pharmacological basis and clinical use of antacids 376
*J.-R. Malagelada and G.L. Carlson*

Anticholinergics in the treatment of ulcer disease 395
*M. Ström, R. Gotthard, G. Bodemar and A. Walan*

Carbenoxolone in the treatment of ulcer disease 406
*M.J.S. Langman*

Prostaglandins: pharmacologic principles 416
*J.I. Isenberg*

$E_2$ prostaglandins – potential agents in peptic ulcer treatment 421
*C. Johansson and B. Kollberg*

Newly developed drugs: modes of action and clinical experience 427
*W.-P. Fritsch, T. Scholten, J. Müller and K.-J. Hengels*

The impact of medical therapy on the natural history of ulcer disease 449
*J. Hansky*

Discussion 460

**Chapter VI: Surgery for ulcer disease**

Rationale of surgical therapy in ulcer disease 473
*E.H. Farthmann*

Effect of surgical procedures on gastric secretory and motor function 482
*K.A. Kelly*

Surgical options for the treatment of duodenal ulcer disease 493
*D. Johnston*

Surgical options for the treatment of gastric ulcer disease 516
*H.D. Becker and J.R. Siewert*

Discussion 527

Surgery for ulcer disease: comments and perspectives for the future 529
*H.W.Schreiber and V. Schumpelick*

Future approaches to the treatment of ulcer disease 534
*K. Wormsley*

Closing remarks 539
*M.I. Grossman*

Genetic heterogeneity of ulcer disease: an overview 545
*I.M. Samloff*

Editorial note 551

Subject index 553

Authors' index 559

# Introductory remarks*

**L. Demling**
*Medizinische Klinik mit Poliklinik, Universität Erlangen-Nürnberg, Federal Republic of Germany*

Today, it is thought that peptic ulceration arises from an imbalance between aggressive and protective factors. In general terms this idea is certainly correct, for the healing of an ulcer can be accelerated both by reducing aggressive factors through the administration of antacids or $H_2$-blockers and by strengthening the protective action of the gastric mucus (for example, by administration of carbenoxolone).

The endoscopist never observes the development of a peptic ulcer, but merely its gradual healing. In this respect, the peptic lesion has something of the characteristics of a myocardial infarction. And, indeed, it is possible that a local disturbance in blood flow is involved in the genesis of an ulcer.

Thus, the aggressive gastric juice develops its corrosive effect rapidly and locally, leading to impaired blood flow. When gastritis causes a reduction in the resistance of the mucosal membrane, the back-diffusion of the hydrochloric acid in the gastric juice is seen as the pathogenic meeting point of peptic activity, inflammation and vascular process. It is feasible that the blood vessels of the gastric mucosa are damaged by the back-diffusing H-ions, so that spasms or thrombotic processes disturb the flow of blood within them; this process can be accelerated by the decrease of blood flow which accompanies an increase of H-ion output under certain circumstances (for example, stress). Our own investigations using autoradiography (HTO) and mass spectroscopy ($D^{18}$ water) provided proof that hydrogen ions, but not whole water molecules, back-diffuse into an experimentally-damaged gastric mucosa, but not into the intact mucous membrane.

A quite different theoretical model is the idea that, in gastric ulceration, a certain amount of acid and pepsin does not leave the glandular channel to

* Excerpt from the Welcome Address given by Professor Dr. L. Demling at the opening of the symposium.

enter into the gastric lumen at all, but rather, as in the case of trypsin in the development of pancreatitis, moves off in the wrong direction by diffusing into the interstitial tissue. The experimental intramucosal injection of gastric juice has demonstrated what damage acid and pepsin can do there: the result is chronic ulceration.

It is possible that gastritis gives rise to changes in the tissue surrounding the glandular channels, thus causing them to leak. The development of ulcers at the line dividing gastritis from normal mucosa could be explained by the fact that, at this point, relatively abundant amounts of acid are produced near damaged tissue. Perhaps, however, gastritis merely promotes such leakage and has only a localizing effect, while other processes are responsible for breaking open the glandular channel.

This idea does not apply to duodenal ulcer, since no hydrochloric acid is produced in the duodenal mucosa. However, theoretical models differing from those so far considered might also be examined, such as the idea that ulceration in the duodenum is not produced by the acid 'breaking into' the mucosa, but that its absorption or transfer might lead to a pathogenic effect. If we assume that the absorption of acid in the duodenum is a physiological process, then it is possible that, as a result of changes in the interstitial tissue, this acid might also follow the wrong path. It is conceivable that an additional mechanism in the duodenum promotes the uncontrolled penetration of the normally harmless acid. Might not the amino precursor uptake and decarboxylation cells responsible for dealing with the biogenic amines provide the initial triggering mechanism, in the form of tissue damage which permits entry to the acid? Brunner's glands are found mainly between the pylorus and the papilla of Vater, and extend into the submucosa. Could it be possible that, under certain circumstances, they might provide the corrosive gastric juice with an access pathway?

Ladies and gentlemen, I should not wish to conclude this welcoming address without paying tribute to the man who is our guest of honor today and at whose suggestion this symposium came into being.

Our colleague, Professor Hans-Peter Wolff, exemplifies the fact that the field of internal medicine cannot be torn apart and robbed of its intrinsic coherence. An active investigator in the fields of nephrology and hypertension, he established the connection to gastroenterology with his work on the pathogenesis of ascites and the metabolism of aldosterone in liver diseases. Special thanks and recognition are due to him for the fact that, while delving deeply into particulars, he has retained a view of the whole and has also promoted international cooperation.

It is our hope that, during this symposium, an atmosphere may be created

which will be conducive to the sowing of seeds of new and fertile ideas. The creative hypothesis is the requisite for the art of recognizing interrelationships in this world. When we are able to hypothesize, we free ourselves from slavery to unknown forces, and become their master.

# Chapter I: Heterogeneity of ulcer disease*

* The review paper for this chapter appears on pages 545–550.

# Genetic aspects of ulcer disease*

**J.I. Rotter and M.I. Grossman**
*Division of Medical Genetics, Departments of Medicine and Pediatrics, Harbor-UCLA Medical Center, Torrance; and Center for Ulcer Research and Education, Wadsworth V.A. Hospital, UCLA School of Medicine, Los Angeles, California, U.S.A.*

## Introduction

The familial aggregation of peptic ulcer disease and its association with such clear-cut genetic factors as blood group O and nonsecretor status is well established. However, the genetics of this disorder or group of disorders has, until recently, been poorly delineated. Polygenic inheritance was the prevailing hypothesis proposed for peptic ulcer, based primarily on the finding of blood group associations and the exclusion of a simple mode of inheritance for all ulcer disease. We have proposed genetic heterogeneity as an alternative hypothesis, which could explain both the familial aggregation of peptic ulcer disease and the lack of a simple Mendelian pattern of inheritance [1]. This concept states that peptic ulcer is not one disease, but a group of disorders with different genetic and environmental causes. Initially based on indirect evidence, genetic heterogeneity has now received direct support from genetic studies using subclinical markers such as serum pepsinogen I [2, 3]. The unravelling of the genetic heterogeneity of peptic ulcer has important clinical and etiologic implications, for if what is termed a 'disease' is in reality a number of disorders that are grouped together because of some common clinical feature, these distinct disorders may differ markedly in genetics, pathophysiology, interaction with environmental agents, natural history and response to therapy.

J.I. Rotter holds a Clinical Investigator Award (AM 00523) and a March of Dimes Basil O'Connor Starter Grant (5-245). M.I. Grossman is a Veterans Administration Senior Medical Investigator. *This work was supported in part by grant AM 17328 to CURE (Center for Ulcer Research and Education).

Peptic ulcer is among the most common of chronic diseases. This results in a number of problems for genetic studies. Is a relative of a patient with peptic ulcer affected because he has the same genotype, shares the same environment, or simply has, by chance, a common disorder? The age of onset of peptic ulcer varies markedly. Therefore, it is impossible to say whether an individual who is clinically unaffected at any given time will become affected later in life. Like many common diseases, genetic studies of peptic ulcer have suffered from confusion engendered by the use of varying definitions of 'affected' by different investigators. Thus, 'affected' may in one case refer to any individual who has abdominal pain, yet in another case it may only apply to one with an endoscopically-demonstrated crater. However, the greatest obstacles to genetic studies have been our ignorance concerning the basic defect(s) in this disorder or group of disorders, and the unavailability of genetic markers to detect individuals with the mutant genotype prior to its clinical manifestation.

Despite these difficulties, we have known for many years that genetic factors play a role in the etiology of peptic ulcer, based on 3 lines of evidence: family studies, twin studies, and blood-group studies.

## Genetic factors

The first approach in looking for genetic factors in a common disease is to determine whether familial aggregation is present, comparing the incidence of the disease in relatives of patients with its incidence in the general population. If increased, this is often the first indication that genetic factors are important in a disease. Family aggregation was noted in the late 1800's but, as with many diseases, the majority of initial reports presented one or few pedigrees with no control data. Subsequently, individuals with peptic ulcer were shown to have an 'increased family history' of the disease [4–6]. Most reports indicated a positive family history in 20–50% of individuals with peptic ulcer, compared to 5–15% in controls. While this information has been used to support the importance of genetic factors, it is of little value in testing genetic hypotheses since the prevalence of a positive family history will vary greatly with the type of interview, family size, number of relatives included, and with the criteria used for defining an affected individual. A more accurate assessment of familial aggregation is obtained by comparing the prevalence of the disorder among specific relatives of an affected individual to that found among similar relatives of a control group. This has been done in several excellent studies [5, 7–12], and the consistent observation was that the frequency of peptic ulcer was 2–3 times greater in first-degree relatives of peptic ulcer patients