Lawrence of Arabia, author of Seven Pillars of Wisdom, wrote ‘All men dream but not in the same way. Those who dream at night ... awake in the morning and consider their dream but vanity. But those who dream during the day are dangerous because they can act upon their dream, eyes opened, and make it possible.’

We feel we belong to these awakened dreamers

_Carmelo Scarpignato_

_Gabriele Bianchi Porro_
Progress in Basic and Clinical Pharmacology

Vol. 11 (Updated Reprint)

Series Editors

P. Lomax  Villefranche-sur-Mer
C. Scarpignato  Parma/Nantes
E.S. Vesell  Hershey, Pa.
Clinical Pharmacology and Therapy of Helicobacter pylori Infection

Volume Editors

C. Scarpignato Parma/Nantes
G. Bianchi Porro Milan

55 figures and 60 tables, 2004
Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

Drug Dosage. The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

All rights reserved. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

© Copyright 2004 by S. Karger AG, P.O. Box, CH–4009 Basel (Switzerland)
www.karger.com
Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel
ISSN 1011–0267
Contents

IX Preface to the Updated Reprint
Scarpignato, C. (Parma/Nantes); Bianchi Porro, G. (Milan)

XI Foreword
Misiewicz, J.J. (London)

XV Preface
Scarpignato, C. (Parma/Nantes); Bianchi Porro, G. (Milan)

Basic Pathophysiology

1 Clinical Spectrum of Helicobacter pylori Infection
Osato, M.S.; Graham, D.Y. (Houston, Tex.)

20 Mechanisms of Helicobacter pylori-Induced Mucosal Damage
Crabtree, J.E. (Leeds); Figura, N. (Siena)

43 Gastroduodenal Mucosal Damage
Interaction between NSAIDs and Helicobacter pylori Infection
Lazzaroni, M.; Bianchi Porro, G. (Milan)

57 Disturbances of Gastroduodenal Physiology in Helicobacter pylori Infection
Gibbons, A.; Calam, J. (London)

Clinical Pharmacology

74 Clinical Pharmacology of Antimicrobials
Goodwin, S. (London)
Bismuth Compounds for Eradication of Helicobacter pylori: Pharmacology and Safety
Scarpignato, C. (Parma/Nantes); Pelosini, I. (Parma)

Sucralfate and Helicobacter pylori
Marks, Solly (I.N.); Louw, J.A. (Cape Town)

Antisecretory Drugs for Eradication of Helicobacter pylori: Antibacterial Activity and Synergism with Antimicrobial Agents
Scarpignato, C. (Parma/Nantes); Pelosini, I. (Parma)

Evaluation of Helicobacter pylori Eradication
Which Test?
De Koster, E.; Jonas, C.; Denis, P.; Otero, J.; Deltenre, M. (Brussels)

Helicobacter pylori Eradication
Drug Regimens
Moayyedi, P.; Axon, A.T.R. (Leeds)

Esomeprazole-Based Regimens for Helicobacter pylori Eradication (Updated Contents)
Scarpignato, C.; Pelosini, I.; Molina, E. (Parma); Vigneri, S. (Palermo)

Quadruple Therapy
Second- or First-Line Eradication Regimen?
de Boer, W.A. (Oss)

Drug Therapy of Helicobacter pylori Infection: A Meta-Analysis
Chiba, N.; Hunt, R.H. (Hamilton)

Drug Therapy of Helicobacter pylori Infection
A Pharmacoeconomic Analysis
Vakil, N.B. (Milwaukee, Wisc.)

Therapy of Helicobacter pylori-Positive Peptic Ulcer Disease
Maconi, G.; Bianchi Porro, G. (Milan)

Therapy of Helicobacter pylori-Positive Nonulcer Dyspepsia
Montague, S.; McNamara, D.; Buckley, M.; O’Morain, C. (Dublin)

Therapy of Helicobacter pylori-Associated Gastric Neoplasms
Meining, A. (Munich); Bayerdörffer, E. (Dresden); Stolte, M. (Bayreuth)

Treatment of Helicobacter pylori Eradication Failure
van der Hulst, R.W.M. (Amsterdam/Haarlem); Tytgat, G.N.J. (Amsterdam)

Resistance of Helicobacter pylori to Antibiotics
Méraud, F. (Bordeaux)
381 Treatment Options for Patients with Helicobacter pylori Infection Resistant to One or More Eradication Attempts (Updated Contents)
Parente, F.; Cucino, C.; Bianchi Porro, G. (Milan)

392 Treatment of Helicobacter pylori Reinfection
Miehlke, S.; Bayerdörffer, E. (Dresden); Malfertheiner, P. (Magdeburg)

399 Progress toward Vaccination against Helicobacter pylori Infection
Ghiara, P.; Covacci, A. (Siena)

419 Treatment of Helicobacter pylori Infection
From Today's Practice to Future Management
Williams, M.P.; Pounder, R.E. (London)

Malfertheiner, P. (Magdeburg); Mégraud, F. (Bordeaux); O’Morain, C. (Dublin); Hungin, A.P.S. (Durham); Jones, R. (London); Axon, A.T.R. (Leeds); Graham, D.Y. (Houston, Tex.); Tytgat, G.N.J. (Amsterdam)

456 Author Index

457 Subject Index
Preface to the Updated Reprint

Significant progress and new insights into *Helicobacter pylori* biology [1] and related diseases [2] have been gained in the four years since the initial publication of this book. In particular, the indications for the treatment of infection have been considered a matter of debate since 1994, when the first Consensus paper was published [3]. Since then a considerable advance has been made in the management of *H. pylori* infection which, paradoxically, resulted in confusion and controversy mainly due to the increasing potential indications of bacterial eradication [4]. To clarify and outline recommendations on indication for eradication therapy, several national and international societies have issued practice guidelines. The most relevant ones, of which a critical update has been recently published [5], were produced by the European *Helicobacter pylori* Study Group [6] during the second Maastricht Consensus Meeting in September 2000. Besides the controversy surrounding the indications for eradication, the real novelties in the field of therapy of *Helicobacter* infection have been the introduction of esomeprazole-based eradication regimens as well as the development of some effective rescue therapies [7]. This is why, when the publisher informed us of his willingness to reprint this book due to the success encountered, we decided to include three new chapters dealing with the above topics in the hope to complement its contents and offer the readers the most recent information.

We are grateful to AstraZeneca for supporting this updated reprint and for making it available to the medical community. They are to be congratulated for their continuous efforts towards the medical education.

August, 2003

Carmelo Scarpignato
Gabriele Bianchi Porro
References

Most people now accept the Darwinian evolutionary theory of the origin of species, although lively debate continues between those favouring a gradualist view, as opposed to abrupt evolutionary jumps, governing the emergence of new species [1]. Progress in medical science seems to, in the main, proceed by a series of evolutionary jumps, which produce a paradigm shift in the way in which causes of disease, or methods of diagnosis or treatment, are perceived and applied in clinical practice. These breakthroughs can occur in any area relevant to medicine, such as basic science, pharmacology, epidemiology and the like. In his recent book describing the rise and fall of modern medicine [2], Dr. James Le Fanu lists 12 definitive movements that occurred during the 20th century; the discovery of Helicobacter pylori (Hp) ranks as one of these.

Until very recently (only 16 years ago!) it was universally accepted that the normal stomach was sterile, because bacteria could not survive in the low pH of the gastric lumen. Bacterial colonisation of the stomach was synonymous with bacterial overgrowth which was the exception rather than the rule and had acute and catastrophic consequences for the patient. Dr. Barry Marshall and Dr. Robin Warren [3] were true iconoclasts, daring ‘to think the unthinkable’ [2], when they convinced the medical community (in many instances, with some initial difficulty) that the stomach was not sterile, even in the presence of very low luminal pH. Instead, in countless individuals, underneath the layer of adherent mucus there lurked large numbers of Hp. Even more shocking and mind-boggling ideas developed, as data rapidly accumulated. Duodenal ulcer, a disease characterized by acid hypersecretion and thought to be related to various environmental factors, such as stress, diet, or smoking, has been shown
in the vast majority of cases (in the absence of ulcerogenic drugs), to be due to chronic infection with Hp. As data poured out of laboratories and clinics, a unifying hypothesis gradually emerged. This linked a wide spectrum of foregut disorders to the effects on the gastric mucosa, on acid secretion and on gastric endocrine function, to the inflammatory and immune response triggered by the colonisation of the stomach by Hp. These pathologies now include duodenal and gastric ulcer, low-grade MALT lymphoma, atrophic gastritis and gastric cancer. The rest, as they say, is history. The medical community has had to revise rapidly and fundamentally its thinking about the causation and its approach to the management of foregut pathology, with the very satisfying outcome in the case of peptic ulcer and MALT lymphoma, for which for the first-time cure, rather than treatment, became available.

One of the many intriguing things about biological science and medicine is that the unexpected can happen, and often does. The clinician confronted by a particular patient for the first time can never be sure what the diagnosis will turn out to be, until the clinical interaction between the doctor and the patient has taken place and until, in most instances, diagnostic tests have been performed. The basic scientist may do experiments to confirm or refute a hypothesis, but unexpected findings are always cropping up and they may, or may not, fit into the preconceived framework of ideas. The scientist may be working on problems that have been suggested by deficiencies in diagnosis, or treatment, encountered in clinical medicine and this stimulating interaction may also operate in the reverse direction, where clinical progress is based on advances in bacteriology, molecular medicine, pharmacology or genetics. It is very exciting and satisfactory when the two disciplines interact fruitfully, with resulting rapid progress in the practical politics of diagnosing and treating patients.

The discovery of Hp is a beautiful example of this fruitful interaction, with extremely rapid progress from the original observation to clinical practice. It is interesting, and perhaps ironical, to reflect that the acquisition of new knowledge did not depend on technological wizardry, or on sophisticated laboratory methodology – all that came later to flesh out the picture and to unravel the mechanisms by which Hp affects gastric function, the common denominator of all the Hp-related diseases being gastritis (or duodenitis) and the host’s inflammatory and immune responses to the invading bacterium.

Progress in all the aspects of Hp has been explosive and few doctors, or scientists, can keep track of developments in the field. The editors of this volume have assembled an international cast of authorities who have written critical and up-to-date reviews of the basic pathophysiology, clinical pharmacology and therapeutics of Hp infection. This book should serve not only as a reference volume, but including, as it does, extensive accounts of the various aspects of Hp infection, backed in each chapter by extensive bibliographies, it
will be useful to the practising scientist or clinician working in this area; it will also help those wishing to update their awareness of the current state of knowledge concerning Hp. Thirteen of the 21 chapters deal with therapeutics, emphasizing the clinical aspects of treatment and providing guidelines regarding the appropriate use of antibiotics, management strategies in the event of therapeutic failure and the like. This is particularly relevant in the presence of considerable residual uncertainty (especially in primary care) regarding the indications for the eradication of Hp, the most efficacious and cost-effective drug regimens and the rising prevalence of antibiotic-resistant strains of Hp.

Although the prevalence of Hp infection is now apparently rapidly falling in the industrialized nations, there remains an enormous reservoir of Hp colonized persons in the emergent countries. This, as well as the still unsolved problems of the prevention of distal gastric cancer and the possible negative link between Hp and carcinoma of the oesophago-gastric junction, provides further justification for this book.

J.J. Misiewicz, MB, BSc, FRCP

References


Honorary Joint Director, Department of Gastroenterology and Nutrition
Central Middlesex Hospital, London, UK
Preface

There are few areas in medical science where the information explosion exceeds the capacity for a busy clinician to keep up to date. One such area is Helicobacter pylori.

The rediscovery of this gram-negative spiral organism by the young investigator Dr. Barry Marshall and his mentor Dr. Robin Warren in Western Australia has revolutionized the pathophysiological and clinical approach to diseases of the foregut, especially gastric and duodenal ulcer. Only 16 years ago the presence of H. pylori was unsuspected, but now it is known to be probably the commonest human infection. H. pylori is undoubtedly pathogenic. It causes an acute illness in around half of the patients infected and is followed by chronic inflammation that in many cases leads to organ failure. In some developed countries this bacterium is actually responsible for more deaths than all other infectious diseases combined.

Since the first paper identifying H. pylori was published in 1983, great progress has occurred concerning H. pylori and its causal relationship to gastritis, duodenal ulcer, gastric ulcer and gastric cancer. In such a fast moving field, a lot of new information is continuously reported at medical meetings, often published only in abstract form, without further appearing in peer-reviewed journals. Even gastroenterologists, unless themselves actively involved in the field of H. pylori research, find it difficult to keep abreast of the field. One is therefore justified in making a critical overview of the available information, often difficult to collect from scattered sources, in an attempt to provide a glimpse of what may lie ahead. Although several volumes and monographs have appeared on Helicobacter pylori, this book in the prestigious series
Progress in Basic and Clinical Pharmacology is the only one entirely devoted to the clinical pharmacology and therapy of the Helicobacter infection. Some effective and safe eradication regimens are today available but several new ones, often simple variations of an old scheme, are being proposed as equally effective and safe. Their effectiveness, however, will ultimately depend on the presence of antimicrobial resistance, whose prevalence rate varies amongst the different countries and often also amongst different regions of the same country. In face of this, the best course of action is to ensure that the most effective regimen is being adopted, so that the risk of emergence of resistant strains of \textit{H. pylori} is minimized. It is fairly obvious that the approach to the infected patient cannot be generalized, since many variables, including compliance, drug availability and health resources, come into play and create some difficulty for the physician who has to write a prescription for his or her patient.

This volume discusses the clinical pharmacology and therapy of the \textit{Helicobacter} infection as well as the basic pathophysiology behind it. It attempts to cover the treatment of all the \textit{H. pylori}-related digestive diseases as well as the management of treatment failure and reinfection. Additional chapters deal with vaccination, future therapeutic options and pharmacoeconomic issues. It is expected that this format will facilitate use of the book by the interested reader and provide deep insights into the wide range of therapeutic options.

As Editors, we are pleased to acknowledge the tremendous support we have received from the contributors to this volume. They come from 9 different countries and are amongst the foremost investigators in this clinical and research area. Despite their many daily commitments, they all provided us with excellent chapters, which were also updated during correction of the galley proofs, in order to give the reader the most recent information.

Editing a book is always a difficult task. Although we have tried our best to control it, we are still guilty of some repetition, almost inevitable in a multiauthored work. No one is perfect! We hope it will be looked upon as educational reinforcement rather than poor editing. It cannot be expected that this volume will solve all controversies; however, data are presented that should help any practitioner in making therapeutic decisions. We sincerely hope that new thoughts and ideas may arise from the reading of the present volume. Its publication, and the efforts of both the authors and the editors, will then have been justified.

This volume would never have gone to press without the careful and thorough assistance we received from people at the Editing and Production Department, S. Karger AG Medical and Scientific Publishers, Basel. They have shown infinite patience in their willingness to accept continually shifting deadlines. In particular, we wish to express our appreciation to Mr. Peter Roth,
who carefully followed the development of the project and to Ms. Andrea Brauns for her puzzling work of supervision and editorial production.

Spiral organisms of the gut will continue to fascinate and challenge doctors and scientists for many years to come. Meanwhile, clinicians should continue to analyze the role of *H. pylori* in disease and learn the best methods to eradicate it. We are proud to offer them this state-of-the-art publication.

August, 1999

*Carmelo Scarpignato*  
*Gabriele Bianchi Porro*