Lung Biology in Health and Disease Volume 202

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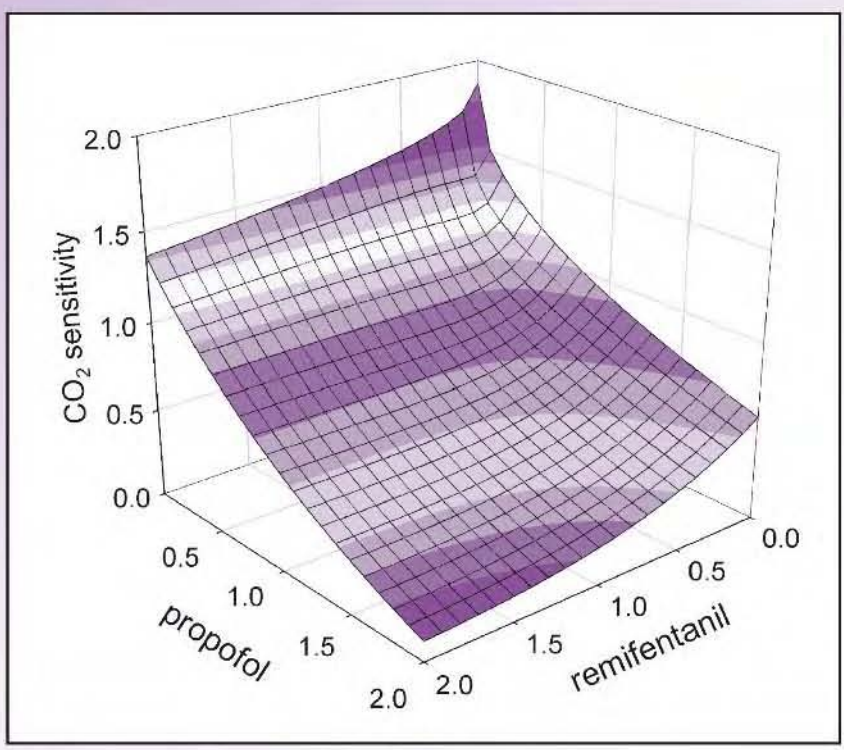
Pharmacology and Pathophysiology of the Control of Breathing



edited by

Denham S. Ward
Albert Dahan
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PHARMACOLOGY AND PATHOPHYSIOLOGY OF THE CONTROL OF BREATHING

LUNG BIOLOGY IN HEALTH AND DISEASE

Executive Editor

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PHARMACOLOGY AND PATHOPHYSIOLOGY OF THE CONTROL OF BREATHING

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Taylor & Francis
Taylor & Francis Group

Boca Raton London New York Singapore

Published in 2005 by
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8247-5890-0 (Hardcover)
International Standard Book Number-13: 978-0-8247-5890-5 (Hardcover)
Library of Congress Card Number 2005043947

Library of Congress Cataloging-in-Publication Data

Ward, Denham.
Pharmacology and pathophysiology of the control of breathing / Denham Ward.
p. cm.
Includes bibliographical references and index.
ISBN 0-8247-5890-0
1. Respiration--Regulation. 2. Lungs--Pathophysiology. 3. Pulmonary pharmacology. 4. Inhalation anesthesia. I. Title.

QP123.W37 2005
612.2--dc22 2005043947

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INTRODUCTION

"What is the use of breathing? That it is not a trifling use is clear from our inability to survive for even the shortest time after it has stopped. Hence also it is obvious that its importance is not for any particular and partial activity, but for life itself."

De Usu Respirationis
Galen (c.120–c.200)

In a second writing titled *De Causis Respirationis*, Galen went on to say: "It is impossible either to confirm the hypothesis of breathing or to put it right if it is impeded or completely stopped, without knowing its causes."

Galen's issues are, in fact, the subject of this latest addition to the series Lung Biology in Health and Disease—*Pharmacology and Pathophysiology of the Control of Breathing*. This topic has fascinated generations of fundamental and clinical researchers, and their contributions have played an essential role in our current understanding of the control of breathing in health and diseases. And today the names of many of these scientific giants grace the virtual walls of the Biomedicine Hall of Fame!

A turning point in the evolution of this work was the presentation of the Silliman Lectures given in 1916 by J.S. Haldane at Yale University. That was followed in 1921 by the publication of *Respiration* by J.S. Haldane and J.G. Priestley. In the preface to this monumental book, the authors acknowledged that "many gaps remain to be filled" but "the observations and experiments required [to fill them] are not yet available."

Today, almost a century later, many of the gaps have been filled thanks to the brilliant and dedicated researchers who have worked in this field. Nonetheless, the road to understanding the control of breathing has

been long and tortuous. First, researchers observed changes in breathing patterns that occur with environmental variations, especially altitude, in an effort to uncover the mechanisms of breathing control. Then, they turned attention to the impact of pathology on this process, and breathing disruptions caused by disease became a fertile topic of investigation.

In many ways, the 15 volumes on (or related to) control of breathing that we have published illustrate the purpose of this series when it was conceived more than three decades ago — namely, to report about and stimulate areas of biology and medicine, especially those that are so amazingly dynamic. This volume takes us to a new level by filling many of the gaps that Haldane and Priestley identified. In addition, as Thomas Hornbein says in his Foreword, "Within this volume are many enticing next steps."

The series of monographs *Lung Biology in Health and Disease* is most pleased to present this volume to its readership and I, personally, owe a great debt of gratitude to the editors, Drs. Denham S. Ward, Albert Dahan, and Luc Teppema, and the many authors for the privilege of introducing this important new contribution.

Claude Lenfant, MD
Gaithersburg, Maryland

PREFACE

We would be seriously remiss if we did not first acknowledge the work of the "fourth editor" of this volume, Debra L. Lipscomb. Without her careful scrutiny of every chapter and her abilities to pick out problems in meaning, grammar, spelling and references, the quality of this volume would have been severely compromised.

Previous volumes in this series have dealt with the regulation of breathing and it was the volume edited by Dr. Thomas Hornbein in 1981 that has served as an essential reference for us during our careers. We are particularly gratified that he has provided a Foreword to this volume. Subsequent volumes in this series dealing with the control of breathing, as well as the two volumes in the American Physiological Society's *Handbook of Physiology* have provided up-to-date summaries of the field in the face of a rapid increase in knowledge.

Pharmacology has long played an important role in the control of breathing, both in providing tools for physiological experiments and in understanding the ventilatory effects of pharmacological agents.

The increase in knowledge in both physiology and pharmacology has greatly extended our knowledge of the cellular and subcellular elements involved in controlling ventilation. Drug effects on control of breathing were covered as a single chapter in both Hornbein's original volume as well as in the *Handbook of Physiology*. However, the increase in our understanding of the mechanisms of action of pharmacological agents on the control of breathing now warrants a separate volume.

We have attempted to organize this knowledge by first reviewing the relevant physiology from a perspective of the substrate for pharmacological action and also by reviewing pharmacology principles as they can be applied to the control of breathing. We then have selected topics

of pathophysiology and pharmacology that are relevant to clinical practice. It is hoped that this organization, rather than organizing by drug, will provide a more useful reference for both clinicians and research scientists.

There are many clinical problems both in respiratory side effects of drugs and in finding drugs that will treat abnormalities in the control of breathing that remain to be solved. The increased understanding of the specific ion channels, receptors and neurotransmitters involved in respiratory control provides important information for pharmacological research. We hope this volume will set the stage for future research and provide as much motivation for beginning reseachers as Dr. Hornbein's volume did for us.

FOREWORD

When I was young I fell in love with the carotid body. Though I did not know it at the time, this infatuation was kindled when my prepubertal proclivity for climbing things—trees and houses—bumped into a teenage discovery: mountains were better. With medical school my addiction to the reading of mountaineering literature was supplanted by exploration of the literature about human adaptation to high altitude. One paper, in particular, became seminal. I found in a report by Hugo Chiodi, a Peruvian clinician-investigator, that when permanent residents of high altitude were compared to lowlanders acclimatized for a time to the same altitude, the highlanders appeared to exhibit less ventilation (higher alveolar P_{CO_2}) and greater polycythemia than the lowlanders [1]. Was there a connection, I wondered, between the two? Did the hypoventilation provoke the greater polycythemia? Or might it be the other way around, that polycythemia somehow enables less ventilation? Or might both possibilities coexist in a kind of positive feedback system?

During my final year in medical school, I seized upon a six-week elective period to embark upon my first research project, to study the effect of polycythemia on breathing. With the oversight of Albert Roos, who would become the mentor for my subsequent research training, I transfused myself with five units of blood to elevate my hematocrit from 45% to 60%. Pedaling away on a cycle ergometer while breathing oxygen mixtures to simulate different altitudes, Dr. Roos and I compared my breathing at high hematocrit with that at normal hematocrit. Not surprisingly, ventilation was less at the higher hematocrit. I cannot say it was *significantly* less, for this paper, 'Effect of Polycythemia on Respiration' was published in spite of being performed on only one subject (other volunteers were hard to find) and hence had no statistical analysis [2].

Next came the question, how does polycythemia result in less exercise hyperpnea? Enter the carotid body and the beginnings of an affair with chemoreception and the chemical control of breathing that directed my scientific exploration for the next quarter century.

At the time I climbed Mount Everest in 1963 [3], I never imagined the numbers that would be thronging to its top four decades later. Nor did I, the first time I hung the Nerve of Hering across a pair of platinum electrodes and listened to the crackling crescendo of neuronal traffic as the animal's P_{O_2} was lowered, anticipate the current profundity of inquiry into the ventilatory control system. The pharmacology of ventilatory control comprised a single chapter in the original volume on regulation of breathing in this series [4], as well as its second edition [5]; that pharmacology could command an entire, rich volume of its own was unimaginable not so long ago.

This book (number 202 In Claude Lenfant's series, Lung Biology in Health and Disease), *Pharmacology and Pathophysiology of the Control of Breathing*, has been creatively conceived and gestated by Drs. Ward, Dahan, and Teppema. The book is divided into three parts: Neuropharmacology and Physiology, Pathophysiology, and Clinical Pharmacology. The first section is, for me, the dessert, even though it comes at the beginning of the meal. This section explores the functional anatomy and physiology of the ventilatory control system from the intracellular to the integrative level, including what is coming to be known about the roles of nervous system plasticity and genes. It's like the woods out back where one could go to explore, full of intrigue and an inexhaustible supply of new questions emerging from every answer.

This first section stirred past wonderings of a time when I puzzled about why inhalational anesthetics, all of which produced anesthesia, differed in the fingerprint each left on the central nervous system with regard to side effects such as breathing. For example, diethyl ether, the founding father of general anesthesia, produced little or no ventilatory depression, as measured by the alveolar or arterial P_{CO_2}, until anesthesia became quite deep. This preservation seemed to result from an increasing tachypnea sufficient to offset the progressive diminution of tidal volume. Most other anesthetics were associated with dose-related diminutions in alveolar ventilation, some much more than others. Each anesthetic seemed to have a ventilatory identity of its own with regard to such dose-related parameters as tidal volume, ventilatory drive (V_t/T_i), relative timing of inspiration and expiration, frequency, and even the nature of inspiratory and expiratory pauses.

How do we explain such differences? Do different drugs act upon different cells, or different receptors, or in different ways to account for their unique signatures? Could understanding where and how they work provide clues about how the various components of the ventilatory control

system are put together and how the separate parts communicate with each other under physiological as well as pharmacological circumstances?

My wonderings never became more than that. But one need only reflect on the potency of the tools currently available to our imaginations to realize there is world of understanding out there waiting to be explored. Within this volume are many enticing next steps.

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