



The YEAR BOOK of

# Drug Therapy

1980

Editor

**LEO E. HOLLISTER, M.D.**

*Professor of Medicine, Psychiatry and Pharmacology,  
Stanford University School of Medicine; Research  
Psychopharmacologist, Veterans Administration  
Hospital, Palo Alto, California*

Associate Editors

**DAVID G. SHAND, Ph.D., M.B., B.S.**

*Professor of Medicine and Pharmacology, Chief,  
Division of Clinical Pharmacology, Duke  
University Medical Center*

**ROBERT L. CAPIZZI, M.D.**

*Co-director, Division of Hematology-Oncology,  
University of North Carolina School of Medicine*

**YEAR BOOK MEDICAL PUBLISHERS, INC.**

CHICAGO • LONDON

Copyright © May, 1980 by YEAR BOOK MEDICAL PUBLISHERS, INC.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Printed in U.S.A.

Library of Congress Catalog Card Number: CD38-23

International Standard Book Number: 0-8151-4618-3



**1980**  
YEAR BOOK OF

**DRUG  
THERAPY**

## THE 1980 YEAR BOOKS

The YEAR BOOK series provides in condensed form the essence of the best of the recent international medical literature. The material is selected by distinguished editors who critically review more than 500,000 journal articles each year.

**Anesthesia:** *Drs. Eckenhoff, Bart, Brunner, Holley and Linde.*

**Cancer:** *Drs. Clark, Cumley and Hickey.*

**Cardiology:** *Drs. Harvey, Kirkendall, Kirklin, Nadas, Sonnenblick and Resnekov.*

**Dentistry:** *Drs. Hale, Hazen, Moyers, Redig, Robinson and Silverman.*

**Dermatology:** *Dr. Dobson.*

**Diagnostic Radiology:** *Drs. Whitehouse, Bookstein, Gabrielsen, Holt, Martel, Silver and Thornbury.*

**Drug Therapy:** *Drs. Hollister, Capizzi and Shand.*

**Endocrinology:** *Drs. Schwartz and Ryan.*

**Family Practice:** *Dr. Rakel.*

**Medicine:** *Drs. Rogers, Des Prez, Cline, Braunwald, Greenberger, Bondy and Epstein.*

**Neurology and Neurosurgery:** *Drs. De Jong and Sugar.*

**Nuclear Medicine:** *Dr. Quinn.*

**Obstetrics and Gynecology:** *Drs. Pitkin and Zlatnik.*

**Ophthalmology:** *Dr. Hughes.*

**Orthopedic Surgery:** *Dr. Coventry.*

**Otolaryngology:** *Drs. Strong and Paparella.*

**Pathology and Clinical Pathology:** *Drs. Carone and Conn.*

**Pediatrics:** *Drs. Oski and Stockman.*

**Plastic and Reconstructive Surgery:** *Drs. McCoy, Brauer, Dingman, Hanna, Haynes and Hoehn.*

**Psychiatry and Applied Mental Health:** *Drs. Romano, Freedman, Friedhoff, Kolb, Lourie and Nemiah.*

**Sports Medicine:** *Drs. Krakauer and Marshall, Col. Anderson and Mr. George.*

**Surgery:** *Drs. Schwartz, Najarian, Peacock, Shires, Silen and Spencer.*

**Urology:** *Drs. Gillenwater and Howards.*

# Introduction

The 1980 YEAR BOOK OF DRUG THERAPY is somewhat different from those of preceding years. A new chapter called "Pain" has been added, following a suggestion submitted by a reader. The self-assessment questions have been omitted. Although the vogue for such questions persists, the editors did not feel that they are particularly appropriate to this volume. We like to think that each YEAR BOOK will be considered as a reference source, as an entry to the recent literature on a particular subject.

For this year's review article, we chose the subject of  $\beta$ -adrenergic blocking drugs. Not only are their indications being expanded, but the number of such agents is increasing.

We hope these volumes will be useful to the practicing physician as well as to clinical pharmacologists. We will welcome your suggestions for improvement, which you can be sure will be carefully considered.

LEO E. HOLLISTER, M.D.

ROBERT L. CAPIZZI, M.D.

DAVID G. SHAND, M.B., PH.D.

# Table of Contents

The material covered in this volume represents literature reviewed up to September, 1979.

INTRODUCTION . . . . .	5
CURRENT STATUS OF $\beta$ -ADRENERGIC BLOCKING DRUGS IN THE UNITED STATES by ALAN S. NIES, M.D. AND JOHN G. GERBER, M.D. . . . .	9
GENERAL INFORMATION . . . . .	27
DRUG ACTION . . . . .	41
ADVERSE DRUG EFFECTS . . . . .	65
ALLERGIC DISORDERS . . . . .	101
BLOOD DISEASES . . . . .	107
CARDIOVASCULAR DISEASES . . . . .	115
ENDOCRINE AND METABOLIC DISORDERS . . . . .	193
EAR, EYE AND FACIAL NERVE DISORDERS . . . . .	215
GASTROINTESTINAL DISEASES . . . . .	223
GENITOURINARY TRACT DISORDERS . . . . .	245
INFECTIOUS DISEASES . . . . .	261
NEOPLASTIC DISEASES . . . . .	283
NEUROLOGIC DISEASES . . . . .	303
OBSTETRIC AND GYNECOLOGIC DISORDERS . . . . .	329
PAIN . . . . .	341
PSYCHIATRIC DISEASES . . . . .	357
RESPIRATORY TRACT DISORDERS . . . . .	377
RHEUMATIC AND ARTHRITIC DISEASES . . . . .	397
SKIN DISEASES . . . . .	407
SURGERY . . . . .	419



**1980**  
YEAR BOOK OF

**DRUG  
THERAPY**



## THE 1980 YEAR BOOKS

The YEAR BOOK series provides in condensed form the essence of the best of the recent international medical literature. The material is selected by distinguished editors who critically review more than 500,000 journal articles each year.

**Anesthesia:** *Drs. Eckenhoff, Bart, Brunner, Holley and Linde.*

**Cancer:** *Drs. Clark, Cumley and Hickey.*

**Cardiology:** *Drs. Harvey, Kirkendall, Kirklin, Nadas, Sonnenblick and Resnekov.*

**Dentistry:** *Drs. Hale, Hazen, Moyers, Redig, Robinson and Silverman.*

**Dermatology:** *Dr. Dobson.*

**Diagnostic Radiology:** *Drs. Whitehouse, Bookstein, Gabrielsen, Holt, Martel, Silver and Thornbury.*

**Drug Therapy:** *Drs. Hollister, Capizzi and Shand.*

**Endocrinology:** *Drs. Schwartz and Ryan.*

**Family Practice:** *Dr. Rakel.*

**Medicine:** *Drs. Rogers, Des Prez, Cline, Braunwald, Greenberger, Bondy and Epstein.*

**Neurology and Neurosurgery:** *Drs. De Jong and Sugar.*

**Nuclear Medicine:** *Dr. Quinn.*

**Obstetrics and Gynecology:** *Drs. Pitkin and Zlatnik.*

**Ophthalmology:** *Dr. Hughes.*

**Orthopedic Surgery:** *Dr. Coventry.*

**Otolaryngology:** *Drs. Strong and Paparella.*

**Pathology and Clinical Pathology:** *Drs. Carone and Conn.*

**Pediatrics:** *Drs. Oski and Stockman.*

**Plastic and Reconstructive Surgery:** *Drs. McCoy, Brauer, Dingman, Hanna, Haynes and Hoehn.*

**Psychiatry and Applied Mental Health:** *Drs. Romano, Freedman, Friedhoff, Kolb, Lourie and Nemiah.*

**Sports Medicine:** *Drs. Krakauer and Marshall, Col. Anderson and Mr. George.*

**Surgery:** *Drs. Schwartz, Najarian, Peacock, Shires, Silen and Spencer.*

**Urology:** *Drs. Gillenwater and Howards.*

The YEAR BOOK of

# Drug Therapy

1980

Editor

**LEO E. HOLLISTER, M.D.**

*Professor of Medicine, Psychiatry and Pharmacology,  
Stanford University School of Medicine; Research  
Psychopharmacologist, Veterans Administration  
Hospital, Palo Alto, California*

Associate Editors

**DAVID G. SHAND, Ph.D., M.B., B.S.**

*Professor of Medicine and Pharmacology, Chief,  
Division of Clinical Pharmacology, Duke  
University Medical Center*

**ROBERT L. CAPIZZI, M.D.**

*Co-director, Division of Hematology-Oncology,  
University of North Carolina School of Medicine*

**YEAR BOOK MEDICAL PUBLISHERS, INC.**

CHICAGO • LONDON

Copyright © May, 1980 by YEAR BOOK MEDICAL PUBLISHERS, INC.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Printed in U.S.A.

Library of Congress Catalog Card Number: CD38-23

International Standard Book Number: 0-8151-4618-3

# Introduction

The 1980 YEAR BOOK OF DRUG THERAPY is somewhat different from those of preceding years. A new chapter called "Pain" has been added, following a suggestion submitted by a reader. The self-assessment questions have been omitted. Although the vogue for such questions persists, the editors did not feel that they are particularly appropriate to this volume. We like to think that each YEAR BOOK will be considered as a reference source, as an entry to the recent literature on a particular subject.

For this year's review article, we chose the subject of  $\beta$ -adrenergic blocking drugs. Not only are their indications being expanded, but the number of such agents is increasing.

We hope these volumes will be useful to the practicing physician as well as to clinical pharmacologists. We will welcome your suggestions for improvement, which you can be sure will be carefully considered.

LEO E. HOLLISTER, M.D.

ROBERT L. CAPIZZI, M.D.

DAVID G. SHAND, M.B., PH.D.



# Table of Contents

The material covered in this volume represents literature reviewed up to September, 1979.

INTRODUCTION . . . . .	5
CURRENT STATUS OF $\beta$ -ADRENERGIC BLOCKING DRUGS IN THE UNITED STATES by ALAN S. NIES, M.D. AND JOHN G. GERBER, M.D. . . . .	9
GENERAL INFORMATION . . . . .	27
DRUG ACTION . . . . .	41
ADVERSE DRUG EFFECTS . . . . .	65
ALLERGIC DISORDERS . . . . .	101
BLOOD DISEASES . . . . .	107
CARDIOVASCULAR DISEASES . . . . .	115
ENDOCRINE AND METABOLIC DISORDERS . . . . .	193
EAR, EYE AND FACIAL NERVE DISORDERS . . . . .	215
GASTROINTESTINAL DISEASES . . . . .	223
GENITOURINARY TRACT DISORDERS . . . . .	245
INFECTIOUS DISEASES . . . . .	261
NEOPLASTIC DISEASES . . . . .	283
NEUROLOGIC DISEASES . . . . .	303
OBSTETRIC AND GYNECOLOGIC DISORDERS . . . . .	329
PAIN . . . . .	341
PSYCHIATRIC DISEASES . . . . .	357
RESPIRATORY TRACT DISORDERS . . . . .	377
RHEUMATIC AND ARTHRITIC DISEASES . . . . .	397
SKIN DISEASES . . . . .	407
SURGERY . . . . .	419



## CURRENT STATUS OF $\beta$ -ADRENERGIC BLOCKING DRUGS IN THE UNITED STATES

ALAN S. NIES, M.D.

JOHN G. GERBER, M.D.

*Division of Clinical Pharmacology and Toxicology,  
University of Colorado Health Sciences Center, Denver*

### Introduction

The popularity and utility of the  $\beta$ -adrenergic blocking drugs in the past 2 decades have exceeded the expectations and imagination of all who have been involved with their development. The  $\beta$ -adrenergic blocking drugs were initially conceived as a means to treat angina pectoris. Since their introduction for this purpose, much has been learned about their pharmacology and the pharmacology of the  $\beta$ -adrenergic receptor. It has become apparent that there are widely variable responses to many of the  $\beta$ -adrenergic blockers. This variability is due, in part, to the interindividual variation in the pharmacokinetics of these drugs, particularly those that are metabolized by the liver. However, not all of the variability in dose requirements can be explained by differences in blood concentrations of drug achieved by a given dose. There is also considerable interindividual variation in the degree to which symptoms respond to  $\beta$ -adrenergic blockade. It must be kept in mind that the  $\beta$ -adrenergic blocking drugs are used to treat diseases that have unknown or multiple etiologies. Thus, it is not surprising that different doses of the drug are required for adequate therapy of such variable conditions as angina pectoris, cardiac arrhythmias, hypertension and migraine headaches.

In using the  $\beta$ -adrenergic blocking drugs, clinicians have become familiar with the concept of a risk-benefit ratio. There clearly are patients who are at risk of serious adverse effects with the  $\beta$ -adrenergic blocking drugs. However, if these patients are identified and excluded from receiving these drugs, then the drugs are generally well tolerated and benefit accrues. The risk-benefit analysis is also a consideration when the drugs are stopped. There may be a greater risk to the patient in stopping the drugs abruptly rather than in continuing the drugs or tapering them. Finally, it is apparent that there is intense competition among pharmaceutical companies for the marketplace. To this end, many  $\beta$ -adrenergic blocking drugs are being developed, and, although only two are now approved by the Food and Drug Administration in the United States, many more are available worldwide. Whether each drug has any unique advantage over the others has not been critically tested in most circumstances.



## Pharmacology

The concept that catecholamines act at receptor sites was suggested by the experiments of Sir Henry Dale, who demonstrated that the pressor effect of epinephrine could be inhibited by treatment with ergot alkaloids.<sup>1</sup> The possibility of more than one type of adrenergic receptor, however, was advanced by Ahlquist,<sup>2</sup> who observed the responses to several different sympathomimetic amines and decided that there must be at least two different adrenergic receptors, which he called alpha and beta. Since that time, Lands et al.<sup>3</sup> have postulated that  $\beta$ -adrenergic receptors can be subclassified. The responses of the adrenergic nervous system that are mediated through these various receptors are listed in Table 1. By and large, the  $\alpha$ -adrenergic receptor mediates constriction of blood vessels and contraction of smooth muscle, whereas the  $\beta$ -adrenergic receptor mediates cardiac inotropic and chronotropic effects, bronchodilation and vasodilation. Metabolic effects of the sympathetic nervous system appear to be mediated by both  $\alpha$ - and  $\beta$ -adrenergic receptors. The subclassification of  $\beta$ -adrenergic receptors into  $\beta_1$  and  $\beta_2$  is such that  $\beta_1$  indicates those receptors in the heart and  $\beta_2$ , essentially all other peripheral  $\beta$ -adrenergic receptors. This classification of adrenergic receptors not only increased the understanding of catecholamine action, but also allowed innovative scientists to devise drugs that might stimulate (agonists) or block (antagonists) one or another of these receptors. It was not until the development of the  $\beta$ -adrenergic blocking drugs<sup>4</sup> that the concept of a  $\beta$ -adrenergic receptor was actually established as fact. In the past several years, drugs have been discovered that are relatively specific for blocking the  $\beta_1$ -adrenergic receptor. However, there remain some  $\beta$ -adrenergic responses that do not appear to fall easily into this subclassification and may be the result of a mixed receptor population or even a third  $\beta$ -adrenergic receptor.

All of the  $\beta$ -adrenergic blocking drugs competitively antagonize the

TABLE 1.—CLASSIFICATION OF THE MAJOR  $\alpha$ - AND  $\beta$ -ADRENERGIC RESPONSES

ORGAN	EFFECT	ALPHA	BETA <sub>1</sub>	BETA <sub>2</sub>
Blood Vessels	Constrict arterioles and venules	+	0	0
	Dilate arterioles, especially in skeletal muscle	0	0	+
Heart	Increase rate of sinoatrial node discharge	0	+	0
	Increase contractility	0	+	0
	Increase conduction velocity in AV node	0	+	0
	Increase ventricular automaticity	0	+	0
Lungs	Dilate bronchial musculature	0	0	+
Gastrointestinal Tract	Inhibit peristalsis	+		+
Metabolic effects	Stimulate lipolysis	0		+
	Block insulin release	+		0
	Stimulate insulin release	0		+
	Stimulate formation of cyclic 3',5'-AMP	0		+
	Increase fasting blood sugar	±		+
	Stimulate renin release	0		+