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.

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This book is dedicated to my wife, Stephany, for her love, patience and strength, and to our new daughter, Jennifer.

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During the past decade, major advances have been made in our understanding of the molecular structure and function of the \( \alpha \)-adrenoceptors.
Indeed, many new subtypes of the \( \alpha \)-adrenoceptor have been identified recently through biochemical and pharmacological techniques, and several of these receptors have been cloned and expressed in appropriate vector systems. At present, at least seven subtypes of the \( \alpha \)-adrenoceptor have been
identified, and the number may increase further. A much more detailed and complete understanding of the molecular structure and biochemical functions of the -adrenoceptor subtypes is beginning to be appreciated. This unprecedented 'explosion' of new information relating to the -adrenoceptors has contributed to this most exciting era in the study of receptors and receptor theory.

At the same time, important advances have been made regarding the biochemical events involved in the signal transduction processes that are activated by the -adrenoceptors, and which ultimately result in the end-organ response. These include the coupling of the various -adrenoceptor subtypes to intracellular second-messenger systems through a family of guanine-nucleotide-regulatory proteins that have been recently discovered and characterized. The mechanisms by which distinct -adrenoceptor subtypes recognize specific, and oftentimes different, guanine-nucleotide-regulatory proteins are now beginning to be understood.

Equally important has been the discovery of new functions mediated by -adrenoceptors which has continued to advance at the cellular, tissue and organ level, as well as the roles that these receptors play in physiological and pathophysiologic processes in animals and in humans. Indeed, the exciting advances made in our understanding of -adrenoceptor structure and function obtained from molecular biology studies have begun to result in practical applications regarding the roles that these receptors may play in homeostasis and in pathological states. As a direct result, the -adrenoceptor subtypes have become increasingly important drug targets in the etiology, pathology and treatment of human disease.

With the recent identification of additional subtypes of the r and 2-adrenoceptors, structure-activity relationships for activation and inhibition of -adrenoceptors have expanded dramatically. Many new, potent and highly selective -adrenoceptor agonists and antagonists have been synthesized by medicinal chemists and serve as important pharmacological tools to investigate the existing -adrenoceptor subtypes, and to aid in the identification of additional, but presently uncharacterized, -adrenoceptor subtypes. Indeed, several new compounds arising from recent structure-activity relationships are finding their way into clinical trials for the treatment of disease.

Although there have been many books written about -adrenoceptors, what distinguishes this book from others is the broadness of its scope. We have compiled and reviewed the most recent and important advances made in relation to the -adrenoceptors, which span from the intracellular level of
the nucleus, including the messenger RNA that encodes for these receptors, through the biochemical processes activated or inhibited by these receptors, up to and including the functional effects they mediate in intact organs, animals and ultimately in humans, both in normal and in disease states. To my knowledge, a comprehensive review dealing with -adrenoceptors from the standpoint of molecular biology, biochemistry and pharmacology has not been attempted previously, and I believe that it is the integration of these disciplines, and the exciting findings that have been generated very recently from them, that makes this volume entitled -Adrenoceptors: Molecular Biology, Biochemistry and Pharmacology most unique.

Molecular biologists, who work at the level of the cell nucleus, and pharmacologists, many of whom work at the intact organ or animal level, can no longer function independently of each other. This has become most apparent in the last two years where these two vastly different disciplines have by necessity grown closer, in large part because of the new subtypes of -adrenoceptors that have been identified through the techniques of molecular biology. As new -adrenoceptor subtypes are identified and/or cloned, pharmacological approaches are used to establish the functions of these new receptors, with the obvious intent to determine whether they are of physiological or pathophysiologic relevance, and whether they may represent appropriate therapeutic targets for which medicinal chemists must design new and selective agonists and antagonists for the treatment of disease.

For these reasons, we have reviewed the most recent information relating to the molecular structure and function of the -adrenoceptor subtypes, and have at the same time attempted to integrate this information with the intracellular biochemical processes that these receptors activate or inhibit to produce the observed organ response, which is further evaluated in more complex systems, including animals and humans. Our attempt to relate these varied aspects of research on -adrenoceptors, originating from the nucleus and extending through to the intact human, we feel is a worthwhile objective, and it is our belief that this compilation of information will be of broad interest to many disciplines, but most especially to molecular and cellular biologists, biochemists, physiologists, medicinal chemists and pharmacologists who study -adrenoceptors.

Robert R. Ruffolo, Jr.