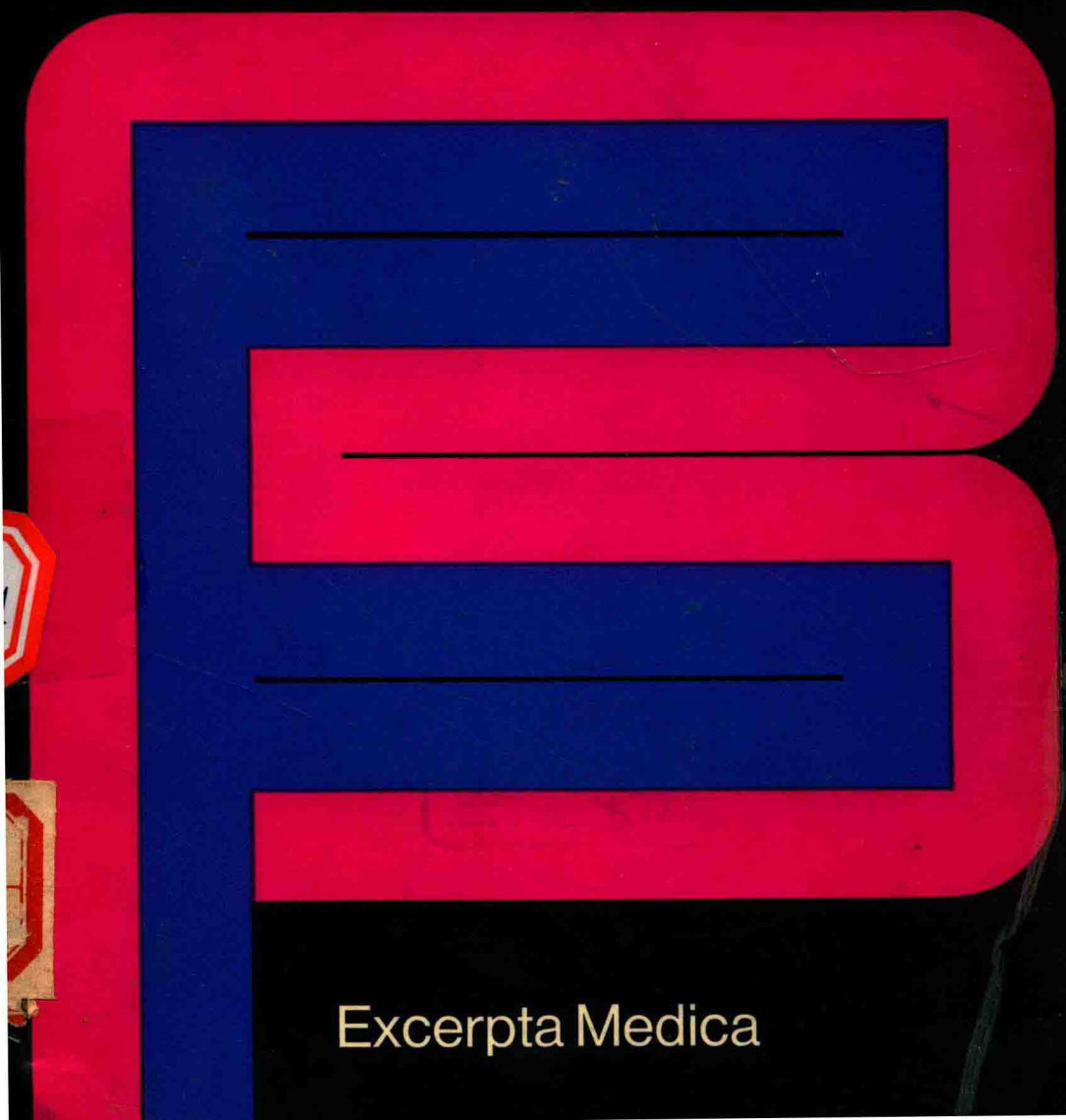
Circulatory Effects and Clinical Uses of Beta-Adrenergic Blocking Drugs

Editor: Donald C. Harrison



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Editor

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Dedication

This book is dedicated to the students and fellows who have trained with the author in the Division of Cardiology at Stanford University School of Medicine during the past eight years, in appreciation for their contributions to his understanding of beta-adrenergic blockade.

Acknowledgments

Many individuals have contributed to my understanding of beta-adrenergic blocking drugs and are indirectly responsible for this book's being written. During the past decade, in addition to those authors contributing directly to the book, Drs. Ralph E. Gianelly, John R. Griffin, Walter L. Henry, Thomas J. Fiene, Bernard E. Treister, Richard L. Popp, and John S. Schroeder have collaborated with me in studies designed to elucidate the effects of beta-adrenergic blockade on the cardiovascular system. Their overall contributions have been invaluable.

The physicians who practice at Stanford University Hospital and those in Northern California who refer patients to the Cardiology Division at Stanford have cooperated fully in allowing their patients to participate in the many clinical studies which have been carried out.

Thanks are also in order for the secretarial staff of the Cardiology Division at Stanford University School of Medicine, who have each contributed their time to type the many drafts of the chapters in this book. Mrs. Dorothy McCain has worked closely with me as an outstanding editorial assistant. Without her major collaboration, I would not have managed to finish this book for publication.

A word of gratitude is due to my wife and children, who have patiently allowed me to work the necessary weekends and nights to finish this book, when they had planned as a family to enjoy the wonders of the outdoors of California.

Donald C. Harrison

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Preface

This book deals with the circulatory effects of beta-adrenergic blockade and the clinical use of drugs with beta-adrenergic actions in the treatment of a variety of diseases in man. Proper utilization of new pharmacologic agents in cardiology requires an understanding of the biochemical, physiologic and hemodynamic properties of the drug; hence, emphasis has been given to these basic principles in each chapter of the book.

Although the concept of beta-adrenergic receptor blockade has been in existence for many years, the practical utilization of drugs with this specific pharmacologic action has occurred only in the past decade. The author has performed biochemical, physiological, and clinical studies with many of the new specific beta-adrenergic blocking drugs as they have become available. During this decade, an increased understanding of the importance of adrenergic influences on the heart and circulation in health and disease has developed. New concepts were evolved and, with the use of beta-adrenergic blocking agents, new hypotheses can readily be tested. A review of all of these basic and important studies is beyond the scope of this book. However, those concepts which this author has found to be important for clinical use of specific beta-adrenergic blocking drugs are presented.

In Chapter One, a review of the relevant historical studies necessary to understand adrenergic receptor blockade is presented. Emphasis has been placed on structure-activity relationships and mathematical concepts whereby receptor theory may be understood. General hemodynamic and metabolic consequences of the administration of beta-adrenergic blocking agents are also described. Specific physiologic effects of beta-adrenergic blockade on isolated cardiac muscle, in isolated perfused organs, and in intact animals, are presented in Chapter Two. The influence of the autonomic nervous system on coronary blood flow and the changes produced by beta-adrenergic blockade are summarized.

In order to understand the actions of beta-adrenergic blocking drugs on the heart and peripheral vasculature in disease, the circulatory actions of specific drugs in normal man are outlined in Chapter Three. One of the early clinical applications for beta-adrenergic blocking drugs was in the treatment and prevention of cardiac arrhythmias. Two specific properties of these agents relate to this antiarrhythmic action, beta-adrenergic blockade, and 'membrane', or local anesthetic effects, which have been summarized in Chapter Four, together with the results of relevant clinical studies.

In the management of patients with angina pectoris, beta-adrenergic blocking drugs provide a new and important physiologically sound mechanism for treatment. While a precise definition of their many interactions in patients with coronary heart disease is not yet available, much has been learned about the relationship of the many interrelated factors controlling myocardial oxygen demands by employing beta-adrenergic blocking drugs in animal studies and in man. The actions of a host of beta-adrenergic blocking drugs in angina pectoris and myocardial infarction are described in Chapters Five and Six.

Hypertrophic subaortic stenosis is being recognized clinically with increased frequency. Much of our present understanding of this disease has developed through the use of beta-adrenergic blocking drugs, as can be appreciated by reviewing Chapter Seven. Beta-adrenergic blocking agents have been administered to patients with many other diseases, such as pheochromocytoma, hypertension, tetralogy of Fallot, thyrotoxicosis, shock, Parkinsonism, and hyperkinetic states, and the rationale and results of clinical studies are summarized in Chapter Eight.

As with all potent drugs, side effects do occur following the administration of beta-adrenergic blocking agents. These are largely predictable, based on an understanding of their physiologic actions, and certain contraindications to their use have been established. These are outlined in Chapter Nine.

When this book was conceived in the author's mind, it was planned to utilize primarily studies which had been performed in a single laboratory. As the scope of the book was expanded, the results of many other studies in laboratories throughout the world were included. Attempts have been made to document with references the important and relevant contributions of others. Any oversight or any misinterpretation of the results of other studies is the responsibility of the author, and is unintentional. In the final analysis, emphasis has still been given to studies from my own laboratory group. It is hoped that this volume provides the basis for a better understanding of the pharmacology of beta-adrenergic blockade and a reasonable guide to the use of these drugs in human disease.

Donald C. Harrison

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I Clinical pharmacology and history of beta-adrenergic blockade*

DONALD C. HARRISON

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INTRODUCTION

Although the concept of the release of a neurohumoral substance from the sympathetic nerve as the mechanism for initiating increased sympathetic activity has been appreciated for many years, the exact relationship of the release of the neurotransmitter, its synthesis in sympathetic nerve endings, and its action in stimulating receptor mechanisms have all been developed during the past fifty years (Dale, 1906; Ahlquist, 1948; Powell and Slater, 1958). One of the most important developments which led to a better understanding of the activity of the sympathetic nervous system was the introduction of highly specific beta-adrenergic blocking drugs (Powell and Slater, 1958; Moran and Perkins, 1958; Black and Stephenson, 1962). During the past ten years, more than 16 substances with a spectrum of beta-adrenergic blocking activities have been introduced for laboratory study (Dollery *et al.*, 1969; Fitzgerald, 1969). Many of these substances have also been studied in man as they relate to the intrinsic activity of the sympathetic nervous system (Harrison *et al.*, 1964; 1965; Epstein and Braunwald, 1966). It is the purpose of this initial chapter to present a detailed history of the concept of beta-adrenergic blockade, to describe what is known about the receptor mechanism for beta-adrenergic stimulation in the various vascular beds throughout the body and to present the basic pharmacology of the series of pharmacologic agents now available for study and clinical use in man.

HISTORY

The concept that neuromuscular cells contained both excitatory and inhibitory receptor sites and that the action of epinephrine was dependent upon the type of receptor substance present was first suggested by Langley more than 60 years ago (Langley, 1905). This concept received additional support when Dale (1906)

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published a comprehensive study on the adrenergic blocking action of ergot derivatives. Although ergot drugs completely antagonized and even reversed the excitatory action of epinephrine on the peripheral circulation, they had no effect on its inhibitory actions. Furthermore, the one excitatory action of epinephrine which was not blocked by ordinary doses of ergot was its stimulatory effect on the heart. These results suggested to Dale (1906) that the effect of epinephrine was dependent on at least two types of receptors, one of which was blocked by the administration of ergot.

Later, following more sophisticated physiologic studies of neurohumoral transmission, Cannon and Rosenbleuth (1937) postulated a dual adrenergic mediator system. The dual mediator concept, namely that there was a Sympathin I and Sympathin E, was used to attempt to explain the fact that responses to sympathetic stimuli could either be excitatory (i.e., vasoconstriction and cardiac stimulation) or inhibitory, that is, bronchial dilatation and intestinal relaxation. However, the only known adrenergic blocking drugs in the 1930's were limited in their antagonistic action and the patterns of blockade produced by them did not fit entirely the scheme of Cannon and Rosenbleuth (1937). The ergot alkaloids and, later, sympathetic blocking drugs such as phenoxybenzamine and phentolamine, antagonized the excitatory effects of adrenergic stimuli except for those in the heart and did not block the inhibitory responses on smooth muscle.

The work of Von Euler in 1946, demonstrating that norepinephrine was the primary and possibly the only neurotransmitter substance, undermined the dual transmitter concept of Cannon. Norepinephrine was demonstrated to be present in sympathetic nerve endings and was present in a higher concentration than epinephrine in all structures except the adrenal medulla. Norepinephrine was also a potent vasoconstrictor and a cardiac-stimulating substance. It was weak as an inhibitor of smooth muscle. Because of the emergence of the single transmitter concept, and the difficulty of explaining the many effects of adrenergic stimuli on the basis of two transmitters, Ahlquist (1948) proposed his concept of two receptor types to account for the diverse effects of various sympathomimetic drugs and for the restricted antagonistic action of adrenergic blocking drugs then known.

By definition, the alpha- and beta-adrenergic receptors are not part of the sympathetic nervous system. They are components of the effector system; that is, those cells such as heart and vascular smooth muscle that respond to the neurohumoral transmitter released from sympathetic nerve endings. Alpha- and beta-receptors have not been defined by biochemical techniques, nor have they been identified by more complex morphological study. Thus, the concept of beta-adrenergic receptors is a pharmacologic one, and the receptors are thought of as hypothetical parts of the effector cell that selectively receive molecules of the general structure of norepinephrine. The interaction of the receptor and the transmitter molecule can then be considered to trigger any specific response of the cell. The antagonism produced by a blocking drug is thought of as an occupation or occlusion of the receptor which prevents the initial triggering event by the neurotransmitter substance. Mathematical calculations have been developed to characterize the nature of the bindings of the receptor and the agonist or antagonist for a variety of organs with symphatetic innovation. Recently, several critical analyses of the mechanism for blockade of pharmacologic receptors have been published (Moran, 1966; Howe, 1963; Ariëns and Simonis, 1964; Furchgott, 1964).

In 1964, Furchgott elucidated a series of steps necessary to define a specific receptor. These were: 1) an agonist must act directly on the receptor, and there must be no demonstrable indirect effects; 2) an appropriate blocking agent must be available to inhibit the agonist specifically, 3) active uptake of the agonist by the receptor should be blocked, and finally; 4) paired controls should be studied to avoid mistaking the effect of a drug for an effect on the system which was mediated by normal physiological control. Thus the classification of adrenergic receptors in various vascular beds is based upon several types of evidence derived from studies of the response of effector organs to adrenergic stimuli in regard to rank order of potency of agonist and of selective antagonism of the responses. The variation in rank order of potency in a group of closely related compounds (sympathomimetic amines) on several different systems is suggestive of variation in receptors. Therefore, if there is but one type of adrenergic receptor in all tissues, there should be preferred structure for one of the series, that is, there should be a

TABLE I

Classification of responses to adrenergic stimuli

Tissue	Receptor	Response
Heart		
S-A node	Beta	Increased rate
Atria	Beta	Increase in velocity of conduction and contractility
A-V node and conducting system	Beta	Increased conduction, velocity and shortening of effective refractory period
Ventricle	Beta	Increased rate and contractility
Coronary vessels	Alpha	Constriction
Blood vessels		
Skeletal muscle	Beta	Dilatation
Skin and mucosa	Alpha	Constriction
Bronchial muscle	Beta	Relaxation
Gastrointestinal tract		
Stomach		
Mobility and tone	Beta	Decrease
Sphincter	Alpha	Contraction
Intestine		
Mobility and tone	Alpha and Beta	Decrease
Sphincters	Alpha	Contraction
Urinary bladder		
Detrusor	Beta	Relaxation
Trigone and sphincter	Alpha	Contraction
Eye		
Radial muscle iris	Alpha	Contraction (mydriasis)
Ciliary muscle	Beta	Relaxation for far vision
Skin		
Pilomotor muscles	Alpha	Contraction
Sweat glands	Alpha	Secretion

best fit or best key and the key should be the same for all systems. Deviation from this preferred structure should be accompanied by a systematic diminution of pharmacologic activity in a regular and consistent way in all tissues and systems. On the other hand, if there is more than one type of adrenergic receptor, the preferred structure of the agonist should differ from one receptor type to another, and the relationship between alterations of structure and the response of tissue should vary in some regular and systematic way. In fact, after many studies with sympathomimetic amine, no single rank order of potency of sympathomimetic amines for all tissues and all vascular beds has been found to exist.

It was on the basis of this alteration in the rank of potency that Ahlquist (1948) classified adrenergic receptors when it became untenable to accept the two-mediator concept of Cannon. Ahlquist tested the activity of six closely related sympathomimetic amines on several physiologic systems and found varied orders of potency. It was clear that one pattern demonstrated that isoproterenol was the least active in one vascular bed and most active in another. Ahlquist arbitrarily designated the responses occurring in beds in which isoproterenol was least active as alpha, and those in which it was most active as beta. Thus, cardiac excitation with an increase in heart rate and contractility was classed with the peripheral vasodilatation produced by isoproterenol. These receptor responses were called beta. Peripheral vasoconstrictor responses were classified as alpha. In Table I, a

TABLE II

Pharmacology of important beta-adrenergic blocking agents

Class*	Generic name	Trade name	Beta-blocking	Membrane activity	Intrinsic stimulating activity	Selectivity	Potency (based on standard isoproterenol blocking action)
I.	dichloroisoproterenol	DCI	+	+	3+	o	0.1
	pronethalol (nethalide)	Alderlin	+	+	2+	o	0.1
	ICI 45,763	Kö 592	+	+	2+	o	1.0
	oxprenolol	Trasicor	+	+	2+	o	2.0
	alprenolol (d, l)	Aptine	+	+	2+	o	1.0
II.	propranolol	Inderal	+	+	2+	o	1.0
	butidrine	—	+	+	o	o	0.1
III.	INPEA	—	+	o	+	o	0.04
IV.	sotalol	MJ 1999	+	o	o	o	0.1
V.	practolol	ICI 50,172	+	o	+	cardio-selective	0.5
	butoxamine		+	?	o	metabolic and peripheral	—

* Based on classification by Fitzgerald, 1969.

complete breakdown of the alpha and beta responses which have been observed in various organs throughout the body is outlined.

Classification of receptor types was also derived from studies utilizing antagonist. In fact, the validity and utility of Ahlquist's classification of adrenergic receptors was not fully apparent until the discovery of a new type of beta-adrenergic blocking drug. In the 1950's, phenoxybenzamine was the best known adrenergic blocking drug (Furchgott, 1960). This drug, however, antagonized adrenergic vasoconstriction and did not effect vasodilatation, bronchodilatation, or cardiac stimulation. In 1958, Powell and Slater of the Lilly Research Laboratories first reported their discovery of the unique blocking activity of a derivative of isoproterenol, dichloroisoproterenol. It was obvious immediately that this compound had blocking actions complimentary to those with phenoxybenzamine. Dichloroisoproterenol blocked the adrenergic stimulatory effects on the heart and the peripheral vasodilatation produced by sympathomimetic amines. It did not block adrenergic vasoconstriction (Moran and Perkins, 1958). Thus, the drug

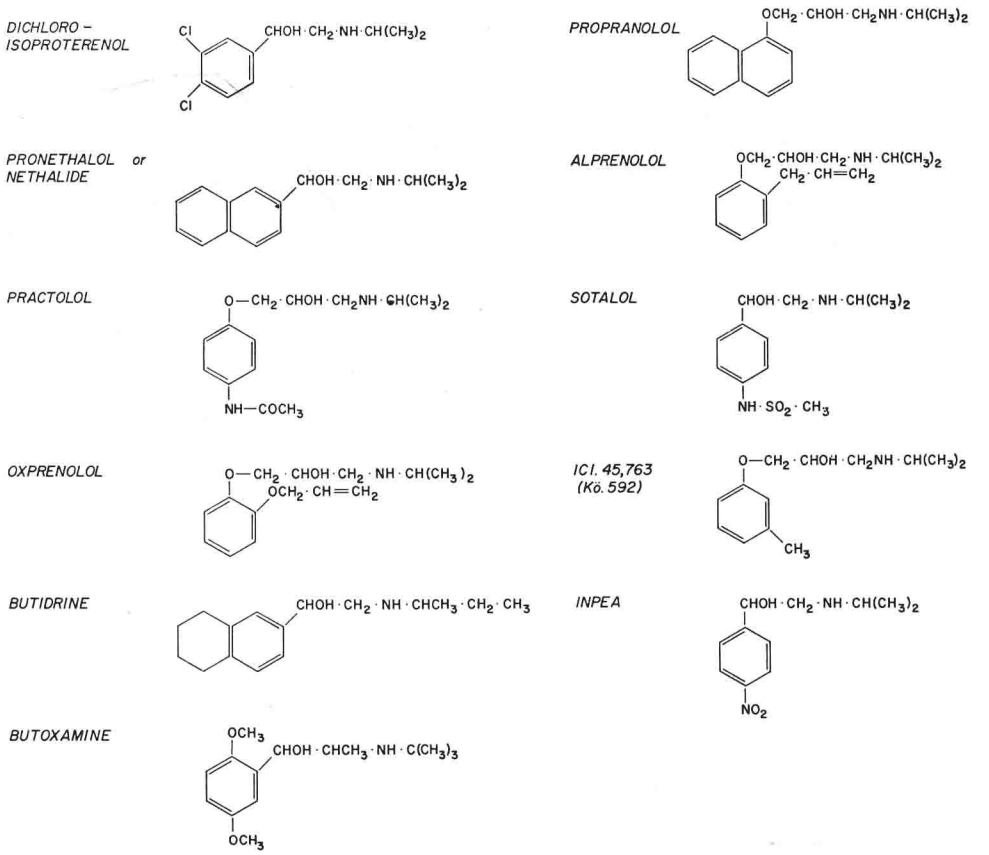

Fig. 1. Structure of beta-adrenergic drugs which have been studied most widely. (Reprinted with permission of Dollery *et al.*, 1969, and *Clinical Pharmacology and Therapeutics*)

was classified as a beta-adrenergic blocking drug, and studies with it then confirmed the Ahlquist concept of two types of adrenergic neuroreceptors. Because of its intrinsic agonist activity, dichloroisoproterenol was never used widely for the purpose of blocking beta-adrenergic receptors in man (Table II).

The synthesis of pronethalol (nethalide) provided the first beta-adrenergic receptor blocking agent that had little, if any, intrinsic alpha- or beta-sympathomimetic effects (Black and Stephenson, 1962). Although pronethalol was studied extensively, demonstration that this agent produced lymphosarcomas in mice limited its clinical use (Paget, 1963). Attempts were made to manufacture an agent without carcinogenic potential, and propranolol, a drug that was shown to have a therapeutic-toxic ratio about ten times greater than that of pronethalol, was synthesized (Black and Stephenson, 1962). Since the introduction of propranolol for widespread pharmacologic and clinical study, more than 16 other compounds with some degree of beta-adrenergic blocking activity have been synthesized (Table II; Fig. 1).

RECEPTOR ACTIVITY AND INTERACTION

All of the compounds shown in Figure 1 produce a competitive type blockade; that is, the dose response curve of the agonist is shifted progressively to the right with increasing concentrations of the antagonist (Figs. 2 and 3) but the maximal response to any agent is not altered when extremely large doses of the agonist are used. Irreversible blockade, such as that seen with the alpha-blocking agent

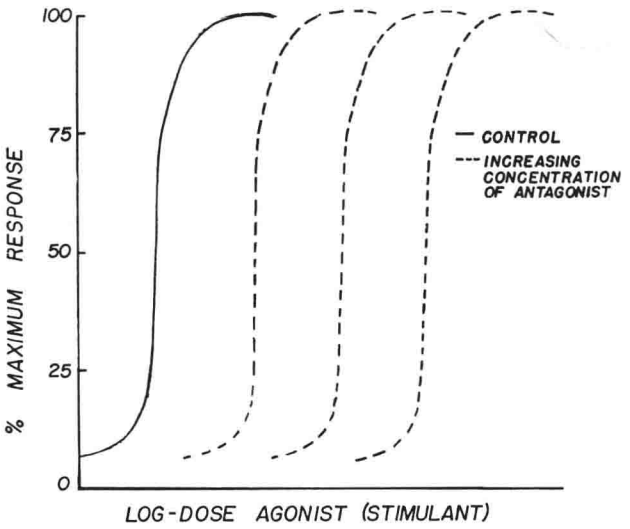

Fig. 2. The characteristics of competitive adrenergic blockade are illustrated. Curves of response are parallel but shifted to the right by the administration of a competitive beta-adrenergic blocking agent. Note that maximal response can be obtained in each instance if large doses of agonist are administered. (Reprinted with permission of Dollery *et al.*, 1969, and *Clinical Pharmacology and Therapeutics*)

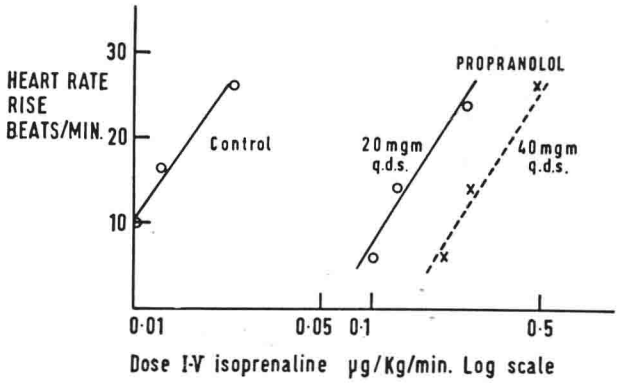

Fig. 3. The heart rate response of a normal subject to graded doses of isoproterenol before and after the administration of two doses of propranolol. Note that competitive antagonism is demonstrated by a shift of the effect curves progressively to the right. (Reprinted with permission of Dollery *et al.*, 1969, and *Clinical Pharmacology and Therapeutics*)

phenoxybenzamine, has not been described. Like several other chemical antagonists, the beta-adrenergic blocking agents are frequently similar structurally to the beta-adrenergic agonist (Fig. 1).

In fact, Gaddam in 1936 wrotes a series of equations to define mathematically competitive antagonism. This equation is still applicable today, and may be reorganized and written as follows:

$$\frac{Y}{1 - Y} = \frac{K_1 AX}{K_2 B + 1}$$

where Y is the fraction of receptors occupied by the agonist, and X is the dose ratio. A and B are concentrations of the agonist and antagonist, and K_1 and K_2 are the affinity constants of the receptor for both the agonist and antagonist.

In experimental situations, K_2, the affinity constant of the competitive antagonist, can be determined experimentally by determining the molar concentration of the antagonist, which would reduce the effect of a dose of the agonist to that of a half dose of the agonist. In fact, measuring the affinity constant for the antagonist, or K_2, provides a valuable method for assessing the relative potencies of antagonists. These values should remain constant for any antagonist reacting with the receptor of the same type, no matter what tissue is involved.

At present, prototypical drugs of the agonist and antagonist group can be described for alpha- and beta-receptors (Fig. 4) (Harrison and Griffin, 1966). Changes in the configuration of the catechol part of the norepinephrine molecule alter its beta-adrenergic agonist and antagonist activity. Alterations in the N-alkyl group alter the alpha-agonist and antagonist activity (Dollery *et al.*, 1969). In addition, the sterical configuration of the hydroxo-bearing carbon atom on the side chain determines the activity of both the agonist and antagonist (Fitzgerald, 1969). The levorotatory isomers of propranolol or alprenolol have greater beta-