Identification of two distinct types of adrenotropic receptors, alpha and beta, by Raymond Ahlquist provided the scientific basis that enabled the development of drugs to selectively block adrenoceptor function. These phar-

"There are two distinct types of adrenotropic receptors . . . the alpha . . . is associated with most of the excitatory functions . . . the beta is associated with most of the inhibitory functions . . . and one excitatory function (myocardial stimulation)" (1).

The recent death of Raymond Ahlquist, PhD, Charbonnier Professor of Pharmacology at the Medical College of Georgia and originator of the theory of alpha- and beta-adrenergic receptors, recalls once again the interdependent relations between basic scientific research and clinical medicine. As stated so well by Dr. Julius Comroe, "... crucial discoveries, essential to later medical miracles, were often made by those not directly concerned with diagnosing or curing or preventing disease, and . . . the work of many . . . was judged to be impractical, impossible, irrelevant or absurd at the time of discovery" (2).

Ahlquist’s neurophysiologic concept of alpha- and beta-adrenergic receptors initially served only to facilitate the understanding of responses of the sympathetic nervous system to stimulation, but shortly thereafter became the basis for specific pharmacotherapy. Drugs were soon found that specifically stimulated each type of receptor, and other substances were subsequently identified that selectively blocked alpha- and beta-receptor function. For example, beta-receptor blockade effectively inhibits the influence of sympathetic neurotransmitters on the heart, with a resultant beneficial effect in patients with angina pectoris, systemic arterial hypertension, cardiac tachyarrhythmias, and so forth.

As recently as the 1940s, the Cannon and Rosenblueth (3) concept of two adrenergic mediator substances dominated the thinking of research scientists about the function of the sympathetic nervous system. They postulated the presence of an adrenergic receptor, a tissue component that reacted with epinephrine from the nerve ending to form sympathin. Epinephrine was believed to exist in two forms; sympathin E was considered excitatory and sympathin I an inhibitory mediator.

**Catecholamine Studies**

Dr. Raymond Ahlquist, a young faculty member in the Department of Pharmacology at the Medical College of Georgia, was intrigued by the paradoxical effects of catecholamine administration, which produced both excitatory and inhibitory responses in many organ systems. The hypotensive response produced by some sympathomimetic amines was generally considered to result from a depressor effect of these drugs on the myocardium; Ahlquist believed that this depressor response was due to sympathomimetic-amine-induced peripheral vasodilation. His study of the differing responses to a series of sympathomimetic amines was encouraged by Professor R. A. Woodbury, Chairman of the Department of Pharmacology at Augusta, because of the latter’s interest in sympathomimetic relaxation of the human uterus to treat dysmenorrhea. Adrenaline, which relaxed the uterus in vitro, could not be used in patients because of its cardiovascular stimulatory effects.

Ahlquist performed detailed evaluations of five catecholamines: norepinephrine, methylnorepinephrine, isoproterenol, cobefrine and epinephrine; he showed that the rel-
ative order of vasoconstrictor potency demonstrated for these compounds (and for their effect on uterine contraction, pupillary dilation and inhibition of intestinal motility) did not parallel their order of efficacy in vasodilation, myocardial stimulation and uterine inhibition. Epinephrine had the greatest potency and isoproterenol the least for the vasoconstrictor responses; the potency of isoproterenol was greatest and that of epinephrine the least for the other set of responses that included vasodilation and cardiac stimulation (1).

Concept of Two Types of Adrenotropic Receptors

In the paper cited earlier, Ahlquist proposed the presence of two types of adrenotropic receptors, which he designated as alpha and beta, and postulated that there was only one sympathetic adrenergic mediator, epinephrine, for both the alpha- and the beta-receptors. Sympathomimetic amine stimulation of alpha-receptors was hypothesized to produce vasoconstriction, with vasodilation resulting when beta-receptors were stimulated by sympathomimetic amines; cardiac stimulation was considered a beta effect, because the relative potency order of the various amines as myocardial stimulants was the same as for their vasodilator actions. He challenged the conclusions of Cannon and Rosenblueth (3) in that no known sympathomimetic amine fulfilled the requirements for either sympathin E or sympathin I. His paper had been submitted earlier to the Journal of Pharmacology and Experimental Therapeutics, but was rejected as not being consistent with the accepted principles of physiology. The new theory, however, generated neither much interest nor significant controversy and, for a number of years, had primarily an educational value, simplifying the teaching of sympathetic nervous system function to medical and graduate students. The concept of two fundamental types of adrenotropic receptors appeared more reasonable than that of two adrenergic mediators. Little attention was focused on Ahlquist’s suggestion that the concept of alpha- and beta-adrenotropic receptors “should be useful when studying the various actions of epinephrine, the actions and interactions of sympathomimetic agents, and the effects of sympathetic nerve stimulation” (1).

Demonstration of Receptor-Specific Blocking Agents

It was not until 10 years later that Ahlquist’s hypothesis was validated by the demonstration of receptor-specific blocking agents. In 1958, Powell and Slater (4) at the Lilly Research Laboratories and Moran and Perkins (5) at the Emory University School of Medicine, respectively, showed that dichlorisoprenaline (DCI) selectively blocked sympathetic inhibitory effects on the blood vessels, uterus and bronchi and sympathetic stimulation of the heart. Moran and Perkins’ (5) designation of the term “beta adrenoreceptor blocking agent” for dichlorisoprenaline (DCI) initiated the current era of the therapeutic possibilities afforded by the application of selective adrenoceptor blockade.

During 1976 to 77, Ahlquist (6) reviewed the current state of alpha- and beta-adrenergic drugs, bemoaning the limited number of drugs available for clinical use in the United States, and predicting more extensive application of these compounds. However, in discussing the existence of two beta-receptors, he suggested that “variable receptor selectivity may have more laboratory interest than clinical application.”

Current Status of Beta-Receptor Blocking Agents

Today both selective and nonselective beta-receptor blocking agents, with and without intrinsic sympathomimetic activity, are in widespread clinical use. Beta-adrenergic blocking agents, because of their competitive inhibition of the effects of catecholamines on beta-receptors, are effective antianginal agents; they reduce myocardial oxygen demand by decreasing the heart rate, cardiac output, blood pressure and myocardial contractility, both at rest and with exercise. Beta-adrenergic blockade also helps control hypertension, in part by decreasing cardiac output; inhibition of renin release and a specific central nervous system effect are also postulated. The prevention or control, or both, of cardiac tachyarrhythmias by beta-receptor blockade relates to combinations of the decrease in sinus rate and the slowing of atrial and atrioventricular (AV) conduction, and the decrease in the spontaneous rate of depolarization of ectopic pacemakers. Recent data suggest that improved survival of
patients after myocardial infarction appears related, at least in part, to blockade of the beta-receptor (7–9); whether this will provide a clue to the pathogenesis of coronary death remains to be determined.

References