Over 50 years ago, norepinephrine (NE) was recognized as an important neurotransmitter, and nearly 40 years ago it was strongly implicated in the pathophysiology and treatment of neuropsychiatric disorders. However, over the past several decades, dopaminergic and serotonergic systems have garnered considerably more attention. This is largely due to the availability of drugs to study these systems (e.g., antipsychotics, antiparkinsonian agents, psychostimulants, and selective serotonin reuptake inhibitors), the burgeoning tools produced by molecular neurobiology and functional brain imaging, and the inferred importance of these systems in the pathophysiology of many neuropsychiatric disorders. Yet, continued advances in molecular and cellular neurobiologic components of the noradrenergic system and the increasing awareness of noradrenergic-targeted therapies, especially in the treatment of depression, have led to renewed interest in NE. We stand on the shoulders of our pioneering predecessors—Schildkraut and colleagues, who promulgated the catecholamine hypothesis of mood disorders, Axelrod, who made the puzzling observations that uncovered the existence of the monoamine transporters, and scores of others who illustrated this path with what are now viewed as relatively insensitive methods.

This month, Pupo and Minneman begin with an overview of adrenergic receptor pharmacology with emphasis on the current classification of various types of adrenergic receptors based upon structure and pharmacologic properties. Unfortunately, little is known about the absolute roles of most of the individual receptor subtypes. Next, Szabo and Blier review the basic neurobiology of the noradrenergic system, with emphasis on the response of forebrain noradrenergic neurons to environmental cues and antidepressant drug exposure. The authors conclude that even drugs selective for other biogenic amines or neuropeptides act indirectly to alter noradrenergic functioning. In the final review this month dealing with the basic neurobiologic aspects of NE, Apparsundaram reviews recent findings regarding regulation of the NE transporter. Known to be direct targets of many antidepressant drugs, data obtained over the past few years show that all of the monoamine transporters appear to be regulated over short time periods by protein phosphorylation, a process well documented to be associated with virtually every receptor, but not previously with transporters.

The remaining articles are more clinically oriented. Ressler and Nemeroff critically review the data implicating noradrenergic circuits in the pathophysiology of a variety of mood and anxiety disorders. Because much of the data regarding a role for NE in various disorders are indirect in nature, careful attention is necessary when evaluating experimental design and the resultant data before any definitive conclusions can be made. The following two articles review more direct assessments of noradrenergic function. Although imperfect, much has been learned about the pathophysiology of many neuropsychiatric disorders through postmortem analysis of brain tissue. Ordway and Klimek review evidence of noradrenergic neuropathology in suicide and depression. Moreover, these authors point out the technical shortcomings, as well as the strengths, of postmortem research. Technological advancements regarding in vivo brain imaging and the development of synthetic positron emission tomography and single photon emission computed tomography ligands herald a new era in the ability to monitor specific transmitter systems in living patients, and may prove extremely beneficial in aiding diagnosis, treatment choice, and therapeutic progress. McConathy and colleagues briefly review the noradrenergic ligands and targets that have been investigated. Although selective ligands are available, penetrability of these ligands into the central nervous system has been limited, and the available data base is sparse to date. Taken together, it is clear that major depression and perhaps certain anxiety disorders are associated with dysregulation of the forebrain noradrenergic projections.

In this month’s final paper, Kasper reviews the efficacy of noradrenergic-selective drugs in the treatment of major depressive, anxiety, and panic disorders. Although many of the classic tricyclic antidepressants have noradrenergic properties, the introduction of highly selective NE reuptake inhibitors or dual NE and serotonin reuptake inhibitors that lack troublesome side effects associated with muscarinic, histaminergic, and α-adrenergic blockade has been a major impetus for the renewed interest in a role for NE in normal and pathologic brain function. Although we are convinced that no single transmitter system is wholly responsible for producing or treating the symptoms of any particular psychiatric disorder, there is no question that the noradrenergic system is instrumental in regulating normal and pathological behaviors, and that drugs targeting this system will increasingly be important in treating a host of neuropsychiatric disorders.