Most clinicians and investigators agree that bipolar disorder as currently diagnosed is phenomenologically heterogeneous and probably represents several distinct subtypes. The inability to reliably define distinct subtypes of bipolar disorder has greatly impaired research into the pathophysiology and treatment of the disorder.

The articles by Angst and Sellaro (2000), Biederman et al (2000), and Strakowski et al (2000) in this issue provide a framework upon which to use data from longitudinal studies of bipolar disorder to further our knowledge of the neurobiological basis of the disorder. Angst and Sellaro, in a highly informative and comprehensive review, indicate that although, in general, bipolar disorder is characterized by poor prognosis, high recurrence rates, chronicity of symptoms, and even premature death, there is considerable variability in outcomes. For example, their summary of the evidence is that cycle length decreases from the first episode to the next few cycles, but thereafter the course is more irregular. They concluded, from these data, that the kindling model (Post et al 1986) is not supported. However, it is likely that a substantial number of patients do demonstrate reduced cycle length throughout the course of their disorder, and for these patients distinct neurobiological mechanisms, akin to kindling or sensitization, may be operative. There are other patients with bipolar disorder who exhibit a chronic unremitting course. In these patients a search for specific neuropathologic mechanisms may be particularly fruitful. Further, there is a group of patients with bipolar disorder who have had a limited number of episodes and who are substantially responsive to mood stabilizer treatments. How these patients with bipolar disorder differ neurobiologically from treatment-refractory patients remains to be discovered.

Biederman and colleagues’ article is an important contribution from several vantage points. Biederman correctly asserts that pediatric-onset mania may be a developmentally based subtype of bipolar disorder. The difficulty in diagnosing pediatric-onset mania, as compared with adult onset, relates to the differential expression of symptoms; pediatric onset is characterized by irritability, temper tantrums, hyperactivity, and no euphoria. The course of pediatric-onset mania is typically chronic and continuous rather than episodic. In many patients, comorbidity is the rule rather than the exception, especially with attention-deficit disorder, conduct disorder, and substance abuse.

Many questions remain unanswered. In the context of the model presented by Cantwell (1996) for classifying child and adolescent psychopathology, much work needs to be done to establish the validity of pediatric-onset mania with specific diagnostic criteria. There is a dearth of longitudinal data to determine the long-term course of pediatric-onset mania. It is not known whether or not pediatric-onset mania alone or comorbid with attention-deficit disorder, conduct disorder, or substance abuse has a distinct neurobiology and therapeutic responsiveness.

The work reported by Strakowski et al (2000) reflects the important complex relationships between adult-onset bipolar disorder and substance abuse. Here again, there may be relevant subtypes of bipolar disorder with neurobiological and therapeutic implications. As suggested by Strakowski et al (2000), there may be a group of patients in which specific types of substance abuse combine with a genetic vulnerability to produce the phenotypic expression of bipolar disorder. In other patients, substance abuse occurs after the onset of bipolar disorder and may alter the course of the illness in a drug-specific fashion, with alcohol abuse relating to the duration of depressive episodes and cannabis to the duration of manic episodes. The provocative but preliminary findings of this investigation need replication.

Considered together, these articles suggest a framework for future research of the genetics, neurobiology, and therapy of bipolar disorder. Investigations should be initiated designed to determine the validity of specific subtypes of bipolar defined by features such as age at onset, recurrence rate, comorbid disorders, impact of substance abuse, and therapeutic response.