Each movement is preceded by certain preliminary sensory signals and is in turn followed by sensory impressions at the end of the action. Each movement is the result of a voluntary capitulation to a demanding and relentless urge accompanied by an extraordinarily subtle sensation that provokes and fuels the urge. Successively sharper movements build up to a climax—a climax that never comes (1).

A MODEL NEUROPSYCHIATRIC DISORDER

Biological models allow investigators to extrapolate from simple to complex systems, to generate and test hypotheses, and to grasp schema that are within range of our intellect, as we reach to conceptualize things beyond this range. Tourette syndrome (TS) is a “model neuropsychiatric disorder” (2,3) that seems tantalizing in its simplicity. The genetic basis is stronger than any common neuropsychiatric disorder other than Huntington disease. The age of onset and the sex distribution of TS are strong clues that neurodevelopmental and hormonal processes are causative in TS. Emerging evidence suggests a role of epigenetic (e.g., hypoxia) or “environmental” (e.g., group A streptococcal infections) factors in the origin of at least some cases of TS, again making TS an ideal model for “nature-nurture” interactions in the pathogenesis of brain disorders. The clinical presentation and responsivity to dopamine antagonists provide strong clues that the critical substrates of TS fall within the basal ganglia, a system implicated in an increasing number of neuropsychiatric disorders and perhaps the one most studied and best understood in the neuropsychiatric literature. The familial and phenomenologic links to obsessive-compulsive disorder (OCD) have led many investigators to conceptualize tics in TS as “movement-equivalents” of obsessions and compulsions, and the apparent connections with OCD and attention-deficit/hyperactivity disorder (ADHD) raise hope that by solving the TS “model,” we will understand a family of disorders that collectively affects close to 10% of the population. By all accounts, the TS model should be readily solvable, like a practice question before the really tough questions on an examination. Although we still lack clear answers for many of the complex questions raised by this syndrome, this chapter reviews the current state of progress in understanding the clinical features and neurobiology of TS and related tic disorders.

TICS: MOTOR, PHONIC, AND BEYOND

The DSM-IV describes tics as “sudden, rapid, recurrent, nonrhythmic, stereotyped movements or vocalizations,” but the self-assessments by Dr. Joseph Bliss (quoted earlier) and others (4) make it clear that tics in TS have a depth and dimension far beyond their motor or vocal components. Tics can be characterized by their anatomic location, frequency, intensity, and “complexity.” Facial and upper torso muscle groups are commonly active in motor tics, but virtually any motor group can be involved, including diaphragmatic muscles, in which rapid contractions can generate sounds by the expulsion of air through the upper airways. Simple tics are brief, circumscribed movements or sounds that are fragments or “chunks” of behavior or speech, rather than “self-contained,” meaningful motor sequences or utterances. These may include blinking, facial grimacing, mouth movements, head jerks, shoulder shrugs, and arm and leg jerks. Complex tics are more elaborate, sustained actions or linguistically meaningful sounds that often give the appearance of an intentional, “willful” event. Examples include facial gestures and movements such as brushing hair back, possibly in combination with head jerk, and body shrugs. Although most tics can be distinguished from chorea and dystonic movements, this differential diagnosis is not
always easily made, and some patients manifest symptoms across the entire range of involuntary movements. Audible tics may or may not involve the vocal cords, but true vocal tics can range from grunts and barking sounds to complete, grammatically correct phrases. Only about 10% of patients with TS express vocal tics with obscene content, termed *coprolalia* (5).

Tics can often be willfully suppressed for brief periods. Unfortunately, voluntary tic suppression can be associated with a buildup of inner tension, so when the tics are expressed, they are more forceful than they would otherwise be. Tics are also diminished during periods of goal-directed behavior that requires focused attention. Jim Eisenreich, who was a lifetime .300 hitter despite having significant motor tics for his entire professional baseball career, explained, “you only have to concentrate for 5 seconds on each pitch” (6). Tics can also be “suggestible,” activated by a verbal suggestion, or they can mimic or “echo” behavior or sounds from other people or the surrounding environment, analogous to stimulus-dependent behaviors in some post-traumatic or vascular orbitofrontal syndromes.

The degree of impairment associated with particular tics is partly dependent on their frequency, intensity, complexity, and duration. For example, a very frequent simple motor wrist tic may be less impairing than an infrequently occurring, forceful obscene (copropraxic) gesture. Very commonly, functional impairment in TS is strongly related to the severity of associated symptoms, including obsessions, compulsions, and attention deficits, as discussed later.

Many patients with tic disorders report a variety of sensory and mental states associated with their tics. Simple sensory tics, like simple motor or phonic tics, are rapid, recurrent, and stereotyped, and they are experienced as a sensation at or near the skin. The sensations are typically bothersome or uncomfortable, like an “itch” or a “crawling” feeling. Patients may be unusually aware, distracted, and distressed by particular sensory stimuli that most persons would not notice. One patient explained, “you know the scratchy feeling of a tag on your neck when you put on a new shirt? I have tags on every part of every shirt, all the time.” This site sensitization to certain forms of sensory information is a relatively understudied phenomenon that may provide important clues to the neurobiology of this disorder (7). *Premonitory urges* are more complex phenomena, which often include both sensory and psychic discomfort that may be momentarily relieved by a tic (7–9). An extension of the sensory-psychic dimension of tics may include a sense of discomfort or distress if sensory information (typically visual, but also tactile) is not experienced as “just right”; the assessment that something is “just right” can reflect complex stimulus properties, including balance and symmetry, texture, or context. The full elaboration of tics therefore can include sequential experience: (a) a sensory event or premonitory urge, (b) a complex state of inner conflict over whether and when to yield to the urge, (c) the motor or phonic production, and (d) a transient sensation of relief.

Further underscoring the importance of the sensory dimensions of TS, many patients with tic disorders are remarkably sensitive to perceptions arising both from within themselves (of somatic origin) and from the external world. Patients may unconsciously mirror the behavior and speech of others as well as of themselves. A related phenomenon is *triggering perceptions* in which some patients report urges to perform dangerous, forbidden, or simply senseless acts, such as to touch a hot iron, to jump from heights, to put the car in reverse gear while driving down a highway, or to shout in a quiet church service (10).

### Diagnosis

The diagnosis of TS is based exclusively on the history obtained from the patient, parents, or other family members and on direct examination. Diagnostic criteria for “Tourette’s disorder” (DSM-IV) (11) and “definite Tourette syndrome” (TS Classification Study Group) (12) differ only slightly: both diagnoses require the frequent occurrence of multiple motor tics and one or more vocal tics, over a continuous interval that involves most of a full year, with the onset of symptoms early in life (before age 18 to 21 years). The controversial requirement that tics cause “marked distress or significant impairment in social, occupational, or other areas of functioning” has been challenged; as currently written in the DSM-IV, this criterion excludes persons who have adjusted well to the presence of tics, because these persons are not considered to have Tourette disorder if the syndrome is not a major source of distress.

The DSM-IV lists two specific tic disorders other than Tourette disorder. The diagnosis of chronic motor or vocal tic disorder is made when tics are limited to one or the other domain, but the patient otherwise meets criteria for Tourette disorder. Chronic motor tic disorder is the more common of these two conditions, and both are often viewed as part of the “broader phenotype” of TS. One clue that TS and related tic disorders reflect some aberration in a normal developmental process is that various tics are exhibited at some point in early development by most children. To bridge this gradient of “normal” versus “abnormal” tic behaviors in childhood, and to span the temporal gap between symptom onset and the 1-year “duration” requirement for the diagnosis of Tourette disorder, a diagnosis of *transient tic disorder* can be made if childhood tics, either motor or vocal, are frequent and cause distress, and they last between 1 and 12 months. As many as one in ten children may meet criteria for this diagnosis (13), and thus by extrapolation, in at most 10% of these children will symptoms continue beyond a year, thereby meeting criteria for one of the chronic tic disorders.
Symptoms in adulthood may typically settle into a more steady decline in tic severity, and by 18 years of age, perhaps up to 23.4 in 10,000 (26). Community surveys yielded prevalence rates that range from 2.9 in 10,000 in Monroe County, NY (27) to 299 in 10,000 in the United Kingdom (16,28). Thus, although a population prevalence of 5 in 10,000 is commonly cited, considerable evidence suggests that the true prevalence of TS may be considerably greater than this.

Comorbid Conditions

Although some persons experience “pure” tic disorders, functional impairment is often more directly related to the partial or full manifestation of comorbid conditions such as OCD and ADHD. Clinical and epidemiologic studies indicate that more than 40% of patients with TS experience recurrent obsessive-compulsive symptoms (8,14). Compared with “pure” TS, patients with comorbid TS and OCD experience more lifetime functional impairment, as rated by standardized scales, and specifically in areas such as employment and social relations. Overall, the level of lifetime impairment in these persons correlates significantly with the severity of OCD symptoms (15). Specific obsessive-compulsive symptoms associated with most impairment in patients with TS include aggressive and sexual obsessions and repeating and counting compulsions. Aggressive and sexual obsessions are also associated with more severe motor and phonic tics, even in patients with TS who do not meet full diagnostic criteria for OCD (15). These relationships underscore the importance of early recognition and treatment of comorbid obsessive-compulsive symptoms in TS.

Studies sharply differ on the rates of ADHD seen among patients with TS. Clinical studies vary according to setting and established referral patterns, but it is not uncommon to see reports of 50% or more of referred children with TS diagnosed with comorbid ADHD (16). In contrast, epidemiologic studies typically indicate a much lower incidence of comorbidity (14,16). Similar to the functional impact of comorbid OCD, patients with comorbid ADHD and TS experience significantly greater impairment than patients with “pure” TS. Longitudinal studies confirm that children with comorbid TS and ADHD are at high risk of anxiety and mood disorders, oppositional defiant disorder, and conduct disorder (17,18), whereas children who only have TS tend to fare better (17,19,20). Levels of tic severity are less predictive of peer acceptance than is the presence of ADHD (19,20), and rates of subsequent psychiatric morbidity in comorbid TS and ADHD are nearly identical to those seen in prior cross-sectional and longitudinal studies of “pure” ADHD (21,22).

Natural History and Epidemiology

Tics typically begin between 3 and 8 years of age. For persons who go on to develop TS, the tics typically follow a waxing and waning course, usually with a progressive pattern of tic worsening. On average, the period of greatest tic severity occurs between 8 and 12 years of age. The onset of puberty is not associated with either the timing or the severity of tics. The early teens are generally followed by a steady decline in tic severity, and by 18 years of age, perhaps as many as 50% of patients with TS are nearly tic free (23). Symptoms in adulthood may typically settle into a more predictable, yet idiosyncratic repertoire, with increases in tic frequency and forcefulness during periods of stress or emotional excitement.

Estimates of the prevalence of TS vary considerably across studies. In studies relying on identified treated cases, prevalence estimates were 0.046 (Minnesota) (24) to 5.2 in 10,000 (North Dakota) (25). School-based surveys yielded much higher estimates, up to 23.4 in 10,000 (26). Community surveys yielded prevalence rates that range from 2.9 in 10,000 in Monroe County, NY (27) to 299 in 10,000 in the United Kingdom (16,28). Thus, although a population prevalence of 5 in 10,000 is commonly cited, considerable evidence suggests that the true prevalence of TS may be considerably greater than this.

NEUROBIOLOGY OF TOURETTE SYNDROME

Interconnected cortico-striato-pallido-thalamic (CSPT) circuitry has long been implicated in the regulation of movement, thought, and affect; abnormalities within this circuitry have also been proposed to contribute to the pathophysiology of many neuropsychiatric disorders (29,30). The “motor” loops of CSPT circuitry are known to be the locus of disease in primary movement disorders such as Huntington disease (31), Parkinson disease (32) and hemiballism (33), and the “limbic” CSPT loops have been proposed as the source of disease in schizophrenia (29), depression (29), OCD (34,35), ADHD (36), substance abuse disorders (37), temporal lobe epilepsy (38), and many other seemingly disparate forms of psychopathology (39). Important models have been proposed to account for a wide range of CSPT disorders, based on variations in responses to “generalized” or “epigenetic” early developmental insults, from neonatal hypoxia to bacterial infections. Despite this departure from the notion of discrete, specific “lesions” and circumscribed clinical presentations, the prevailing model in the search for the pathophysiology of TS is perhaps closest to that previously applied to Huntington disease, in which a unique mutation in a single gene causes—by as yet unknown cellular mechanisms—a characteristic disease that leads to a fairly predictable clinical presentation and course. Yet the actual pathophysiology of TS remains quite elusive. The scant tangible evidence of the pathophysiology of TS comes primarily from studies in neuropathology and neuroimaging; supportive evidence comes from other fields of investigation, including neuropsychology and psychophysiology, and from ties between TS and other disorders, such as OCD and ADHD, providing indirect evidence based on what is known about the pathophysiology of these other disorders.

The published literature of TS neuropathology studies now includes seven presumed TS cases; of these, informative clinical and histologic data are available from five cases. Interpretation of the findings from even these five cases is
clouded by issues of diagnostic uncertainty, comorbidity, and potentially confounding neurologic insults. Preliminary findings have identified four different locations of potential pathology within CSPT circuitry: (a) intrinsic striatal neuron abnormalities, including increased packing density of neurons in the striatum \((n=1)\) (40); (b) a diminished striatopallidal “direct” output pathway, with reduced dynorphin-like immunoactivity in the lenticular nuclei \((n=5)\) (41,42); (c) increased dopaminergic innervation of the striatum, with increased density of dopamine transporter sites \((n=3)\);(43); and (d) reduced glutamergic output from the subthalamic nucleus, based on reduced lenticular glutamate content \((n=4)\) (44). Thus, in a manner more reminiscent of neuropathologic findings in schizophrenia than, for example, Huntington disease, these preliminary neuropathologic findings in TS do not converge to identify a specific, circumscribed “hole” in CSPT connections, but instead they suggest a range of disturbances or imbalances that affect the “whole” circuit \((45)\). Many other measures of CSPT biology in TS, including amine levels and receptors, have been reported to be normal, also in these preliminary, small studies. Clearly, postmortem studies are hampered by limitations in the nature and number of the brains that have been studied \((46)\). Efforts by the Tourette Syndrome Association (TSA) to secure adequate material for neuropathologic studies are currently under way and should allow a new generation of tissue-based research during the next decade.

Neuroimaging findings may ultimately provide information critically important to our understanding of the pathophysiology of TS. Volumetric imaging studies demonstrate minimal, if any consistent, abnormalities in persons with TS. Among reports of enlarged corpus callosum volume \((47)\), reduced caudate volume \((48)\), or diminished right-to-left asymmetry for the caudate nucleus \((49)\) and left-to-right asymmetry for putamen and lenticular nucleus \((48)\), the magnitude of such changes is small, typically on the order of 5%; furthermore, some reports fail to support even these small abnormalities. The specific cellular or structural processes that may be responsible for these anatomic abnormalities are unknown. Concerns regarding sample heterogeneity, comorbidity, and effects of chronic medication exposure, described earlier in relation to neuropathologic studies, are equally applicable to neuroimaging studies in TS.

Neuroimaging studies of regional perfusion or glucose uptake presumably measure features indicative of neuronal metabolism. In general, these studies in TS report reduced glucose uptake in orbitofrontal cortex, caudate, parahippocampus, and midbrain regions \((52)\), as well as reduced blood flow in the caudate nucleus, anterior cingulate cortex, and temporal lobes \((53–56)\). Regional glucose uptake patterns may reflect distributed CSPT dysfunction, as suggested by the observed covariate relationships between reduced glucose uptake in striatal, pallidal, thalamic, and hippocampal regions \((56)\). The single greatest consistency across metabolic imaging studies in TS—that of distributed hypometabolism—contrasts sharply with the observed corticostriatal hypermetabolism reported by many groups in patients with OCD \((33,34)\). The only suggestion of regional activation in TS comes during active tic suppression, which is associated with increased right caudate neuronal activity, as measured by functional magnetic resonance imaging \((fMRI)\) \((57)\); however, tic suppression is also accompanied by bilaterally diminished neuronal activity on fMRI measures, in the putamen, globus pallidus, and thalamus. The most analogous paradigm in OCD—obsession provocation—is associated with increased metabolic activity at every level of CSPT circuitry \((35)\), in sharp contrast to the pattern observed in TS.

Neurochemical imaging studies have reported relatively subtle abnormalities in levels of dopamine receptors \((58)\), dopamine release \((59)\), and dopamine transporter \((60)\) in the striatum of some patients with TS. Some of these findings have not been replicated \((61,62)\), others await replication, even internally \((60)\), and others are evident only in a small subgroup of TS, such as four of 20 patients \((58)\), issues raising concern about their generalizability to the pathophysiology of TS. A potentially important report of 17% greater caudate D2 receptor binding among more symptomatic TS identical twins \((63)\) was based on five twin pairs and reached statistical significance at the \(p < .04\) level, by nonparametric analyses. Significant correlations between symptom severity and D2 binding were obtained using aggregate symptom scores from three clinical measures. These latter findings do not directly address the brain mechanisms that distinguish persons with TS from those without TS, but rather, point to the need to understand specific factors that contribute to the heterogeneity of the TS phenotype among affected persons.

Various techniques have been used to demonstrate a wide array of abnormalities in the levels of many major neurotransmitters, precursors, metabolites, biogenic amines, and hormones in blood, cerebrospinal fluid and urine of patients with TS, compared with controls \((64–66)\). Attempts to understand the relation of these abnormalities to the pathophysiology of TS have ranged from a proposed causal role ascribed to a single metabolic abnormality, such as the reported cerebrospinal fluid elevation of the potential excitotoxin kynurenine \((67)\), to models for imbalances in norepinephrine, dopamine, and serotonin \((5-HT)\) systems similar to “imbalance” models proposed for other complex forms of psychopathology. One qualitatively different finding, reported by Singer et al. \((68)\), is that of approximately 40% elevations of serum antiputamen antibodies in children with TS. This finding may have particular importance, based not only on its magnitude and specific linkage to basal ganglia circuitry, but also on converging evidence of autoimmune contributions to at least some forms of TS \((69)\). Additional evidence of disorders in CSPT circuitry in...
TS comes from neuropsychological and psychophysiologic studies (69–77). Even these findings generally suggest mild deficits, at most: response distributions overlap greatly among patients with TS and control subjects, with most patients with TS performing within the normal range. The most consistently observed deficits occur on tasks requiring the accurate copy of geometric designs, that is, “visual-motor integration” or “visual-graphic” ability (69,77); somewhat similar deficits are reported in patients with OCD (78). No compelling evidence links these deficits in TS and OCD with a specific frontal or frontal corticostriatal territory, although visuospatial functions have generally been conceptualized to be regulated by dorsolateral prefrontal cortex and descending cerebrospinal fluid inputs to the head of the caudate nucleus (79). Neurophysiologic studies have documented a reduced cortical silent period after repeated transcranial magnetic stimulation (rTMS) in TS (80). This increased cortical excitability could result from impaired inhibition through disinhibited thalamocortical inputs or through abnormalities intrinsic to cortex, or both. Further support for the role of basal ganglia circuitry in TS comes from anecdotal reports of symptom exacerbation or reduction in patients with tumors within, or transections of, CSPT elements, respectively (81,82).

**GENETICS OF TOURETTE SYNDROME**

TS may be the most clearly inheritable common neuropsychiatric disorder. First-degree relatives of TS probands appear to be 20 to 150 times more likely to develop TS, compared with unrelated persons (83). Concordance rates for TS among monozygotic twins approach 90%, if the phenotypic boundaries include chronic motor or vocal tics, versus 10% to 25% concordance for dizygotic twins, across the same boundaries (84). The mode of inheritance remains elusive, even after more than 15 years of studies. Some segregation analyses have supported transmission through an incompletely penetrant autosomal dominant major locus (85, 86), but in other studies, more complex models could not be excluded (87). The impact of assortive mating on inheritance may be particularly strong in TS, based on higher-than-predicted rates of bilinear transmission (88–90). Other findings suggest different inheritance patterns for maternal versus paternal transmission (91). Approaches using candidate genes or chromosomal translocations have offered results that were exciting but thus far not generally informative (92–94). Perhaps the most conservative assessment is that susceptibility to TS may be determined by a major gene in some families and by multiple genes of small relative effect in others, with a “dose-effect” of greater susceptibility for individuals homozygous versus heterozygous for these genes.

The TSA International Genetics Consortium completed the first genome-wide scan in an affected sibling-pairs (sib-pair) study. The sib-pair design relies on the comparison of the number of alleles at a given locus that are shared by two affected siblings, across all families in the sample. If the number of affected siblings sharing an allele or alleles is significantly higher than that expected by chance, it suggests a gene or genes of etiologic importance for TS. Using 76 affected sib-pair families with a total of 110 sib-pairs, the multipoint maximum-likelihood scores (MLS) for two regions (4q and 8p) were suggestive of high sharing (MLS greater than 2.0). Four additional regions also gave multipoint MLS scores between 1.0 and 2.0 (95). Collection of a second, replication set of approximately 100 sib-pairs is nearly complete, and it will be used to map these broad chromosomal regions more narrowly.

**ENVIRONMENTAL FACTORS**

Evidence of nongenetic environmental factors in the genesis of TS supports an interactive role for at least three sets of environmental factors: adverse prenatal and perinatal events, acute and chronic psychosocial stressors, and postinfectious autoimmune mechanisms.

Retrospective studies have identified an association between adverse events during the prenatal and perinatal period and an increased risk for the development of TS. Although the strongest evidence points to chronic mechanisms that influence the supply of nutrients by the placenta (96,97), other risk factors have been proposed including severe nausea and vomiting during the first trimester, severe maternal stress during pregnancy, exposure to high levels of androgenic steroids, and chronic or acute hypoxic and ischemic injury (98–101). Although no specific mechanism is known to connect these early life events and the development of TS, preclinical studies have shown that various neural insults during the prenatal and perinatal period result in the delayed emergence of pathology within interconnected CSPT circuitry and in specific behavioral abnormalities that are also manifested by individuals with TS, such as reductions in sensorimotor gating of the startle reflex (102–106). These early insults may also set the stage for a heightened stress response in adulthood and altered immune function (107–109).

As with several other disorders associated with CSPT dysfunction, including OCD, schizophrenia, and affective disorders, increased life stressors are associated with symptom exacerbation in TS. More than 98% of patients with TS report worsening of tic symptoms during periods of stress and anxiety (110). A direct assessment of the relationship between stress and tics revealed that anticipation of a stressful medical procedure, a lumbar puncture, has been shown to produce greater elevations in plasma adrenocorticotropic hormone in patients with TS than in control subjects and an elevated urinary excretion of catecholamines that correlated with symptom severity (66). Patients with
TS also have been reported to have elevated levels of cerebrospinal fluid norepinephrine and corticotropin-releasing factor (66,111). Importantly, although stress clearly alters CSPT dynamics and increases symptoms of numerous different neuropsychiatric disorders, no existing data implicate a specific etiologic relationship between stress and TS.

It is well known that group A β-hemolytic streptococcal (GABHS) infections can trigger immune-mediated disease in genetically predisposed persons (112). Acute rheumatic fever (RF) can occur approximately 3 weeks after an inadequately treated GABHS infection. In addition to inflammatory lesions involving the heart (rheumatic carditis) and joints (polymigratory arthritis), rheumatic fever can be accompanied by CSPT disease responsible for the manifestation of Sydenham chorea. Patients with Sydenham chorea frequently display motor and vocal tics, obsessive-compulsive, and ADHD symptoms suggesting the possibility that at least in some instances these disorders share a common origin (113,114). As in Sydenham chorea, antineuronal antibodies have been reported to be elevated in the sera of patients with TS (68).

It has been proposed that pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) represents a distinct clinical entity and includes Sydenham chorea and some cases of TS and OCD (115). The most compelling evidence that acute exacerbations of TS and OCD can be triggered by GABHS comes from two independent reports that most patients with childhood-onset TS or OCD have elevated expression of a stable B-cell marker (116,117). The D8/17 marker identifies close to 100% of patients with rheumatic fever (with or without Sydenham chorea), but it is present at low levels of expression in healthy control populations. Dr. Susan Swedo and her colleagues reported that in children who met PANDAS criteria, GABHS infection was likely to have preceded neuropsychiatric symptom onset for 44% of the children, whereas pharyngitis (no culture obtained) preceded onset for another 28% of the children. In a minority of cases (31%), neuropsychiatric symptom exacerbations were associated with documented GABHS infection, and in another 42%, they were associated with symptoms of pharyngitis or upper respiratory infection (no throat culture obtained) (115). Although these results are intriguing, they are not compelling with regard to specific immunologic mechanisms linking PANDAS and TS. Clearly, independent replication and systematic study of this intriguing phenomenon may provide a basis for the rational design of therapeutic and preventative interventions. The need for accurate and complete information in this area is underscored by the finding that, based solely on the existing minimal data, parents are actively seeking for their children invasive treatments such as plasmapheresis and intravenous immunoglobulins. With emerging preliminary findings suggesting possible links between streptococcal infections and some aspects of OCD and ADHD, this area of investigation has become a major public health issue.

**TREATMENT**

Therapeutic models of TS emphasize the importance of flexible, integrated biopsychosocial strategies. Flexibility is important because the nature of the disorder and its impact on patients and families change dramatically across its course. It is often the case that, when families first present for assessment of TS, confusion, fear, anger, and embarrassment fill an “information void” and are exacerbated by the very public outward manifestations of tics, their deceptive “volitional” appearance, and their sometimes socially unacceptable content. Although parents may worry about a child’s counting rituals or may be exacerbated by a child’s continued disruption of a school class, the child’s tics often evoke in them a more intense, visceral sense of desperation. Such reactions reverberate throughout the family and affect the child. The familial nature of the illness means that, almost invariably, when a child first manifests symptoms, close relatives (often parents or siblings) are, or were once, also affected; this sets the stage for a range of “generational” psychological consequences for parents, as painful memories are rekindled.

**Education**

Initially, much of the distress associated with TS can result from a lack of understanding of the illness. Education about the natural history of TS, emphasizing the involuntary, “no-fault” nature of certain brain-behavior relationships, is an essential part of the early treatment of this disorder. This process can begin in the diagnostic assessment: faced with a set of simple, matter-of-fact questions about tic symptoms, many of which are found in printed, standardized scales such as the Yale Global Tic Severity Scale (118), parents and patients recognize that other people must have had experiences much like their own. As information displaces the “mystery” of a child’s tic behaviors, the urgency to make immediate somatic interventions can diminish.

Physicians, parents, and patients should be aware of the waxing and waning nature of the illness. An initial clinical visit may be precipitated by a recent exacerbation of previously subclinical or tolerable symptoms. Given the cyclic pattern of TS, such periods are often followed by a gradual diminution of symptoms, even in the absence of a specific biological intervention. One danger of rapidly initiating medication treatment in TS is that a “false-positive” response, based on the normal cyclic fluctuation of symptoms, will convince patient, family, or physician that a particular medication is “effective.” This false-positive response, and the false hope that it creates, can result in unnecessary medication exposure and side effects and, ultimately, in height-
enhanced frustration when the illness follows its natural course toward the next phase of exacerbation. Observing the cyclic fluctuations, while the patient is free of medications, can provide a more clear impression of a patients' natural illness course and can thereby be a useful basis for interpreting future medication effects.

The "bigger picture" of the natural history of TS is also critically important: persons with TS can and should be expected to live full, productive lives; as many as half of these persons will be largely symptom free by the time they enter their twenties; and every persons has strengths that must be nurtured and developed and that will ultimately be more significant determinants of life quality and character than are tics or other TS symptoms. Within this broader context, parents and patients should understand that, at present, the benefits of medication treatments of TS are relatively modest, and the potential social, psychological, and biological side effects are not trivial.

Pharmacotherapy

Medications can play an important role in the treatment of TS. Because functional impairment in this disorder is most closely linked to comorbid conditions such as OCD and ADHD, symptoms of these disorders (and even their "subclinical" manifestations) are often the first targets of pharmacotherapy in TS. Effective treatment of these comorbid conditions can often markedly diminish tic severity. The basis for this therapeutic interaction is not well understood, but it may include some or all of the following: (a) simple interactions at a neural level, such as a direct medication effect within multiple or interacting CSPT "open loops," including, for example, those that mediate both obsessions and tics; (b) interactions related to the stressful nature of comorbid conditions; for example, tics are reduced by a diminution of stress that follows successful treatment of OCD or ADHD symptoms; (c) interactions at a level of cognition resources, such as improved volitional "suppressibility" of tics because of improved attentional allocation; and (d) interactions at a symptom level, such as diminished need for repetition or complex rituals that could otherwise make tics more elaborate. Regardless of the mechanism, treatment of comorbid OCD or ADHD (as well as mood disorders, discussed later) should be a high priority because these conditions are responsible for significant functional impairment, they are generally responsive to appropriate pharmacotherapy, and their treatments are relatively free of significant side effects. Even the prolonged use of stimulants in comorbid TS and ADHD, once avoided because of fears of stimulant-potentiation of tics, was shown to be safe and effective in a large TSA-funded study with a 2-year longitudinal design (119). Clearly, close clinical monitoring is important in all pharmacotherapy, particularly in children.

Dopamine Antagonists

When tic-suppressing agents are necessary, the cost-to-benefit ratio differs among medications and across clinical conditions. Dopamine antagonists, particularly high potency, D2-preferential blockers such as haloperidol, fluphenazine, and pimozide, are the most potent and rapid-acting tic-suppressing agents that have been studied in controlled trials. These medications may be most useful in patients with severe, intractable tics, but they also have undesired side effects, causing blunting of cognitive skills, mood, and motivation (120–121); when discontinued, these high potency D2 blockers can precipitate withdrawal dyskinesia and significant worsening of tics (120). In adults, these drugs are clearly linked to an increased risk of tardive dyskinesia, although in children, this relationship has not been as clearly defined. One newer, "atypical" antipsychotic, risperidone, is a mixed dopamine/5-HT receptor blocker that is proving to be a useful anti-tic medication, with a side effect profile somewhat preferable to that of haloperidol or pimozide (122). Controlled studies of risperidone efficacy in TS are in progress; however, experience suggests that significant, undesired weight gain with this drug is not infrequent. Dopamine antagonists are also useful in conjunction with a primary antiobsessional agent (e.g., selective serotonin reuptake inhibitors) in treatment refractory OCD with comorbid tics; risperidone is frequently used in this capacity. A double-blind trial of ziprasidone in TS yielded encouraging short-term results without the weight gain associated with risperidone (123). The utility of other "atypical" antipsychotics such as olanzapine or quetiapine in the treatment of TS or tic-related OCD is not known.

α₂-Agonists

The α₂-adrenergic agonists, clonidine and guanfacine, are often used as first-line anti-tic agents, both because of their relatively favorable side effect profile and because of some evidence linking these drugs to improved attentional abilities in children with ADHD (124,125). These drugs have relatively weaker anti-tic abilities, compared with dopamine antagonists, and their benefit generally evolves more gradually than with dopamine antagonists. Still, there are advantages to prescribing these medications in lieu of antipsychotics; aside from the somatic side effects of neuroleptic agents, it is often not inconsequential for a child when his or her teacher researches these drugs in the Physician's Desk Reference and reads "for severe psychotic states only."

Newer Pharmacologic Approaches

Several new therapeutic avenues for TS are being explored in controlled studies. Preliminary studies suggest that one severely impairing feature of some forms of TS—rage attacks—may be sensitive to treatment with selective seroto-
Tempted.
with intermittent brief patch exposure, have not been at-
abuse or dependence (131), but relevant studies in children,
thenicotine patch does not increase the liability for nicotine
receptors. Studies in adults suggest that sustained use of
in TS reflect a rapid and sustained desensitization of nico-
mecamylaminemaysuggestthatnicotine’sbeneficialeffects
seemingly paradoxical effectiveness of both nicotine and
after exposure to the patches for only a few hours. The
patcheshasbeenreportedtobesustainedforseveralweeks
these agents (128–130). Tic reduction after nicotine
studies replicate the impressive series of case reports with
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patches has been reported to be sustained for several weeks
after exposure to the patches for only a few hours. The
seemingly paradoxical effectiveness of both nicotine and
mecamylamine may suggest that nicotine’s beneficial effects
in TS reflect a rapid and sustained desensitization of nicotine
receptors. Studies in adults suggest that sustained use of
the nicotine patch does not increase the liability for nicotine
abuse or dependence (131), but relevant studies in children,
with intermittent brief patch exposure, have not been at-
tempted. Δ9-tetrahydrocannabinol was also reported to di-
minish tic severity in TS, in a large case series (132); con-
trolled studies with this agent are in progress. Obviously,
such putative therapeutic effects may provide clues relevant
to the pathophysiology of TS. Various other agents, ranging
from opiate antagonists to androgen antagonists, have been
reported to have beneficial effects on tic symptoms; gener-
ally, these effects have been modest (133) or accompanied
by a worrisome liability for side effects (134).

certain intractable and localized tics have also been
treated successfully with repeated injections of botulinum
toxin. Generally, tic location and type shift across the course
of an illness, so such a “peripheral” approach may be effective
only for short periods of an illness. Still, substantial
case series evidence suggests the utility of this approach for
some patients, and even vocal tics have been treated effect-
vively with botulinum toxin (135). At another extreme,
habit reversal therapy involves the application of cognitive
and behavioral therapy principles to TS (136), analogous
to the successful use of these therapies in the treatment of
OCD. Although studies with habit reversal therapy are only
now being completed, initial results appear promising, off-
ering the possibility of a true, “nonpharmacologic” ap-
proach to this disorder. Conceptually, once it is effectively
learned, habit reversal therapy may be easy to apply over a
period of years, to a variety of different types of tics.

One novel approach being studied in TS, as well as OCD
and depression, involves the therapeutic use of rTMS. Al-
though clearly at an investigational phase, technical ad-
vances in rTMS may ultimately allow localized, stereotoxic-
guided activation of frontal and striatal CSPT elements
implicated in the pathophysiology of TS. Proponents of
rTMS emphasize that the procedure can be administered on
an outpatient basis, at relatively low cost, without apparent
significant side effects. More heroic efforts for intractable
TS and OCD have included psychosurgical interventions,
particularly anterior cingulotomy or capsulotomy (80–82).
Even this more extreme approach is now being accom-
plished on an outpatient basis, through the use of a gamma
knife. However, the most promising psychosurgical ap-
proach may involve high-frequency electrical stimulation
after the placement of deep brain electrodes (137).

**Alternative Therapies**

The void created by a lack of fully effective medication
treatments for TS has been filled by *alternative therapies*,
as parents and patients use self-experimentation to identify
treatment strategies that work for themselves and then share
this information with others in the TS community. The
dissemination of this information has been greatly facilitated
by internet communications. Proponents of alternative ap-
proaches, which generally include nutritional and vitamin
supplementation, believe that these interventions are natu-
ral, safe, and effective and may be targeting a metabolic or
biochemical defect that underlies TS, but that has thus far
eluded detection by scientific investigations. Just as for con-
ventional therapies, symptom reduction with alternative
treatments must be interpreted in the context of the natural
waxing and waning course of TS. Perhaps even more so
than for conventional therapies, these alternative approaches
carry a potential for improvement based on expectation or
“placebo” effects. For an individual patient, a placebo effect
is not necessarily problematic, but tremendous cost and
hardship are created if such treatments are applied on a
larger clinical scale and ultimately fail to deliver the prom-
ised therapeutic benefit. Nutritional or related interventions
may be “natural,” but they ultimately cause biochemical
changes in the body and can impart significant side effects.
Other “side effects” occur when patients substitute these
alternative approaches for treatments that are known to offer
some efficacy and that keep them in contact with clinicians
who can monitor their overall medical condition. Ulti-
mately, it is critically important for these alternative treat-
ments to be tested in controlled trials, in which their tolera-
bility, safety, and efficacy can be established in an objective
manner. Unfortunately, the cost of such studies is often
prohibitive, and they are generally not a high priority for
funding from the pharmaceutical industry. Clinicians
should ask patients and parents whether alternative thera-
pies are being used, particularly if medications are being
added or changed, to avoid potentially harmful drug–drug
interactions.

**Treating Tourette Syndrome and Depression**

As is true with most neuropsychiatric conditions, comorbid-
ity of TS with affective disorders deserves special attention,
owing to the insidious and often profound morbidity im-
parted by depression. Comorbid affective illness accompa-
nying TS is generally sensitive to standard pharmacothera-
pies for these disorders. These can often be used in combination with anti-tic regimens, but the possibility of iatrogenic depression from dopamine antagonists should always be considered, because this may dictate a reduction in neuroleptic dose rather than the addition of an antidepressant. As with comorbid OCD or ADHD, it appears that comorbid depression can often cause a worsening of tics in TS, and there are reports of severe, refractory, mood-dependent tics in comorbid TS and depression that show dramatic sensitivity to electroconvulsive therapy (138,139). Whereas more representative epidemiologic data are necessary, the lifetime prevalence of comorbid mood disorders in TS patients seen in specialty clinics may be as high as 70%, comparable to that reported in patients with OCD (140).

**FUTURE DIRECTIONS**

Several lines of inquiry are positioned to make major advances in our understanding of the etiology and treatment of TS, based on the tremendous progress that has already been made in each of these areas:

The clinical “phenotype” of TS has been particularly well characterized. However, compared with motor and phonic tics, sensory phenomena in TS are relatively less well understood and are more difficult to study. A full understanding of the TS phenotype will clearly enhance research efforts, by permitting stratification in measures from all levels of analysis, from genetics to neuropsychology. Detailed clinical characterization, and the experimental analysis that it facilitates, will also be important in clarifying the potentially critical distinction between the form of TS that undergoes substantial remission by the early twenties and that which is lifelong and unremitting. This issue has tremendous importance, because these two “types” of TS are not generally (and often cannot be) segregated in genetic, neuroimaging, or other biological measures in this disorder. For example, it may not be appropriate to generalize to all forms of TS the biology that is described by neurochemical brain imaging studies, which, because of ethical concerns, exclusively involve adults with TS. At another level, current TS studies that include children will likely involve both “types” of TS, without any clear way to stratify this heterogeneous sample. A full understanding of the TS phenotype may also be of value in developing symptom “clusters” or “factors,” like those that provide meaningful segregating strategies in OCD.

Future efforts in TS neuropathology will result in the collection of an adequate number of well-phenotyped, optimally prepared brains, to permit meaningful studies. Through the efforts of the TSA Neuropathology Program and the Harvard Brain Tissue Resource Center, approximately three new, optimal TS brains are collected each year, and in 1998, eight TS brains were cut for neurochemical and neuroanatomic studies. A common “library” of matched control tissue is also being collected, to diminish variability across different studies. These systematic efforts, combined with the judicious but timely distribution of brain tissue for studies, should help to overcome many of the limitations of past TS neuropathologic studies. Our ability to utilize this material effectively and to interpret the information that it provides depends entirely on our progress in understanding the complex interconnections within CSPT circuitry. Although we have useful maps of the major thoroughfares within CSPT circuitry, we will need to be equally knowledgeable regarding the detailed input-output relationships of functionally and neurochemically distinct striatal subterritories. Important pathologic findings can be lost if they are unknowingly averaged across heterogeneous anatomic domains.

**Neuroimaging** efforts in TS will focus on two strategies that have been so informative in studies of OCD: pretreatment versus posttreatment repeated measures and on-line behavioral or psychophysiological probes in conjunction with functional imaging. Nonpharmacologic treatment effects on regional brain metabolism or brain activation may be studied before and after habit reversal therapy, similar to such studies using cognitive and behavior therapy in OCD (141). Appropriate on-line probes for fMRI studies must be carefully developed. Optimally, these probes should either (a) detect deficits in patients with TS, or (b) in healthy persons, selectively activate relevant brain substrates, including the basal ganglia or frontal circuitries. Event-related fMRI techniques appear especially promising as investigators seek to identify the sequence of neural events that precede and follow tics.

Replication of the initial genome scan from the TSA International Sib-Pair Study is in progress, and fine mapping of the most promising regions is planned. Verification and extension of this work within several extended TS families are also anticipated. Parallel efforts will continue in targets of opportunity, including informative chromosomal translocations. Ultimately, genes conferring a risk of TS will be identified and cloned. Experience from similar efforts that are already completed with the Huntington disease gene suggest that identification of the TS genes will be followed by a substantial amount of work designed to understand their normal function and the pathologic impact of their abnormal products.

Even with the most detailed description of the “clinical phenotype” of TS, it is possible that a full understanding of the functional relevance of the “TS genes” will require the use of endophenotypes—physiologic or neuropsychological markers of gene function that can be identified in patients with TS and that could also be abnormal in unaffected, first-degree relatives. These markers could greatly enhance the power of linkage analyses, by allowing a “physiologic” parsing of the phenotype of affected and at-risk individuals. A variety of such markers has been explored in TS, including antisaccade measures (74), eyeblink measures of prepulse...
inhibition of startle (73) or condition-test paired pulse paradigms (76), and measures of cortical silent periods after rTMS (80). The neural bases of these various measures are consistent with our present conceptualization of CSPT substrates of TS, but the effect sizes of existing measures are small or moderate and thus are suboptimal for use in genetic analyses. This area of work in TS, however, has been relatively understudied.

Until recently, TS research suffered from the relative lack of informative animal models. Mutant rodent models may prove useful (142), particularly in understanding the behavioral and physiologic consequences of the selective loss of a specific neural element, such as the dopamine transporter (143). Essentially, such models provide a nonpharmacologic, nonsurgical means of studying the effects of a chronic perturbation in basal ganglia circuitry. Animal models can also be used, however, in guiding the development of candidate endophenotypes; particularly valuable would be measures that can be assessed across species and that can be shown in preclinical studies to have predictive or construct validity for TS.

One animal model that promises to be particularly informative regarding the neurobiology of TS involves the manipulation of the relative activity of medium spiny projection neurons within the striosomal and matrix compartments of the striatum (144). These two compartments differ with respect to their cortical inputs: striosomal neurons receive limbic and prelimbic inputs, and neurons in the matrix receive inputs from ipsilateral primary motor and sensory motor cortices. Dopamine projection neurons from the pars compacta of the substantia nigra serve to “tune” this system as it determines responsivity to certain cues (interoceptive or exteroceptive). As noted by Leckman and Riddle (145), this model may provide a meaningful integration of knowledge drawn from different perspectives that may be directly relevant to certain important clinical issues, including (a) the stress responsiveness of tics, (b) the presence of premonitory sensory urges and “just-right” perceptions, (c) the need to “even-up” sensory and motor stimuli in a bilaterally symmetrical fashion, (d) the reduction of tics when a person is engaged in acts that require selective attention and guided motor action, and (e) the timing of tics and the course of tic disorders. Such a model may also guide hypothesis-driven studies in other areas of TS research. For example, based on the distinct input-output characteristics of neurons in the striatal matrix versus striosomes, it may be useful to determine whether there is a differential involvement of these neurons in Sydenham chorea and postinfectious forms of TS. Even more subtle clinical distinctions within the “TS spectrum” may be predicted to reflect a differential involvement of these striatal components, with more affectively laden symptoms common to “tic-related OCD” reflecting the involvement of striosomal elements and more affectively “neutral” motor and sensory symptoms of “pure” TS reflecting the involvement of the striatal matrix (15).

Although several new therapeutic approaches to TS are being developed, as discussed earlier, there is clearly a significant need to understand the proposed role of streptococcal infections in the pathogenesis of TS and to assess the potential role of antistreptococcal or immunosuppressive therapies. Penicillin prophylaxis is gaining increasing use in patients with childhood tic disorders and OCD, without any controlled studies demonstrating efficacy for this approach; an analogous pattern has been seen in the recent rush for unproven, experimental treatments for autism (146). Certainly, repeated injections or even oral treatment with antibiotics can have detrimental consequences in children. Even more concerning is the increasing use of plasmapheresis or intravenous immunoglobulin therapies in affected children, with only preliminary data from controlled studies demonstrating efficacy for these costly and invasive interventions (147). Given the expanding clinical boundaries of streptococcal-associated conditions, controlled, large sample studies of penicillin prophylaxis in TS, and perhaps of other related therapies as well, should be a major priority from a public health standpoint.

**SCIENTIFIC HURDLES**

Major obstacles impede the search for the pathophysiology of TS. Serious ethical issues complicate invasive studies in children and affect TS research tools ranging from the use of radioisotopes in neuroimaging studies to the acquisition of meaningful age-matched control samples. The longevity of patients with TS is certainly a blessing, but it also precludes the availability of neuropathologic material for systematic studies. The lifelong interval between diagnosis and study increases the likelihood that the “lesion” will melt into the compensatory milieu of nervous tissue or will be camouflaged by the many other insults that befall an aging brain. The medical care of patients with TS is rarely focused on “end-of-the-life-spectrum” issues, and thus pediatricians and families rarely consider procedures for brain donation. Indeed, the optimal therapeutic approach to TS is often to downplay the notion of TS as a “disorder,” to not “pathologize,” but rather to emphasize the ways to survive and thrive with TS. Neuropathologic material is thus most readily available from persons whose TS has remained severe throughout adulthood and who are identified by family and physicians as being particularly impaired by this disorder. As noted earlier, refractory TS may reflect pathologic features quite distinct from the more common forms of this illness, and thus neuropathologic studies with tissue acquired from elderly patients with TS may not be generally informative about TS and potentially could be scientifically misleading.

Despite these hurdles, with centralized research coordination by the TSA, and increased attention to critical issues of clinical heterogeneity and comorbidity, future studies will
be much better equipped to overcome the obstacles that have left us, to date, with wide gaps in our understanding of the pathophysiology of TS. The formidable hurdles facing TS research are not unique to this disorder, but are equally relevant to conditions that span the range from primary movement disorders (148) to disorders with primary psychiatric manifestations (149). In this manner, the quest to understand the neurobiology of TS does serve as a practice question for more complex disorders, and the strategies developed to overcome challenging scientific hurdles will be invaluable lessons, with applications across a wide range of neuropsychiatric disorders.

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