Recent Developments in Neurobiology of Obsessive-Compulsive Disorder

Chairperson: Michael A. Jenike, M.D., Scott L. Rauch, M.D., Jeffrey L. Cummings, M.D., Cary R. Savage, Ph.D., and Wayne K.Goodman, M.D.

This section of The Journal of Clinical Psychiatry *summarizes the highlights of a symposium held on May 5, 1996, at the 149th annual meeting of the American Psychiatric Association in New York, New York. This symposium was supported by an unrestricted educational grant from Solvay Pharmaceuticals, Inc. and Pharmacia & Upjohn, Inc. The chairperson was Michael A. Jenike, M.D., Professor of Psychiatry at Harvard Medical School in Boston, Massachusetts, and Associate Chief of Psychiatry at Massachusetts General Hospital in Charlestown, Massachusetts. Also participating in the symposium were Scott L. Rauch, M.D., Assistant Professor of Psychiatry at Harvard Medical School in Boston, Massachusetts, and Director of Psychiatric Neuroimaging Research at Massachusetts General Hospital in Charlestown, Massachusetts; Jeffrey L. Cummings, M.D., Professor of Neurology and Psychiatry at UCLA School of Medicine in Los Angeles, California; Cary R. Savage, Ph.D., Instructor in Psychology in the Department of Psychiatry at Harvard Medical School in Boston, Massachusetts; and Wayne K. Goodman, M.D., Professor of Psychiatry at the University of Florida College of Medicine in Gainesville, Florida.*

Exciting new developments in the neurobiology of obsessive-compulsive disorder (OCD) and related disorders have emerged in the past few years, said Michael A. Jenike, M.D., chairperson of the symposium. The combination of advanced neuroimaging techniques along with collaboration between clinicians and researchers has contributed to greater understanding of the clinical implications as they relate to biological issues, he said. Dr. Jenike and fellow symposium presenters gathered to discuss the latest findings in neuroimaging, neuropsychology, and pharmacology and designed the conference to address the neurobiological and clinical implications of OCD, rather than the comprehensive treatment modalities for this disorder.

Neuroimaging in Obsessive-Compulsive Disorder and Related Disorders

Obsessive-compulsive disorder (OCD) occurs commonly and affects 1% to 3% of the population, said Scott L. Rauch, M.D. The disorder is characterized by obsessions, which are intrusive, repetitive, unwanted thoughts; and compulsions, which are repetitive behaviors performed in a stereotypical fashion in response to obsessions. The phenomenology of the disorder can be used to help understand the relationship between functional neuroanatomy and the clinical picture of OCD and related disorders. Currently, OCD is categorized as one of the anxiety disorders in the 4th edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). With some of the neurobiological data accruing, he said, we may question whether different OC spectrum disorders really belong together.

Tourette's syndrome (TS) is thought to be related to OCD and is typically included as one of the OC spectrum disorders, Dr. Rauch noted. The syndrome shares some phenomenologic similarities with OCD, such as repetitive tics; these are complex tics that can sometimes be difficult to distinguish from compulsions. As for comorbidity, probably a tenfold higher risk of repetitive tic disorders occurs in OCD. Additionally, probably a tenfold higher risk of OCD occurs in TS than in the general population. The examination of genetic data in some families indicates that (in some pedigrees) these two disorders may represent different manifestations of the same genetic anomaly. Pathophysiologically, both are considered to be corticostriatal disorders.

A heuristic about OCD and TS is, even though they are separate and distinct disorders, both are characterized by intrusions.[1,2] OCD is characterized by cognitive intrusions (obsessions) that result in compulsions. In the case of TS, the intrusions are sensations; spontaneous motor movements (tics) are actually performed in response to the intrusions. Both responses are carried out in an intentional manner and both disorders have accompaniments that might be characterized as affective. The accompaniment in OCD is anxiety, which accounts for its classi-

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fication as an anxiety disorder; in TS, the accompaniment is experienced as an urge. Anxiety is rarely present in TS.

Dr. Rauch then read a quote from Hippocrates (written in the 5th century B.C.): "From the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, grief, and tears." So, 250 decades before the Decade of the Brain, it was appreciated that the brain might be a good place to look for a better understanding of the phenomena of behavior, he said.

A universal concept is that different brain territories subserve different functions; contemporary neuroscientists believe that different brain systems subserve different functions. The heuristic that described cognitive intrusions versus sensorimotor intrusions, along with affective accompaniments for both OCD and TS, finds an analog in functional neuroanatomy. In the mid-1980s, Alexander et al.[3] first described segregated parallel corticostriatal pathways; i.e., pathways or circuits from specific territories in the cortex through specific territories in the striatum to specific territories in the thalamus and back again to the cortex by making a loop or circuit through the same territories.

Many theorists have used this model to describe different psychiatric disorders by relating each of these circuits to a different function; so that, a cognitive corticostriatal pathway runs from the lateral prefrontal and anterolateral orbitofrontal cortex to the caudate nucleus in the striatum, and the sensorimotor pathway runs from the sensorimotor cortex through the putamen, and the affective or motivational circuit runs from the paralimbic cortex (territories such as the cingulate cortex and posteromedial orbitofrontal cortex) through the nucleus accumbens. This paralimbic belt serves as a conduit from other cortical territories to the limbic system proper, and, for the most part, responds to information in a highly idealized fashion. The meaning and importance of information that comes through the brain are categorized in the paralimbic territories.

Dr. Rauch explained that this simplified version of the circuitry reflects present-day imaging resolution capabilities that cannot segregate out different subterritories of the striatum. In neuroimaging, the topography of dysfunction within the striatum may reflect (or actually govern) the clinical picture. Given this scheme, he said, one might surmise that OCD represents dysfunction within the cognitive corticostriatal pathway whereas TS might represent dysfunction within the sensorimotor pathway, and a variety of affective disorders (including anxiety disorders) might involve dysfunction in the pathway that mediates emotion.[4]

Currently, the place of neuroimaging in the assessment of OCD is fairly limited. The clinician occasionally orders magnetic resonance imaging (MRI) or computed tomography (CT) studies to rule out organic pathology. However, for the most part, functional neuroimaging studies are not indicated for the routine workup of OCD because the specificity and sensitivity for distinguishing OCD from other disorders (or from normal) are insufficient to make these tests of clinical utility.

Neuroimaging tools allow us to measure structure and function of the brain, said Dr. Rauch. Correlates of gross neuronal activity can be assessed by observing which territories are relatively more or less active. This is accomplished by making images that reflect metabolism or blood flow since both are tightly coupled to neuronal activity. Modalities used to acquire such images include positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional MRI. In general, if the blood flow in an area is high we can infer that brain activity is also high. In addition, neuroimaging tools are also available that allow us to characterize brain chemistry. It is worth mentioning, Dr. Rauch said, that we now have relatively noninvasive techniques, utilizing PET and SPECT, that characterize brain receptor systems in vivo. We can also measure the concentration of some compounds by using magnetic resonance spectroscopy.

Investigators perform morphometric MRI studies to review structural data by tracing different territories on every slide or section through a very high resolution acquisition of the brain in a group of interest, such as an OCD or a control group. The volume of the selected territory is then precisely calculated because volumetric abnormalities may be associated with the disease. Of the three contemporary morphometric OCD studies, all have found abnormalities in caudate volume—either increased volume of the right caudate, decreased bilateral caudate volume, or the suggestion of a rightward shift in caudate volume.[5–7] Although these studies found caudate volumetric abnormalities, the consistency of the findings was not impressive, Dr. Rauch noted. All three studies were done in a relatively small number of subjects with parameters that were varied, not only between individuals but also across gender and age. It may be that some of the different findings reflect the composition of the cohorts who were studied as well as the specifics of structure segmentation.

Investigators are now beginning to appreciate the fact that caudate volume is a dynamic parameter. It can change as a consequence of infection or medication, and can oscillate from day to day. Therefore, Dr. Rauch noted, the significance of a large or small caudate nucleus is not fully understood. We can only infer that anything other than normal volume may reflect dysfunction because clinical evidence of dysfunction has been seen in patients with both large and small caudate nuclei. In contrast, two groups studying TS had analogous findings of a rightward shift in volume within the putamen.[8,9]

Another volumetric study, by O'Sullivan et al.,[10] found abnormalities in patients with trichotillomania similar to those of patients with TS, i.e., a rightward shift of volume within the putamen. One might have predicted similar volumetric findings with TS and trichotillomania, said Dr. Rauch, because the phenomenology of trichotillomania is that of compulsive hair twirling—often preceded by sensations rather than by cognitions—performed in a somewhat unconscious manner. In analysis of the structural data, volumetric abnormalities were found in the caudate (the cognitive pathway) in the OCD group, and in the putamen (the sensorimotor pathway) in the TS and trichotillomania groups. Most of the functional neuroimaging data of OCD are from neutral state studies.[11] In neutral states, the function of the brain is studied in patients at rest; they are told to relax and do nothing while sitting in a dark room with the tracer uptake ongoing. Some convergence of the data in neutral state studies indicates hyperactivity or hyperfunction within the orbitofrontal cortex and the caudate and also in the anterior cingulate area—part of the paralimbic system that plays some role in emotion.

In addition to resting state studies using comparisons between OCD groups and control groups during a neutral state, numerous studies have measured brain function before and after treatment (medication and behavioral) in an OCD cohort.[12–14] When patients are scanned before treatment, hypermetabolism is seen in the caudate nucleus. After successful treatment, when their symptoms resolve, the activity within the caudate is reduced toward normal. An elegant study, performed by Baxter et al. at UCLA in 1992,[15] underscores the idea that hyperactivity of the circuit correlates with the symptomatic state in OCD. When patients improve, they no longer show hyperactivity within the system. Dr. Schwartz et al., also at UCLA, have since replicated those findings.[16]

The use of oxygen-15-labeled tracers to produce blood flow images has long been the workhorse of normal, human brain mapping. A whole realm of ongoing research is now being designed to better understand the functional anatomy of normal cognitive function, said Dr. Rauch. The technique involves imaging the subject for several minutes in different states, then mathematically and graphically contrasting the images. PET is used, by means of oxygen-15 tracers, to measure blood flow, which is coupled to neuronal activity. The brain activity profile associated with a baseline condition is subtracted from the brain activity profile associated with an activated condition, to yield a statistical difference image. In this way, the network of brain regions that are differentially active can be highlighted, and the mediating anatomy of the state or function in question can be inferred. Data may have to be averaged over a cohort of several subjects in the case of subtle activations, such as those associated with emotional state changes or cognitive functions.

This approach was used to determine the brain systems that mediated the symptoms of OCD, explained Dr. Rauch. The subjects were scanned twice during control states to improve the statistical power, and the patient helped to decide on the provocative stimulus to be used so that it would optimally provoke their OCD symptoms. The control state consisted of having the patient lie in the scanner and be touched with an innocuous stimulus (e.g., a sterile glove) that was matched with a provocative stimulus (e.g., a "dirty" glove). In this way, the contrast between activation during the provoked symptomatic state and the control baseline state could demonstrate graphically the brain system that mediated symptoms of OCD. When patients were having symptoms in the provoked state, activation of the orbitofrontal cortex bilaterally, the right caudate nucleus, and the anterior cingulate cortex—as indicated by increased regional cerebral blood flow (rCBF)—was associated with the obsessional state.[17]

When this study was replicated using functional MRI technology, the findings converged nicely.[18] Moreover, a small control of cohorts failed to show these activation patterns when exposed to comparable stimuli.

During these studies, investigators asked if the activation of blood flow could be a reflection of nonspecific anxiety rather than an OCD symptom. To answer that question, other provocable anxiety disorders were studied. By using analogous methodology, patients who had a phobia of small animals showed activation in the paralimbic system but no activation in the anterior orbitofrontal cortex or caudate nucleus. A script-driven imagery paradigm was used to study posttraumatic stress disorder and the findings again showed activation of the limbic and the paralimbic system, but no activation of the anterior orbitofrontal cortex or the caudate nucleus. Pooled analysis of PET symptom provocation studies across anxiety disorders, as well as a study of normal subjects given intravenous cholecystokinin tetrapeptide to induce anxiety, showed similar findings.

In conclusion, Dr. Rauch said, corticostriatal circuits are implicated in both OCD and TS. The frontal-caudate pathway is implicated in OCD, whereas (based on volumetric data) the sensorimotor-putamen pathway is implicated in TS. The limbic and paralimbic systems are implicated in nonspecific anxiety, both in patients with anxiety disorders and in normal controls.

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Obsessive-Compulsive Behavior in Basal Ganglia Disorders

Part of the excitement engendered by contemporary neuropsychiatry is the ability to look at the psychiatry of a neurologic illness (basal ganglia disease) and the neurology of a psychiatric illness (obsessive-compulsive disorder) and find a convergence of symptoms, said Jeffrey L. Cummings, M.D.

A large number of disorders affect the caudate nucleus and produce obsessive-compulsive disorder (OCD). These include Tourette's syndrome (TS), Sydenham's chorea, Parkinson's disease, and Huntington's disease. Neuroacanthocytosis is a rare autosomal recessive disorder that produces tics and OCD and affects the caudate nucleus similar to Huntington's disease. It is a remarkably sound model of the relationship between caudate degeneration and the occurrence of OCD and tics. Dr. Cummings also noted that one manifestation of basal ganglia calcification syndromes can be OCD, with or without tics. Caudate anoxia and ischemia also can produce localized lesions that may result in a tic syndrome with OCD. Rett's syndrome is a disease of young girls characterized by obsessions, compulsions, and stereotypical movements of the hands that resemble both tics and chorea. Patients with Lesch-Nyhan syndrome, another rare disorder, also have obsessions and compulsions; a particular compulsion (lip-biting) may lead to destruction of the lips.

Tourette's syndrome is a disorder characterized by tics and involuntary vocalizations that wax and wane. By definition, the disease begins before 18 years of age. Obsessions and compulsions are present in many TS patients; however, those patients may not meet the full criteria for OCD because the symptoms are of insufficient severity to be disabling. Approximately half of TS patients actually meet the criteria for OCD; among others, less severe obsessional and compulsive symptoms are common.

Evidence of increased dopamine activity within the caudate nucleus has been found in patients with TS. A study by Singer et al.[1] compared dopamine carrier sites (or transporters) in patients with TS and in controls, and found more carrier sites in both the putamen and caudate in the patients with TS. In the case of TS, we believe that the putamen abnormality is largely responsible for the tics, and the caudate abnormality is largely responsible for the obsessive-compulsive symptoms, Dr. Cummings said. An earlier study done at UCLA[2] used a modified Leyton Obsessive-Compulsive Inventory to score patients with pure OCD (without tics) against patients with TS, compared with normal controls. Although the mean scores for TS patients were lower than the mean scores for the pure OCD patients, the highest score in the study was achieved by a TS patient, and much variation was seen within that group. Samuel Johnson, as described by Boswell, was probably the most famous "tic-er" in history, according to Dr. Cummings. Johnson demonstrated that complete compatibility exists between superior intellect and an almost disabling case of Gilles de la Tourette's syndrome, he said.

Sydenham's chorea is a post-streptococcal infection with choreiform movements, and OCD or obsessive-compulsive (OC) behaviors occur in 70% of these patients.[3] There was evidence of dopaminergic hyperactivity, as in TS, and the patients had antineu-

ronal antibodies directed against components of the basal ganglia. A childhood version of an obsessional inventory was given which showed that intrusive thoughts interfered with daily activities in the children with Sydenham's chorea, but not in those children with rheumatic fever without chorea.

Parkinson's disease shows classic mid-brain pathology. As L-dopa is given to offset dopamine depletion in the putamen and caudate nucleus, tics and OCD emerge in states of L-dopa toxicity; 57% of these patients tested on an obsessional inventory scale have elevated OC scores.[4]

Huntington's disease is an autosomal dominant disorder characterized by chorea and dementia. Remarkable progress has been made in the last 3 or 4 years in defining the actual genetic mutation that causes the disease. Patients with Huntington's disease have 34 or more CAG triplicate repeats on chromosome 4, instead of the normal count of fewer than 27 repeats. This increase in the number of simple repeating units in the gene results in regional neurotoxicity to the caudate nucleus that causes degeneration—expressed in a variety of psychopathologic symptoms including irritability, apathy, depression, psychosis, mania, OCD, and OC behavior.

Dr. Cummings then made a case presentation of a 58-year-old male patient with late onset Huntington's disease who developed marked cleaning compulsions. The patient, with severe and advanced chorea, had typical cleaning compulsions and was constantly removing garbage from the house to outside bins. Prior to the onset of Huntington's disease, he had experienced no compulsions. Haloperidol treatment reduced his chorea but had no effect on the compulsions; he later showed a modest response to serotonin selective reuptake inhibitors. In general, Dr. Cummings said, the same therapeutic interventions are used whether the OCD is idiopathic or associated with basal ganglia disease.

A variety of globus pallidus disorders associated with OCD have also been described. These include postencephalitic parkinsonism, manganese intoxication, pallidal anoxia and ischemia, and progressive supranuclear palsy (a parkinsonian-like state).

Postencephalitic parkinsonism is an extremely important, historical disease, said Dr. Cummings. Over a million persons were victims of Von Economo's encephalitis in a worldwide pandemic from 1917 to 1929. Parkinsonism occurred in 80% of the survivors, usually within 10 years of the original encephalitis. One of the features of the resulting parkinsonian state was oculogyric crisis. Many of the patients had OCD within the context of the oculogyric crisis; i.e., they would have the compulsion to count to a thousand and their eyes could not come to midpoint until they reached that number. They might also have intrusive, violent thoughts during the oculogyric crisis but not at other times. This demonstrated a remarkable concurrence of two circuits—eye control and cognitive—involving forced ocular movements and forced thinking.

The globus pallidus is preferentially affected in postencephalitic parkinsonism. Focal pallidal lesions can also result from stroke and anoxia. The lesions are almost always bilateral when OCD occurs. A remarkable case in the literature described a patient who sustained a left-sided globus pallidus lesion with no development of OCD. She later had a second stroke with resulting right globus pallidus lesions. She was in an apathetic state but gradually recovered from the stroke, and then developed OCD. Perhaps the right-sided lesions were particularly important, said Dr. Cummings. The onset of OCD usually follows recovery from the focal event, so that apathy may evolve into OCD and parkinsonism may be absent or mild. Discrete lesions of the globus pallidus may be seen on both MRI and CT scan.[5]

Until 10 years ago, the basal ganglia were thought to be primitive motor structures involved in tremor and chorea. We are on the threshold of understanding them more profoundly, Dr. Cummings said, and we now know that they are critically involved in human emotion and cognition. Most disorders that produce OCD have bilateral anatomic lesions in the caudate and the globus pallidus only—the remaining areas of the basal ganglia, the temporal lobe, and the thalamus are not involved in OCD.

Five circuits outlined by Alexander et al.[6] connect the frontal lobe to subcortical structures, and different diseases may affect different levels of these circuits. Two of these circuits are particularly important for our understanding of obsessive-compulsive disorder, noted Dr. Cummings. Executive dysfunction can occur with injury to circuits including the dorsolateral prefrontal cortex, caudate nucleus, globus pallidus/substantia nigra, and the thalamus. OCD occurs as a result of injury to a parallel, independent, and segregated circuit that begins in the orbitofrontal cortex and projects to the caudate nucleus, the globus pallidus/substantia nigra, and the thalamus (Figure 1).

This is a working model of how OCD might be produced and how the syndromes that cause OCD fit into the same anatomical framework. Because of the close anatomical relationship, it is not uncommon to have both executive dysfunction and OCD in the same patient.

Glutamate is the transmitter to and from the cortex in this circuitry (Figure 2). It is used in the projection from the orbitofrontal cortex to the caudate nucleus and from the thalamus back to the cortex. Gamma-aminobutyric acid (GABA) is the primary transmitter between the basal nuclei. Although glutamate and GABA are the exclusive

transmitters within the basic anatomical framework, dopamine and serotonin are important modulating transmitters. Dopamine projects primarily from the substantia nigra to the caudate nucleus and the putamen, while serotonin projects primarily from the raphe of the brain stem to the globus pallidus. These transmitters also have different involvement in the circuits; when a dopaminergic agent is given, the motor circuit and parkinsonism is improved. A serotonergic agent affects the orbitofrontal circuit and OCD symptoms improve. This provides us with a pharmacoanatomy for understanding where drugs work. Drugs have very specific regional effects in the brain; they do not work diffusely. Measurements of glucose metabolism show hypermetabolism of the right caudate nucleus in the obsessive-compulsive patient compared with a normal control.[7]

Psychosurgery is not a frequent intervention, but is still considered in extreme cases of OCD. Surgical interventions include cingulotomy, subcaudate tractotomy, limbic leukotomy, and anterior capsulotomy. The two most successful surgeries—bimedial leukotomy and anterior capsulotomy—are those that follow the same precise pathway as the different disease states, those that disrupt the orbitofrontal subcortical circuit.

The neurologic evaluation of OCD should include the following considerations, said Dr. Cummings:

- Late onset of the disease should suggest a neurologic disorder because pure OCD typically begins early in life.
- Since OCD frequently occurs in families, the absence of a family history should suggest an acquired OCD.
- A careful neurologic examination is mandatory for detection of early parkinsonism or mild chorea.
- A neuropsychological evaluation has a definite role in the assessment of an OCD patient.

Figure 1. Behaviorally Relevant Frontal-Subcortical Circuits

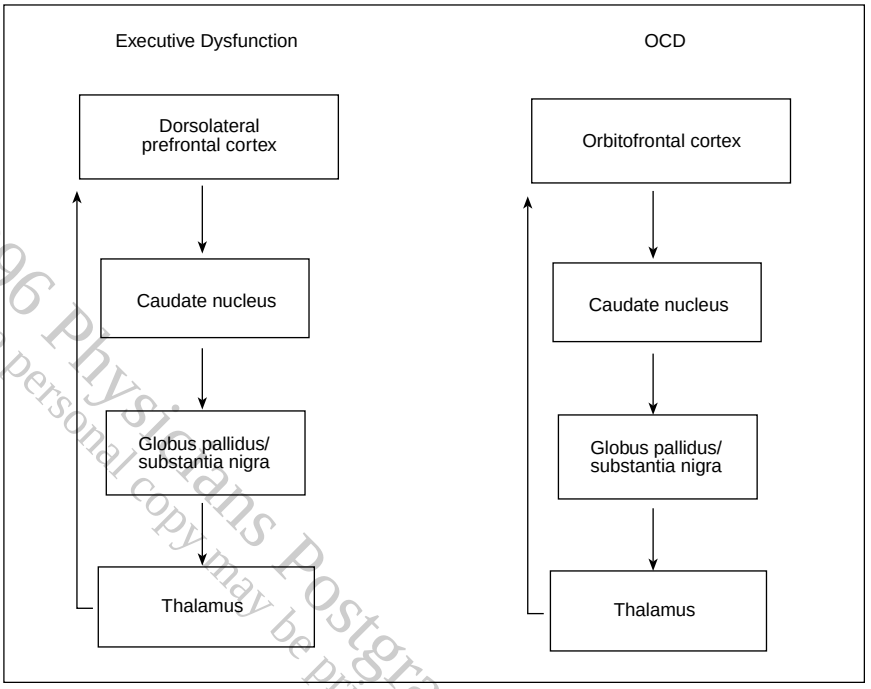
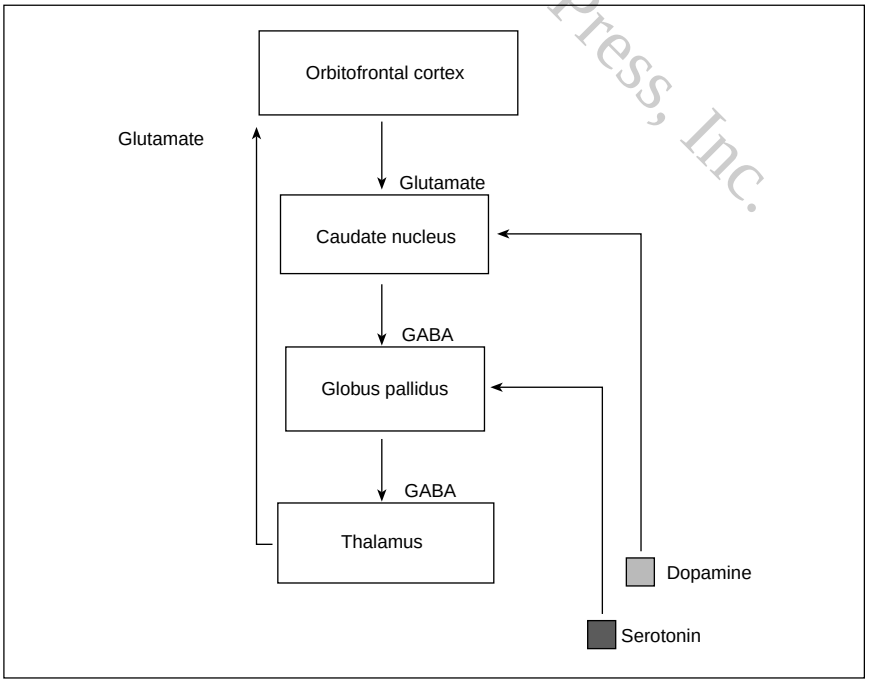


Figure 2. Orbitofrontal Circuit With Neurotransmitters



- If an acquired disorder is suspected, the laboratory workup may include:
  – an MRI, looking for structural lesions
  – blood tests including antineuronal antibodies, anticardiolipin antibodies, an ESR (erythrocyte sedimentation rate) and ANA (antinuclear antibodies) for collagen vascular disease that frequently affects the caudate nucleus, and an antistreptococcal DNase-B assay, the best test to detect a previous streptococcal infection.
  – a pregnancy test in a female of childbearing age because chorea gravidarum is a reactivation of the post-streptococcal choreic state.

In summary, Dr. Cummings reviewed the main points of the presentation. OCD occurs with caudate and globus pallidus lesions. It can present as a pure, full-blown OCD state or as OC behavior—obsessions and compulsions that are not disabling but are definitely present phenomenologically and have diagnostic importance. The disorders can be mapped onto frontal subcortical circuits connecting the frontal lobe, the basal ganglia, and the thalamus. Direct and modulating transmitters suggest a pharmacoanatomy that is the basis for intervention with SSRIs. Finally, there is a neurological differential diagnosis for OCD that needs to be considered when evaluating an OCD patient.

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Neuropsychology of OCD: New Findings and Applications

Neuropsychology, according to Cary R. Savage, Ph.D., is a branch of psychology that focuses on the study of the relationship between the functioning of the brain and cognitive processes of behavior, specifically, higher cognitive functions such as memory, spatial abilities, and language. The neuropsychologist is interested in brain function (or dysfunction) and how it affects the mental life of a patient. Many neuropsychologists have their own perspectives on psychiatric disorders such as obsessive-compulsive disorder (OCD), said Dr. Savage. Neurologic disorders that affect the corticostriatal system such as Parkinson's disease and Huntington's disease are well-defined, and the cognitive characteristics of these disorders have been used to develop concepts that can be specifically tested in patients with OCD.

Cognitive difficulties may be the outcome of brain dysfunction, but they may also be part of the problem itself, in effect, creating a vicious cycle that maintains and compounds the obsessions and compulsions. Dr. Savage cited the example of a person who worries about catastrophic events that may happen when a stove is not turned off. If that obsession is compounded by a memory problem, then the memory deficit can contribute to the symptomatology.

Neuropsychology has several applications. It can be used to demonstrate the impact of changes in brain function on cognitive ability and the effect these changes can have on the daily life of a patient relative to work, school, and interpersonal relationships. Neuropsychologists are also involved in cognitive activation studies such as symptom provocation and functional neuroimaging. Neuropsychologists work to devise cognitive probes to activate particular brain systems. As investigators focus on identifying key underlying cognitive problems, newer treatments may focus on the cognitive symptom as the point of intervention.

OCD patients frequently have abnormalities in the caudate nucleus and the frontal lobes. These regions form a distributed corticostriatal system that mediates certain cognitive abilities. Since the basal ganglia mediate important cognitive as well as motor functions, certain characteristic cognitive problems relate to the connections of the basal ganglia to the prefrontal cortex.[1]

Some OCD hypotheses have been developed by examining neurologic disorders such as Huntington's disease and Parkinson's disease. In addition to gross motor disability in these two disorders, difficulties also occur with higher level motor function such as planning and sequencing complex motor movements.

The term *executive functioning* refers to high-level functions that control lower functions. Persons with executive dysfunction have difficulties with attention and working memory—the ability to keep something in mind long enough to work with it. He cited the solution of a mathematical problem as an example of using working memory. One needs working memory to retain the problem long enough to perform the operations necessary to solve it. Persons with executive dysfunction

cannot easily initiate, maintain, and shift abstract mental sets. They cannot understand how things are related and then shift them (when appropriate) to see how they may be related in a different way. OCD patients also have difficulty planning and organizing material that impacts on their memory.

Dr. Savage said that patients with basal ganglia disorders tend to have visuospatial disabilities that influence how they operate in the outside world. These disabilities include poor constructional ability (drawing) and lack of understanding how pieces come together to make a whole. Another characteristic of patients with basal ganglia disease is difficulty with explicit (or conscious) memory. Memory is a three-stage process that includes encoding (the learning of material), storage (the ability to maintain material over time), and retrieval (the ability to recall the material at will). Patients with basal ganglia disorders have difficulty with the encoding and retrieval aspects of memory; this is the case with OCD patients as well.[2]

Studies of neurologic disorders point to the important effects of disease on prefrontal systems. Increasing evidence shows that cognitive problems in OCD patients may be associated with corticostriatal system function, including difficulties with nonverbal memory, visuospatial skills, and visual attention (the ability to focus attention on the visual world). Memory problems may be the result of frontal system dysfunction that leads to impairment in executive functioning. If a person has difficulty with planning and organization of material, it may affect how memories are encoded and retrieved. These patients do not forget information; because of organizational problems, they have difficulty in the initial absorption of material. Subsequently, they have difficulty retrieving those memories because of the way they were encoded.

Investigators are interested in how executive functioning relates to nonverbal memory, said Dr. Savage. Until recently, it has been difficult to link memory findings to specific underlying brain systems. The Rey-Osterreith Complex Figure Test[3] provides a measure of both construction and nonverbal memory. Other tests that measure executive functioning are the Odd Man Out Test, that measures the ability of the individual to initiate and maintain an abstract mental set, and the Visual Verbal Test, that measures the ability to shift mental sets.

When taking the Rey-Osterreith Complex Figure Test, the subject is asked to look at a complicated figure and draw it (construction), then asked later to recall the figure from memory and draw it again (nonverbal memory). This test also has a significant executive function component that is reflected in the way the person organizes the initial drawing. Dr. Savage then asked members of the audience to take the test in order to appreciate its use in recent studies. He explained that when study subjects took the test, colored pencils were shifted every 15 seconds to assess organizational strategy. In his studies using this test, control subjects have usually had an organized approach and have focused on large objects, whereas OCD patients have concentrated on "details, details, details." All these details are difficult for the brain to remember, he said. The brain is expecting rectangles, crosses, and triangles, and is getting nonsense instead.

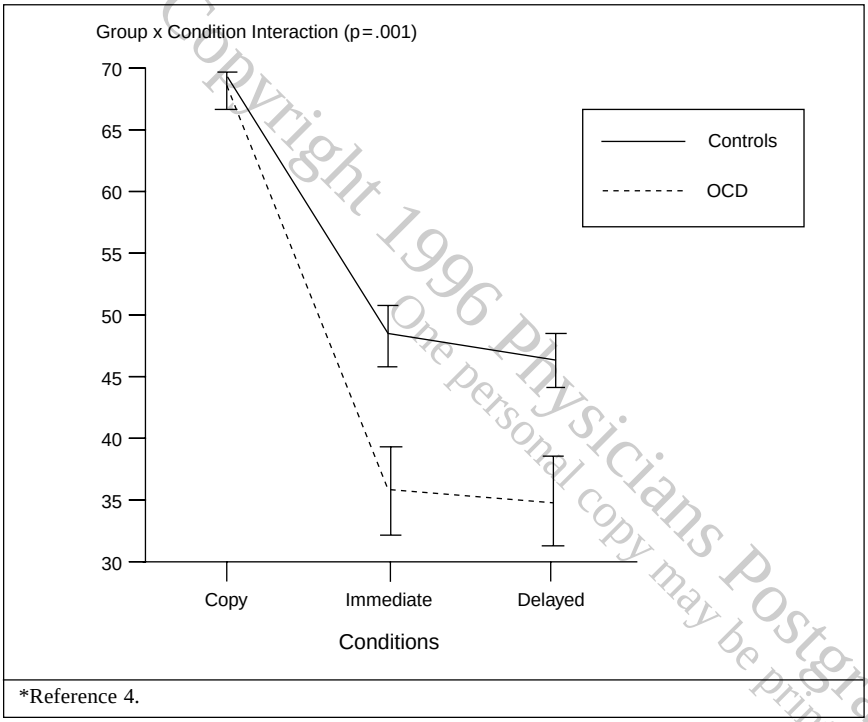
Investigators think that patients with OCD (and other frontal system disorders) may have more of a problem with executive function—i.e., how they organize when they copy the figure—than with memory. Dr. Savage presented a drawing to the audience that was done by a 32-year-old patient with OCD. The patient was articulate and intelligent, with a master's degree in education, and an intelligence quotient (I.Q.) of 132. The original drawing had no overall contour or shape, and it was so disorganized that the patient had difficulty recalling it later.

Dr. Savage then presented a study that looked specifically at the mediating effects of executive functioning on nonverbal memory and OCD. Twenty right-handed OCD patients were compared with 20 controls who were matched for age, education, and estimated verbal I.Q. All subjects took the Yale-Brown Obsessive-Compulsive Scale, the Maudsley Obsessive-Compulsive Inventory, the Beck Depression Inventory, and the Beck Anxiety Inventory. None of the OCD patients had taken medication for at least a month, they were not depressed, and they were free of other comorbid psychiatric disorders.

Subjects were given the Rey-Osterreith Complex Figure Test. Investigators looked at accuracy—the way the figure was drawn in relation to the model—and at organizational strategy. The subjects were asked to copy the model, to draw it from memory (immediate recall), then to draw it again after 30 minutes (delayed recall). An organizational score was calculated and measured against performance, based on memory. Both groups copied the figure accurately, but the OCD subjects did not learn as much information from copying the figure as the control group, so that there was a significant difference between the two groups in immediate and delayed recall (Figure 3).

This interaction indicates that this was a problem in learning new information not a memory problem. The inability to learn and recall new information can contribute to some of the symptoms that OCD patients exhibit, he said. The investigators also tested a mathematical model to explain the impact of organization on retention of information between the controls and OCD subjects. Initially, there was a significant difference in retention between the groups; the OCD patients did not learn as much information after copying the figure. When organization

Figure 3. Rey-Osterreith Complex Figure Test*



*Reference 4.

was included as a mathematical covariant, Dr. Savage said, investigators could explain most of the variance in the groups. Once the effects of organizational impairment were considered, the memory differences were no longer significant.

These studies showed that disturbances in executive function play a significant role in nonverbal memory problems in OCD and the results were consistent with current theories of corticostriatal system dysfunction in OCD. Neuropsychologists hope to use knowledge of specific cognitive strengths and weaknesses to design new, adjunctive treatments to complement existing medication and behavioral therapies for OCD patients, especially those who have been treatment-refractory. For example, after determining the impact of organizational problems on nonverbal memory, the OCD patient could be taught strategies to compensate for organizational deficits that might have an impact on memory-related symptoms.

Neuropsychology may one day be part of the overall evaluation and treatment plan formulation for OCD. Information obtained from neuropsychological research can be used to guide treatment, to evaluate the effectiveness of treatment, and perhaps to target specific cognitive characteristics and underlying brain functions. Neuropsychological techniques are highly cost effective and noninvasive and may be a useful means of evaluating patients in the future.

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Neuropharmacology of Obsessive-Compulsive Disorder

Great strides have been made in the treatment of obsessive-compulsive disorder (OCD) in the past decade, said Wayne K. Goodman, M.D., because of the advent and refinement of serotonin reuptake inhibitors (SRIs) and antidepressants. Three drugs now have FDA approval for the treatment of OCD: clomipramine, fluvoxamine, and fluoxetine. Despite these advances, only 40% to 60% of OCD patients respond to SRI monotherapy, and even those patients we call responders may have only a partial response, he said. A number of pharmacologic approaches have been employed; a combination of behavior therapy and drugs likely provides the most effective treatment for OCD.

The strategy for combining SRI agents with other drugs is to select a medication that acts on the serotonin system in a way that is synergistic or additive. A few agents have shown encouraging results based on this strategy. Unfortunately, there have been few controlled studies and those that were done (in the cases of lithium and buspirone) had negative results. Pindolol may be familiar as a β–blocker, but it is also a 5-HT_{1A} antagonist. Based on some preclinical studies and studies in depression, there is reason to believe that it may act to accelerate or enhance serotonergic transmission. Pierre Blier had insignificant to mixed findings in using a combination of pin-

dolol with an SRI in the treatment of OCD.

In response to increasing numbers of nonresponders, clinicians have given consideration to the use of neuroleptics for the treatment of OCD patients. While standard neuroleptic treatment does not seem to be indicated in the general treatment of OCD patients, Dr. Goodman stated, certain target groups might respond to a combination of an SRI and a neuroleptic. These target groups include OCD patients that meet Axis-II criteria for schizotypal personality disorders—the patients for whom Dr. Jenike has coined the term *schizo-obsessive*. Patients with OCD who cross the line and become frankly delusional and patients with delusional depression might also respond to a neuroleptic. Research has also focused on the relationship between OCD and Tourette's syndrome (TS) and the possible role of neuroleptics in the treatment of these disorders, he said. Multiple and converging lines of evidence indicate that the neuroanatomical seat of OCD may be the basal ganglia.

The textbook definition of tics places emphasis on the involuntary nature of the movements, a distinction that may help to differentiate tics from compulsions. However, many tics (particularly complex tics) can be suppressed for seconds, minutes, or even hours. A compulsion characteristically occurs after an obsession and is preceded by a thought that seems to drive the behavior. However, in a minority of cases, some compulsions may occur without a preceding thought. It becomes particularly difficult to differentiate tics from compulsions in patients with tic-like compulsions and complex motor tics. An example of this behavior is in a person who must repeatedly touch or tap the surface of a doorway when leaving a room. The way to decide if this is a tic or a compulsion is to ask why the behavior is being performed. If the behavior is preceded by a thought that seems to drive it, we tend to call it a compulsion. If there is no ideation behind the behavior (like an itch that must be scratched), we are more likely to call it a tic. We are also more likely to call the behavior a tic if there are other tics occurring at the same time, Dr. Goodman noted.

Some studies have suggested that certain types of OC symptoms are more common in those patients who have both tics and OCD, particularly obsessions with symmetry or exactness, counting compulsions, and evening-up behaviors. Dr. Goodman and colleagues conducted a study[1] in which the types of OC symptoms were compared between a group of 35 OCD patients with tics and a matched group of 35 OCD patients without tics. A remarkably high degree of overlap in the types of obsessions was noted between the two groups. However, there were significant differences in compulsions between the two groups, particularly in compulsions involving touching, blinking, ordering, and counting. These differences were noted despite a conservative definition of compulsions—the patient clearly had to have a thought preceding the behavior.

Perhaps the most compelling data of a relationship between certain forms of OCD and TS come from family genetic studies that have found a much higher rate of tics, chronic tic disorders, and OCD in TS probands.[2] Differences do occur between the two disorders, however, noted Dr. Goodman. The number of males affected with TS is approximately three times the number of females, whereas equal numbers of males and females are affected with adult OCD (childhood OCD affects more males). The onset of TS occurs, by definition, in childhood; although the onset of OCD occurs before age 18 in 50% of patients, a number of patients (particularly females) have an adult onset.

As for treatment response, the SRIs are preferentially effective in OCD, whereas the dopamine D_2 antagonists, as well as clonidine, are the most effective drugs in suppressing tics. The fact that both serotonergic and dopaminergic systems have a modulating effect on elements of the basal ganglia circuit that are implicated in OCD and TS (see Dr. Cummings' presentation, Figure 1) causes us to wonder if certain cases of comorbid OCD and TS may require dual manipulation of those two systems to achieve adequate control of the OC behavior, Dr. Goodman said. McDougle and Delgado have published several case reports suggesting that certain cases of OCD with tics respond best to an SRI-neuroleptic combination.

In 1994, McDougle et al. published a double-blind, controlled study[3] in which a sample of OCD patients—enriched with patients who had a comorbid tic disorder—were given a serotonin reuptake inhibitor and a neuroleptic to reduce OCD symptoms. A careful attempt was made to differentiate tics from compulsions. The concomitant use of fluvoxamine and haloperidol significantly reduced symptoms of OCD in 11 of 17 fluvoxamine-refractory patients, including all 8 patients with comorbid tic disorders. Haloperidol was less effective in patients without tics.

These findings led us to review our total clinical experience of patients who had OCD and tics, said Dr. Goodman. We identified two groups of 33 patients each; one group with both OCD and tics, and the other group with OCD only.[4] Using the Clinical Global Impression scale, we found that the response to fluvoxamine in the comorbid tic group was 21% (N = 7) whereas the response in the group that had OCD alone was 52% (N = 17). The same response was reflected in the Yale-Brown Obsessive-Compulsive Scale. These findings suggest that comorbid tics may be a poor prognostic indicator and may indicate that an individual is less likely to respond to SRI treatment alone.

Dr. Goodman emphasized that he is not suggesting that all OCD is related to TS; comorbidity data and family genetic studies indicate from 10% to 20% of OCD cases probably bear a biological relationship to TS. Nevertheless, that relationship is established at several levels, he said. Evidence based on segregation analysis data indicates that OCD and TS may be transmitted together as an autosomal dominant trait with mixed expressivity. This may be influenced to some degree by gender; a woman carrying the diathesis will likely express it as OCD.

Groundbreaking work on the relationship between OCD and another movement disorder has been done by Swedo and colleagues at the Child Psychiatry Branch of the National Institute of Mental Health, said Dr. Goodman. Swedo has recently proposed that Sydenham's chorea may serve as a medical model for some forms of childhood obsessive-compulsive disorder or Tourette's syndrome.[5] Sydenham's chorea is a late manifestation of rheumatic fever, which, in turn, is a complication of an upper respiratory infection with the group A beta-hemolytic streptococcus (GABHS). The lag time between the streptococcal pharyngitis and manifestations of chorea may range from 1 to 6 months, which may represent a problem in establishment of a diagnosis. Rheumatic fever with manifestations of carditis and arthritis has a latency period of 10 to 20 days.

Thomas Sydenham first described the syndrome of Sydenham's chorea over 300 years ago, but the inciting role of the streptococcus was not recognized until the 1930s. Sydenham's description of the condition was referred to as St. Vitus dance because of the role St. Vitus played as the protector of individuals who suffered from dancing mania. More likely, this mania was a form of mass hysteria. It is thought that the streptococcal infection triggers antibodies to the streptococcal bacterium that cross react with antigenic determinants (epitopes) of the host located in cardiac muscle and other tissues. This cross-reaction may also include some structures within the basal ganglia. In a study done some 20 years ago by Husby et al., circulating antibodies that were directed at the caudate nucleus and subthalamus were isolated from patients with Sydenham's chorea; these antibodies also cross-reacted with elements of the streptococcal cell membrane.

The Jones criteria for rheumatic fever previously required some evidence of a preceding streptococcal infection, either from direct methods (throat culture) or from indirect methods (antistreptococcal antibodies) and major manifestations of carditis, polyarthritis, and chorea. In a modification of the Jones' criteria, it is now permissible to diagnose rheumatic fever if chorea alone is present plus some evidence of prior streptococcal infection. Antistreptolysin O titers (ASO) and antistreptococcal DNase B titers are examples of the general pattern of antibody response to streptococcal extracellular antigens. These titers rise quickly but begin to decline around 6 months after the streptococcal infection; thus, the levels may be equivocal at the onset of motor manifestations of Sydenham's chorea.

Rheumatic fever is a significant problem throughout the developing world. Since the mid-1980s, there has been a resurgence of cases in 25 states across this country with some feature different from previous outbreaks. The isolated streptococcal strains responsible for recent outbreaks seem to be less virulent with respect to producing symptomatic pharyngitis. In a survey of 173 cases, only 46% had clinically detected pharyngitis. If a streptococcal pharyngitis goes undetected, adequate treatment is less likely and the risk of rheumatic fever increases. In addition, these particular strains of streptococci appear to be more rheumatogenic, i.e., more likely to produce complications of rheumatic fever, in particular, chorea.

Swedo was prompted to investigate the relationship between Sydenham's chorea and OCD for two reasons, said Dr. Goodman. One, there was evidence that basal ganglia structures might be involved in the etiology of Sydenham's chorea. Second, earlier accounts had described OC symptoms as well as a wide range of other emotional and psychiatric problems associated with Sydenham's chorea. More recently, Swedo confirmed that OC symptoms were present in over 70% of patients with Sydenham's chorea,[6] and that a higher rate of OC symptoms occurred in patients who had rheumatic fever with chorea than in those who had rheumatic fever alone.[7]

In a group of 21 patients (predominantly female), Swedo reported that OC symptoms in patients with Sydenham's chorea were indistinguishable from those found in the idiopathic condition.[8] In contrast to usual case histories of OCD, Dr. Goodman said, the onset of OC symptoms in the Sydenham group was abrupt and usually preceded the onset of choreiform movements. Unlike most cases of OCD—that tend to follow a more chronic trajectory—the course in these patients seemed to be episodic. Other psychiatric symptoms observed were separation anxiety, emotional lability, inattentiveness, and hyperactivity.

In addition to chorea, tics and dystonic movements were also described in Swedo's studies. Dr. Goodman pointed out that a wide array of involuntary movements occur in both Sydenham's chorea and Tourette's syndrome. In fact, he said, not all involuntary movements in Tourette's syndrome are tics; some may be characterized as dystonic or choreiform movements. The mean duration of chorea was 6 months (with a range up to 21 months) and 24% (N = 5) of the cases had Sydenham's chorea as the only mani-

festation of rheumatic fever. The earliest motor sign in these cases was loss of fine motor control; teachers would often detect handwriting problems in children who formerly had good penmanship. A cardinal sign of motor impersistence, or loss of fine motor control, is "milkmaid's grip"—the inability to maintain a tetanic contraction. Two percent to 3% of patients infected with GABHS develop rheumatic fever and 10% to 30% of rheumatic fever patients develop Sydenham's chorea. Pathogenic factors, host-related factors, and familial tendencies all determine the vulnerability of patients to develop both rheumatic fever and Sydenham's chorea.

A monoclonal antibody, referred to as monoclonal antibody D8/17, has been developed by Zebriskie and colleagues at Rockefeller University. The antibody was originally prepared from mice that were immunized repeatedly with B cells or B lymphocytes from a patient who had rheumatic carditis. A monoclonal cell line of the antibody was then developed that recognizes a B-cell antigen present in all patients with rheumatic fever and in 7% of controls. Dr. Goodman emphasized that this is not a test for circulating antibody levels; rather, it measures the percentage of peripheral B lymphocytes that express the D8/17 antigen. The percentage of positivity is highest in index cases of documented rheumatic fever, intermediate in noninfected family members, and low in controls. This monoclonal antibody may ultimately serve as a marker for both the susceptibility and presence of rheumatic fever.

Another D8/17 positivity study by Murphy et al.[9] was conducted on clinic patients, aged 7 to 24 years, with a childhood onset of OCD or TS. In the 31 patients who participated in the study (mean age of 14 years), 29% (N = 9) had pure OCD, 16% (N = 5) had pure TS, and 55% (N = 17) had both OCD and TS. The subjects were matched by 21 healthy controls with a mean age of 13.9 years. The number of males in both the patient group (22 males/9 females) and the control group (12 males/9 females) reflected the higher rate of TS in males. An indirect immunofluorescent assay was used to evaluate the D8/17 antigen present on B cells or B lymphocytes. An arbitrary figure of greater than 12% expression of lymphocytes was used because it represented 1 SD above normal values.

All 31 patients and 1 control showed an elevated percentage of D8/17 antigen. No significant differences were found between controls and patients in ASO titers and antistreptococcal DNase B assays—two standard tests for extracellular products of streptococcal infection. No evidence of rheumatic carditis occurred in any of the patients. ACHO, an antibody directed against the cell membrane of the streptococcus bacterium that is elevated in nearly all patients with rheumatic carditis, was not present in either group. An insignificant but slight increase of circulating antineuronal antibodies—prepared from postmortem human caudate and putamen tissue—was found in the patient group.

An increase in peripheral B cells expressed in D8/17 antigen occurred despite the absence of documented rheumatic fever or Sydenham's chorea in this cohort. Retrospectively, one could reconstruct the histories and argue that as many as four patients had a preceding pharyngitis with a clinical picture that might have been diagnosed as Sydenham's chorea had they gone to a neurologist first. By and large, all of these patients would have been recognized as having OCD and TS.

In conclusion, Dr. Goodman stated that his conservative interpretation of these findings is that D8/17 may serve as a common marker for vulnerability, not only to the development of rheumatic fever but also to the development of some forms of childhood-onset OCD or TS. Sydenham's variant of OCD should be considered in a child with an acute onset of adventitious movements, hypotonia, and behavioral changes. An inquiry into the possibility of a preceding streptococcal pharyngitis should be made, and serology should be obtained while searching for other major manifestations of rheumatic fever, including carditis and migratory arthritis. Treatment strategies, including plasmapheresis, intravenous immunoglobulin, prednisone, and penicillin prophylaxis, are now being studied by investigators at the Child Psychiatry Branch of NIMH.

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