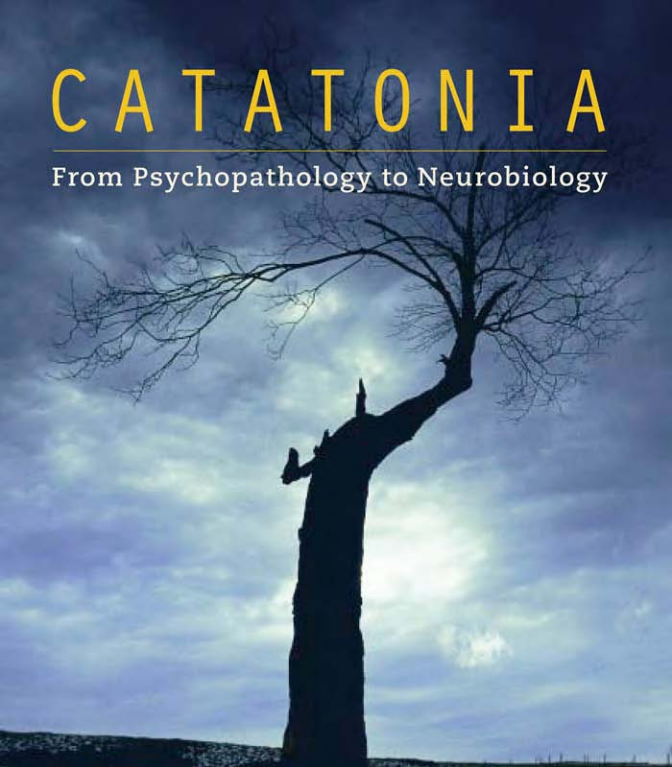
CATATONIA

From Psychopathology to Neurobiology



EDITED BY

STANLEY N. CAROFF M.D.

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PREFACE

There was a game called "Statues" played by children on the streets of New York City. In the game, children in turn were spun around by hand by one child who was chosen to be "it." Once released after spinning, the children had to freeze in whatever posture they assumed after coming to a stop. After all were frozen in place, the child who did the spinning watched for and called out the name of the first child observed to move, who then became "it," and the game began anew. Like many games and nursery rhymes, "Statues" most likely represents the use of mimicry by generations of children to overcome anxiety stemming from the observation of historical and frightful disease states—in this case, catatonia.

Apart from children's games, the phenomena associated with catatonia, especially catalepsy, are deeply ingrained in human culture and consciousness. The biblical depiction of Lot's wife becoming a pillar of salt as punishment for witnessing the terrifying destruction of Sodom and Gomorrah and the fearsome power of the Gorgon sisters in Greek mythology to turn victims to stone may represent two well-known examples of catalepsy from ancient Western literature. In common parlance in English, someone who is paralyzed with fear in the face of overwhelming stress is said to be "catatonic," "petrified," "stupefied," "struck dumb," or "scared stiff."

Catalepsy and stupor have also been recognized as clinical phenomena for at least two millennia (Berrios 1981; Johnson 1993; Lohr and Wisniewski 1987). Critical analysis and debate concerning the nature of these phenomena and their relationship with other neuropsychiatric conditions peaked in the nineteenth century. Although several influential authorities throughout Europe invoked catatonic signs in the classification of mental disorders, the modern concept of catatonia as a neuropsychiatric disorder of brain function is credited to and was popularized by Kahlbaum (1973) in his famous monograph of 1874.

During the twentieth century, interest waned and catatonia all but dropped off the agenda of mainstream psychiatric research. However, several dedicated research groups, represented in this volume, continue to report original data that highlight catatonia as a relevant and ideal subject for clinical study and research investigation. Catatonia is uniquely suited and ripe for neuropsychiatric research; it is a reliably and objectively observable motor disorder, easily measurable by standardized instruments; it is a frequent and integral part of the course of major psychotic disorders; it responds dramatically to specific drugs and electroconvulsive therapy (ECT); there are reproducible pharmacologic and behavioral animal models; and it has clear familial and genetic inheritance patterns. In addition, promising etiologic hypotheses testable by neuroimaging and neurophysiologic strategies have already been proposed. Focusing on the psychopathology and neurobiology of catatonia and related motor phenomena could provide an innovative, alternative research strategy in furthering understanding of the brain-behavior relationships involved in psychotic disorders.

The clinical significance of catatonia is obvious and compelling. Catatonic phenomena are frequently encountered in practice and have important therapeutic and prognostic implications. There are three basic clinical skills related to catatonia that are necessary to achieve competence in the practice of psychiatry: 1) recognizing the signs of catatonia, 2) understanding that it is a syndrome caused by many disorders that affect brain function, and 3) knowing that it is effectively treated with benzodiazepines or ECT. However, viewing catatonia simply as a nonspecific syndrome responsive to somatic therapies fails to convey the true richness and diversity of catatonic phenomena and the potential significance of the syndrome in relation to the endogenous psychoses. Important questions remain concerning the clinical implications of differences between positive and negative symptoms, as well as acute and chronic, and retarded and excited forms of catatonia. The meaning of acute, excited catatonia observed during a manic episode may be entirely different from the meaning of chronic, retarded catatonia associated with schizophrenia or postencephalitic states. Other unresolved and relevant clinical issues include the relationship between catatonia and extrapyramidal disorders; the prevalence and validity of idiopathic catatonia; and the reconciliation of nosologic, physiologic, and genetic findings based on the Wernicke-Kleist-Leonhard system with other diagnostic systems. We believe that greater awareness of the wealth of knowledge on catatonia derived from historical and contemporary work will directly enhance management and improve outcomes for patients with serious mental illnesses.

We organized this book with these promising research and clinical opportunities in mind, together with the endlessly fascinating history, nosology, phenomenology, and treatment responsiveness of catatonia. Our purpose is to inform clinicians of the striking advances in scientific knowledge and evidence-based management of catatonia. We also hope to stimulate further clinical and basic investigations of this classical disorder. Finally, we hope to remedy the lack of availability of a current and comprehensive resource text on catatonia that reflects the wide-ranging and rigorous body of work and opinions of diverse international research groups.

We would like to acknowledge the gracious efforts and contributions of each of the chapter authors in describing their work. We also owe our gratitude to the editors and staff of American Psychiatric Publishing, Inc., for their patience and guidance. Drs. Brendan T. Carroll and Gabor S. Ungvari deserve special thanks for their collegial comments and editorial support. Dr. Ungvari deserves the credit for the wonderfully descriptive title of the book. We are deeply grateful to our parents, wives, and children for the sacrifices they have made and the absences they have endured in supporting us in this endeavor. We therefore dedicate this book to our families and also to our patients, from whom we have much more to learn.

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C H A P T E R 1

HISTORY

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Catatonia is a neuropsychiatric syndrome with a unique combination of mental, motor, vegetative, and behavioral signs. It was first described in relation to mental illness at a time when psychiatrists had just begun to associate psychiatric disorders with brain dysfunction. The subsequent history of catatonia is fascinating as an example of great minds creating great concepts and causing great misunderstandings.

In Kahlbaum's original concept of catatonia, all endogenous psychoses with prominent psychomotor symptoms were classified as a single disease entity (Kahlbaum 1874). Although his idea of catatonia as a single disorder was not shared by the majority of his contemporaries, the syndrome of Kahlbaum has remained a source of fascination for clinicians regardless of the changing trends in psychiatric theory. During the past 50 years, however, catatonia became a stepchild of clinical psychiatry and for a while disappeared into oblivion. Thus, it is not only of historical but of contemporary clinical relevance to review the development of the concept of catatonia across time. In this chapter we provide a comprehensive overview of the major historical influences on the concept of catatonia as a clinical disorder and of the psychiatrists who created them.

Catatonia or Tension Insanity (Kahlbaum)

Kahlbaum was one of the most important psychiatrists of the nineteenth century, in that he developed the first comprehensive scientific classifi-

cation of psychiatric disorders (Kahlbaum 1863; see Bräunig and Krüger 1999). Kahlbaum believed that mental illnesses were disorders of the brain that were best understood as "state-course entities"—that is, both the acute symptom manifestations and the longitudinal course were significant defining features. Thus, he was a strong supporter of empirically based scientific research in understanding psychiatric disorders (Bräunig and Krüger 2000).

Kahlbaum became well known for his monograph *Catatonia or Tension Insanity*, in which he described a cerebral disorder accompanied by mental (cognition and mood), physical (motor and vegetative symptoms), and behavioral (negativism, positivism, mannerisms, stereotyped/ritualistic and impulsive behavior) symptoms. In his view, catatonia was characterized by a strong association between motor and behavioral pathology. Using clinical descriptions, Kahlbaum showed that the majority of catatonic symptoms included motor and behavioral components; for example, negativism was expressed by noncompliant behaviors and by active resistance on the motor level. In addition, catatonia was considered a distinct disease entity. Its course consisted of a prodromal state, followed by an initial state, reaching its peak when catatonic symptoms were most severe, and ending with a period of symptom remission. This view was derived from the widely accepted nineteenth-century concept of *unitary psychosis*, according to which every patient with insanity passed through the same stages of illness (Neumann 1859).

On the basis of symptom severity and prognosis, Kahlbaum differentiated between three subtypes of catatonia. *Catatonia mitis* was the mildest and the most frequent form and consisted of melancholia with stupor. *Catatonia gravis* was a more severe form, which is equivalent today to a manic-depressive mixed state with catatonic features, or to schizoaffective disorder with catatonic features. The third subtype was *catatonia protracta*, or chronic catatonia, which Kahlbaum considered to be of marginal importance. This subtype was characterized by an insidious onset with mild catatonic symptoms, which slowly progressed to a residual state with persistent catatonic motor and behavioral symptoms.

On the symptomatic level, Kahlbaum emphasized dystonic muscle cramps, rigidity and stiffness, chorea-like movements, grimacing, trismus, mutism, stupor, stereotypies, mannerisms, verbigerations, excitement, negativism, and positivism. The term *tension insanity* was derived from the predominance of dystonic, stiff, and rigid symptoms in catatonia. It is important to note that chorea-like and dystonic involuntary movements were considered by Kahlbaum to be among the cardinal symptoms of catatonia. Similar to Kahlbaum, other early investigators included extrapyramidal disorders within the broader concept of catatonic phenomena (see Bräunig

1995; Rogers 1985). Kleist (1912) and Boström (1928) observed that dystonic crises occurred predominantly in the neck; around the mouth, lips, and eye muscles; and in the proximal limbs. Essentially, these symptoms had the same localization and phenomenology as neuroleptic-induced acute dystonia, suggesting a similar mechanism. Several authors described parkinsonian rigidity, chorea, and dystonia in patients with catatonia and emphasized the close association between catatonic movements and extrapyramidal motor disorders (Bleuler 1911; Dide et al. 1921; Farran-Ridge 1926; Guiraud 1924; Kahlbaum 1874; Kleist 1912, 1923; Kraepelin 1899, 1913; Leonhard 1935; Steck 1927; Sterz 1925; Wernicke 1900). In 1926, Reiter coined the term *dementia praecox parkinsonoides* to describe a psychotic motor syndrome characterized by immobility, mutism, and rigidity. Leonhard (1935) saw a particularly close relation among manneristic catatonia, parakinetic catatonia, and extrapyramidal motor disorders. The implications of these observations for distinguishing functional from organic disorders, and for the subsequent phenomenon of neuroleptic-induced extrapyramidal symptoms, remain subject to debate.

With the exception of some cases with poor and even lethal outcomes, Kahlbaum considered catatonia to have overall a good prognosis. In 1863, Kahlbaum had already differentiated between catatonia and hebephrenia. He emphasized that the two disorders differed in symptomatology, and he noted the poorer prognosis of hebephrenia. This view was supported by Hecker in 1871, who considered hebephrenia and catatonia to be clinically and prognostically separate entities. However, starting in 1877, there were increasing reports of chronic catatonias with severe residual states and of hebephrenias with motor symptoms (Arndt 1902; Aschaffenburg 1898; Brosius 1877; Schüle 1898). This development led to a critical reassessment of Kahlbaum's idea of a distinct catatonic disease entity. In addition, it paved the way to regarding chronic catatonia and hebephrenia as subtypes of a single disease process, which would be called *dementia praecox* by Kraepelin (1899).

In 1886, Schüle, another one of Kahlbaum's contemporary critics, wrote a chapter in a textbook on catatonia in which he differentiated between nonspecific catatonic syndromes in organic brain disorders and the true catatonias (Schüle 1886, 1898). Among his true catatonias were hysterical catatonia, catatonic-circular periodic degeneration psychosis, and catatonic-hebephrenic dementia. This concept was a precursor of today's classification of psychiatric disorders into psychogenic, mood, schizophrenic, and organic catatonias. Schüle (1867) also described delirium acutum, which was later termed *acute lethal catatonia* by Stauder (1934).

Catatonia and Dementia Praecox (Kraepelin)

On the basis of clinical observations (Figure 1–1), Kraepelin (1899) supported Kahlbaum's comprehensive nosologic approach and his interpretation of mental disorders as state-course entities. However, he challenged Kahlbaum's unitary concept of catatonia (Kraepelin 1893). He felt that mood disorders with catatonia were significantly different from chronic psychoses with catatonia in symptoms, course, prognosis, and etiology. Kraepelin considered juvenile catatonias with insidious onset and poor prognosis to be a separate diagnostic entity (dementia praecox, catatonic type) and thus considered only a very small portion of Kahlbaum's catatonic cases (catatonia protracta) to be true or primary catatonias. He stated that the catatonic subtype occurred in approximately 20% of dementia praecox cases (Kraepelin 1913). Kraepelin (1913) also noted the nonspecificity of individual catatonic symptoms and emphasized that they occurred in other disorders, particularly in organic brain disorders and oligophrenia. Kahlbaum's melancholia attonita and catatonia gravis were no longer part of Kraepelin's concept of catatonia. He renamed them "delirious mania" and "delirious melancholia" or subsumed them under manic-depressive mixed states.

Kraepelin's concept of catatonia differed in five aspects from that of Kahlbaum.

1. Catatonia does not follow a cyclic course and does not pass through several stages as the concept of unitary psychosis suggested.
2. Symptoms of volitional disturbance (e.g., negativism, positivism) are emphasized more than motor cramps and tension.
3. Catatonia is associated with a chronic course and a poor prognosis, (Kahlbaum had suggested a remitting course and a good prognosis).
4. Catatonia and hebephrenia are subtypes of the same disease process (Kahlbaum had placed them in two different categories).
5. Melancholia attonita, catatonic mania, and catatonic mixed states are excluded from the concept of chronic catatonia.

In addition, Kraepelin provided a more detailed clinical description of chronic catatonias and catatonic residual states.

Catatonic Symptoms as Manifestations of Freudian Complexes (Bleuler)

Bleuler (1911) renamed dementia praecox as schizophrenia and revised its definition. He also extended the inclusion criteria in that he stated that nei-

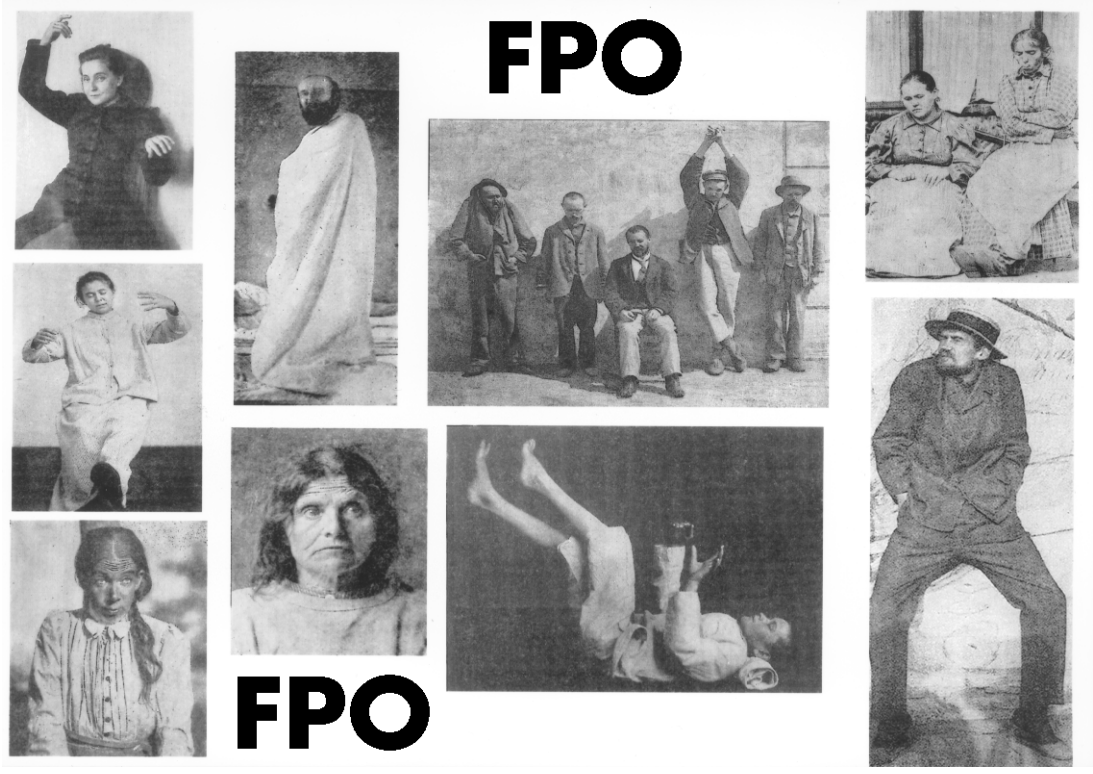


Figure 1–1. Catatonic patients observed by Kraepelin around 1916 in Universitätsnervenklinik Breslau.

ther the onset in late adolescence or early adulthood nor the chronic course or the poor prognosis was obligatory for the diagnosis of schizophrenia.

Bleuler (1911) considered essentially the same motor and behavioral signs as Kahlbaum and Kraepelin in defining the catatonic syndrome. He diagnosed catatonia in about 50% of his chronically hospitalized schizophrenic patients and interpreted catatonic signs as evidence of greater intensity of the illness. In contrast to Kahlbaum, Kraepelin, and Wernicke, however, Bleuler considered catatonic symptoms not to be connected in any way with each other or with other symptoms of psychosis.

Bleuler interpretation of catatonic symptoms was psychoanalytically based (Bleuler 1911). He rejected pathophysiologic explanations of catatonia (Kleist 1912; Wernicke 1900). According to Bleuler, catatonic symptoms were manifestations of subconscious Freudian complexes. However, he could not completely deny the biological origin of catatonic symptoms. Bleuler considered catatonic symptoms to be accessory symptoms and hence of lesser importance. His views influenced generations of psychiatrists, and over time, catatonic symptoms became marginalized in the diagnosis of schizophrenia.

Catatonia and Manic-Depressive Illness

Kahlbaum (1874) based his concept of catatonia on a single mood disorder, which he called *melancholia attonita*. He had observed several similarities in symptomatology, course, and prognosis between circular insanity and catatonia and therefore, in his view, the two disorders belonged to one nosologic category. Between 1875 and 1900, several other authors described periodic and circular psychoses with catatonic symptoms (Bräunig et al. 1998, 2000). These authors considered catatonia to be a marker of severity of periodic manias, melancholias, and other circular disorders. In Kraepelin's nosologic system, bipolar disorders with catatonic symptoms were classified as delirious mania, delirious melancholia, or mixed states (Kraepelin 1899). Delirious mania was diagnosed when motor activity was excessive, and delirious depression or depressive stupor was identified when motor inhibition was extreme.

Wilmanns (1907) was one of the first to give a comprehensive description of acute manic-depressive states with catatonic symptoms. Wilmanns emphasized that catatonia occurred predominantly in manic-depressive mixed states. Lange (1922) examined more than 700 patients with manic-depressive illness and found catatonic symptoms in 13% of the patients with mania and in 28% of the patients with mixed states. In North America, Kirby (1913), Hoch (1921), and Bonner and Kent (1936) described the occurrence of catatonic symptoms in manic-depressive illness.

Motility Psychoses (Wernicke)

Wernicke (1900) adhered to a neurologic model of mental illness based on the idea that all psychopathologic disorders were caused by interruptions in the continuity of association pathways. Wernicke was the first neuropsychiatrist to develop a completely pathophysiologic concept of catatonia. He did not use Kahlbaum's term *catatonia* but coined the term *motility psychoses* for those psychoses that were characterized by a predominant dysfunction of psychomotor activity (Wernicke 1900). He distinguished hyperkinetic, hypokinetic, akinetic, cyclic, complete, and compound types. He considered mania and melancholia in close association with hyper- and hypokinetic motility psychoses, just as he linked cyclic motility psychoses with manic-depressive illness. Rapid alternation of hypo-, hyper- and parakinetic symptoms or a mixture of these symptoms was termed *complete motility psychosis*.

Wernicke used the term *compound psychosis* for all acute psychoses in which episodes were characterized by various stages or a cyclic pattern. If catatonic or psychomotor symptoms were present during the course of such a compound psychosis, Wernicke applied the diagnosis "compound motility psychosis." Thus, according to Wernicke, Kahlbaum's cyclic catatonia was a compound motility psychosis. Wernicke's ideas were a source of inspiration for a later nosologically oriented clinical school, led by Kleist and Leonhard.

Cycloid Motility Psychoses (Kleist and Leonhard)

Kleist contributed significantly to catatonia research. He distinguished remitting bipolar cycloid motility psychoses from the chronic catatonic schizophrenias. Kleist (1912) separated all psychoses that had been subsumed by Kraepelin under the category *manic-depressive insanity* into those with and those without psychotic features, and he applied the term *cycloid psychoses* to those affective disorders that were characterized by mixed bipolarity and psychotic symptoms. Kleist (1928) later divided them into three groups: anxiety-elation psychosis, confusion psychosis, and motility psychosis. The latter term was chosen in accordance with Wernicke's nomenclature and described manic-depressive illness with predominantly motor symptoms.

Kleist (1912, 1928) emphasized that the early stages of acute episodes of motility psychoses were often characterized by pure manic or melancholic symptoms, whereas motor symptoms and psychotic or delirious fea-

tures were markers of greater severity of the mood disorder. Remission was characterized by pure mania or melancholia without motor features. The long-term course could be interspersed with manic and depressive episodes without disturbance of motility.

Kleist and Leonhard both stated that cycloid psychoses were part of Kraepelin's broad concept of manic-depressive insanity regarding phenomenology and course (Leonhard 1957). They considered the psychomotor symptoms of motility psychoses to be quantitatively but not qualitatively different from normal psychomotor activity. Psychomotor symptoms could be classified into symptom clusters of motor excitement or motor inhibition.

At the beginning of the twentieth century, several authors published reports of the association between episodic or periodic catatonia and manic-depressive illness (Gjessing 1960; Krüger and Bräunig 1995; Urstein 1912). In his nosologic system, Leonhard (1957) differentiated three groups of disorders with an episodic or cyclic bipolar course; manic-depressive illness (without psychotic features); cycloid or motility psychoses (with psychotic features, good prognosis); and unsystematic schizophrenias (with psychotic features, poor prognosis). In his view, periodic catatonia had an extremely poor prognosis and a high genetic loading and was a form of unsystematic schizophrenia. He believed that in periodic catatonia, patients at first exhibit the typical features and course of illness of bipolar disorder with catatonic features. As the illness progresses, cycle frequency shortens and the course becomes more chronic. Between episodes, patients exhibit negative symptoms. Leonhard (1957) emphasized that periodic catatonias were more closely related to bipolar motility psychoses and manic-depressive illness than to catatonic schizophrenia. According to Leonhard, the catatonic syndrome in periodic catatonia is characterized by the simultaneous occurrence of motor excitement and inhibition (e.g., psychomotor restlessness and rigid posture). Other catatonic symptoms (e.g., catalepsy and stereotypies) may occur in addition to this mixture of excitement and inhibition.

Catatonic Schizophrenias—A Group of Cerebral System Disorders

In considering schizophrenia, Kleist developed his "polytypical concept of schizophrenia" with several subtypes of hebephrenia and paranoid and catatonic schizophrenia (Kleist 1923, 1928, 1934). He felt that the group of psychomotor disorders called catatonia was not a single entity but a group of heterogeneous disorders (Kleist 1943). In analogy to some neu-

rologic disorders, he considered chronic catatonic schizophrenia to be a disorder of cerebral system degeneration. In several prospective studies published between 1938 and 1943, Kleist validated his observations on the long-term stability and homogeneity of his subtypes of schizophrenia. In addition, Kleist (1943) described organic catatonias—that is, catatonias based on infectious, vascular, and degenerative brain disorders, and brain injuries, tumors, and intoxications (see also Kleist 1934). The neuropathologic findings in these organic catatonias were the basis for Kleist's hypotheses on the dysfunctional neuroanatomy of catatonic schizophrenias.

Inspired by Kleist, Leonhard (1936) also delineated several subtypes of catatonic schizophrenia. Kleist and Leonhard collaborated in distinguishing among three opposite pairs of chronic catatonias in schizophrenia (Kleist 1943; Leonhard 1957). *Parakinetic catatonia* was characterized by abnormal involuntary movements that were mild and tic-like in the beginning and then became more severe and more bizarre as the illness progressed. In addition, patients with this type of catatonia exhibited impulsivity and symptoms resembling complex tics. In contrast, *manneristic catatonia* was characterized by bizarre and rigid movements; paucity of expression in speech, facial movements, and gestures; compulsive behavior; and rituals. Patients became robotlike and showed a paucity of spontaneous movements.

Speech-prompt and *speech-retarded catatonia* were characterized by vorbeireden and reduction of spontaneous speech and extreme motor inactivity, respectively. *Proskinetic* and *negativistic catatonia*, respectively, were dominated by symptoms of volitional disturbance (positivism, negativism) and by catalepsy (waxy flexibility or rigid catalepsy).

Catatonia in Childhood and Adolescence

Whereas Kahlbaum (1874) only briefly mentioned the occurrence of catatonic symptoms in childhood, subsequent authors covered this field in more detail. In 1909, Raecke described the occurrence of catatonic symptoms in 10 children between ages 12 and 15. Raecke believed that catatonic symptoms in childhood did not differ from those of adult catatonic schizophrenias. Pönitz (1913) coined the term *early catatonia*. He was one of several authors who emphasized the fact that many children with catatonic schizophrenia were misdiagnosed as mentally retarded (Neumärker 1995; Trott 1999). Catatonia in childhood disorders remains a neglected area of study.

Catatonia and Hysteria

Charcot (1886) demonstrated catatonic phenomena such as automatic obedience, waxy flexibility, and stupor in his patients diagnosed with hysterical disorders. Much later, Kretschmer (1920, 1927) described "hypobulia" in patients with hysteria and catatonia who had been severely traumatized or who experienced extreme anxiety. Kretschmer interpreted hypobulia as a lower level of healthy volitional function and, ultimately, a dysfunction of volition. In Kretschmer's view, negativism, positivism, impulsivity, and catalepsy were hypobulic symptoms. He considered hypobulia to be the link between hysteria and catatonia.

Catatonia and Obsessive-Compulsive Disorder

Obsessive-compulsive (OC) symptoms in catatonia had already been described by Kahlbaum (1874). In the twentieth century the phenomenologic and pathophysiologic connections between OC symptoms and specific catatonic symptoms in schizophrenia were discussed (Krüger et al. 2000). Heilbronner (1912) coined the term *progressive obsessive-compulsive psychosis* for disorders of childhood that started with OC symptoms and progressed into chronic psychoses. Jahrreis (1926) and Schneider (1925) described catatonia in schizophrenic patients with OC symptoms.

The Swiss school (Bleuler 1911; Kläsi 1922; Spoerri 1967) suggested placing OC symptoms and selected catatonic symptoms along a phenomenologic continuum (Krüger et al. 2000). In their classification of catatonic schizophrenias, Kleist (1943) and Leonhard (1957) considered the manneristic subtype to be associated with compulsive symptoms. Manneristic catatonia had its onset in childhood and was characterized by OC symptoms that became more bizarre over the years. Schizophrenic symptoms were also present from the outset and over time predominantly comprised bizarre behavior, mannerisms, stereotypies, and rituals. In support of this view, Faust (1953) found a high incidence of OC symptoms in families of patients with manneristic catatonia.

Conclusion

Despite nosologic differences, most classical researchers in the field of catatonia agreed on catatonic core symptoms that were necessary for a diagnosis of catatonia (Bräunig et al. 2000; Taylor et al. 1990). The catatonic syndrome consisted of generalized movement disorders (excitement or inhibition), abnormal involuntary movements and dystonias, stereotyped movements and behaviors, motor and behavioral positivism or negativ-

ism, rigidity and waxy flexibility, impulsive motor acts and behavior, and vegetative symptoms.

Kahlbaum's innovative concept advocating the use of motor symptoms in defining endogenous psychoses was of fundamental importance to psychiatry. Subsequently, the interpretation of catatonia strongly depended on the dominant psychiatric school of each epoch, and therefore, theories of unitary psychosis, brain dysfunction and degeneration, and hysteria, as well as psychoanalysis, all had their impact on the concept of catatonia. It is not difficult to understand that in addition to inspiring new ideas about catatonia, these sometimes diametrically opposed ideas and hypotheses resulted in confusion, lingering misconceptions, and misunderstandings.

With regard to the clinical heterogeneity of catatonia, the traditional psychiatric literature holds a treasure of empirical material. Although most historical authorities recognized the nonspecificity of individual catatonic symptoms, their important contributions to the significance of catatonia in understanding cyclic bipolar disorders and schizophrenias have been neglected. As long as our present concepts of mood disorders and schizophrenia remain reductionistic and fail to encompass findings on catatonia, research in this area will be hampered.

One approach to reconciling the various concepts of catatonia would be not to focus on the symptoms of catatonia but to regard catatonia as part of a motor-behavior continuum and to interpret it as an independent dimension reflecting a disturbance of executive function that cuts across diagnostic categories. The heuristic value of the concept of catatonia could lie in the fact that these symptoms reflect the association between motor and behavioral systems. For the last 130 years, this association has been repeatedly observed and described and may offer interesting ideas for future research.

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C H A P T E R 2

EPIDEMIOLOGY

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The recognition of catatonia as an important component of mental illnesses played a pivotal role in the early development of diagnostic systems based on empirical observation. However, catatonia receives only passing notice in current standardized diagnostic schemes and is considered to be esoteric (Mahendra 1981; Rosebush and Mazurek 1999; Stompe et al. 2002). What can account for this dramatic change?

To address this question, we reviewed the literature on the epidemiology of catatonia, keeping in mind Eagles's (1991) admonition that "[f]luctuations over time in the incidence of a disease can yield important information about its aetiology" (p. 834). We divided published data into three categories: 1) the cross-sectional incidence or prevalence of catatonia in a defined patient group at a particular site and time, 2) the change over time in the rate of catatonia in a defined patient group at a particular site, and 3) the distribution of underlying conditions diagnosed among catatonic patients at a particular site and time.

Rates of Catatonia

General Psychiatric Patients

Investigations of the rate of catatonia observed in general psychiatric populations are listed in Table 2–1. Differences in design and diagnostic crite-

ria between these studies limit comparisons and conclusions. Also, comparisons with studies of the incidence of catatonia conducted during the last decade are hampered by the lack of prospective studies prior to mid-century. Nevertheless, contemporary evidence from prospective studies indicates that catatonia continues to be reported among 7%–17% of patients hospitalized with acute psychotic episodes.

Patients With Mood Disorders

Similar to evidence on catatonia in general psychiatric populations, prospective data on the rate of catatonia among patients with mood disorders is limited in the historical record. However, catatonic signs have been observed consistently in association with mood-related illnesses, with rates ranging from 13% to 31% in the last century (Table 2–2). Although catatonia has been reported in both manic and depressed patients, several investigators observed that catatonic signs are particularly common in patients with bipolar disorder, patients with mixed manic episodes, and patients with more severe affective disease (Bräunig et al. 1998; Lange 1922; Starkstein et al. 1996).

Patients With Schizophrenia

There have been numerous studies in which the rate of catatonia in schizophrenia was reported (Table 2–3). Overall, differences in design and criteria among these studies may have obscured trends over time and, therefore, render conclusions moot (Lohr and Wisniewski 1987). Although several prospective studies in the last quarter century yielded rates of catatonia in schizophrenic patients of less than 5%, other studies revealed rates comparable to figures from early in the twentieth century.

Changes in Rate of Catatonic Schizophrenia at Single Sites

Several investigators compared the rate of catatonia among patients studied during different periods at single sites using consistent criteria (Table 2–4). For example, Leff (1981) wrote that records from the Bethlem Royal Hospital showed that catatonia accounted for 6% of admissions in the 1850s but only 0.5% in the 1950s. Referring to another London registry, Leff reported that catatonia accounted for only 1 (3.6%) of 28 first admissions for schizophrenia in 1965 and that no cases of catatonia were observed among first admissions in 1976.

Table 2–1. Rate of catatonia among psychiatric patients in general

Author(s)	Years	Study design	Rate	Diagnostic criteria	Sample *N*	Catatonia *N* (%)
Joyston-Bechal (1966)	1948–1961	R	I	Stupor	15,625	250 (1.6)
Guggenheim and Babigian (1974)	1960–1966	R	I/Pr	"Catatonic schizophrenia"	39,475	798 (2.0)
Fein and McGrath (1990)	1983–1985	R	I	≥5 signs	2,591	12 (0.5)
Pataki et al. (1992)	1985–1990	R	I	DSM-III	2,040	43 (2.1)
Rosebush et al. (1990)	1990	P	I	≥4 signs	140	12 (9.0)
Ungvari et al. (1994)	1992–1993	P	I	≥3 signs	212	18 (8.0)
Peralta et al. (1997)	1988–1995	P	I	≥1–2 signs	567	96 (16.9)
Bush et al. (1996a)	1996	P	I	≥2 signs	215	15 (7.0)
Lee et al. (2000)	1996–1997	P	I	≥3 signs	160	24 (15.0)
Peralta and Cuesta (2001)	1999	P	I	≥3 signs	187	32 (17.1)
Stöber (2001)	2001	P/R	I/Pr	DSM-III-R	749	183 (24.4)

Note. I=incidence rate; P=prospective; Pr=prevalence rate; R=retrospective.

Table 2–2. Rate of catatonia among patients with mood disorders

Author(s)	Years	Study design	Rate	Diagnostic criteria	Sample *N*	Catatonia *N* (%)
Lange (1922)	1922	R	Pr	—	700 (mania)	(13.0)
Taylor and Abrams (1973)	1972	P	I	—	52 (mania)	7 (13.5)
Abrams and Taylor (1974)	1972	P	I	—	50 (mania)	7 (14.0)
Taylor and Abrams (1977)	1972–1973	P	I	≥1 sign	123 (mania)	34 (27.6)
Starkstein et al. (1996)	1996	P	I	DSM-IV	79 (depression)	16 (20.2)
Bräunig et al. (1998)	1998	P	I	≥4 signs	61 (mania)	19 (31.1)
Krüger and Bräunig (2000)	2000	P	I	≥4 signs	99 (mania)	27 (27.3)

Note. I=incidence rate; P=prospective; Pr=prevalence rate; R=retrospective.

Table 2–3. Rate of catatonia among patients with schizophrenia

Author(s)	Years	Study design	Rate	Diagnostic criteria	Sample *N*	Catatonia *N* (%)
Bleuler (1911/1950)	1911	R	Pr	—	—	(50.0)
Kraepelin (1919)	1913	R	Pr	—	500	(19.5)
Thomas and Wilson (1949)	1949	R	Pr	—	70	12 (17.1)
Leonhard (1979)	—	R	Pr	Leonhard	833	295 (35.4)
Astrup (1979)	1938–1960	R	Pr	Leonhard	990	167 (16.9)
Guggenheim and Babigian (1974)	1960–1966	R	Pr	—	8,094	798 (9.9)
Mimica et al. (2001)	1962–1975	P/R	I	ICD-8	402	59 (14.7)
Morrison (1974)	1973	R	Pr	—	2,500	250 (10.0)
Carpenter et al. (1976)	1976	P	I	ICD	600	54 (9.0)
Saugstad (1989)	1977–1978	R	I	ICD	344	6 (1.7)
Manschreck et al. (1982)	1982	P	I	DSM-III	37	1 (2.7)
Povlsen et al. (1985)	1983	R	Pr	—	182	8 (4.4)
Kane et al. (1988)	1988	P	I	DSM-III	319	6 (2.0)
Naber et al. (1992)	1992	R	Pr	—	480	55 (11.5)
Simpson and Lindenmayer (1997)	1997	P	I	DSM-III-R	523	5 (1.0)
Cernovsky et al. (1998)	1998	P/R	I	—	112	45 (40.2)
Stompe et al. (2002)	1994–1999	P	I/Pr	DSM-IV	174	18 (10.3)

Note. I=incidence rate; P=prospective; Pr=prevalence rate; R=retrospective.

Table 2–4. Change in rate of catatonic schizophrenia at single sites

Author(s)	First period	Rate	Second period	Rate	Decrease
Leff (1981)	1850s	6.0%	1950s	0.5%	91.7%
Templer and Veleber (1981)	1905–1909	8.7%	1975–1979	2.0%	77.0%
Morrison (1974)	1920–1944	14.2%	1945–1966	8.5%	40.1%
Achte (1961)	1933–1935	40.0%	1953–1955	11.0%	72.5%
Hogarty and Gross (1966)	1953	38.0%	1960	25.0%	34.2%
Stompe et al. (2002)	1938–1968	35.4%	1994–1999	25.2%	28.8%

Templer and Veleber (1981) analyzed data on 54,839 patients with schizophrenia registered in Missouri between 1905 and 1979 and found a statistically significant decline in the percentage of catatonic patients. Similarly, Morrison (1974) reported a significant decrease in the catatonic subtype among schizophrenic patients admitted between 1920 and 1966. Comparing schizophrenic patients admitted between 1933 and 1935 with those admitted between 1953 and 1955, Achte (1961) found that the percentage of catatonic patients decreased from 40% to only 11%. Hogarty and Gross (1966) reviewed first-admission schizophrenic patients and found a significant decrease in catatonia between 1953, before psychotropic drugs were introduced, and 1960, when drugs were widely available. Stompe et al. (2002) compared their own data on catatonic schizophrenia with data from earlier studies by Leonhard (1979) using the same criteria and reported a significant decrease, from 35.4% between 1938 and 1968 to 25.2% between 1994 and 1999. Furthermore, Stompe et al. (2002) showed that the frequency of periodic catatonia remained stable for over 60 years, whereas the rate of chronic systematic forms decreased from 25% to 12.4%, accounting for most of the decline in catatonia. The selective decline in systematic catatonia had also been noted by Astrup (1979). In contrast to the studies just described, Guggenheim and Babigian (1974) maintained that catatonic schizophrenia had not decreased in frequency from 1948 to 1966. Apart from the last-mentioned study, these data support the impressions of clinicians (Grinker 1973; Mahendra 1981) that catatonic schizophrenia became less common during the course of the twentieth century.

Distribution of Disorders Associated With Catatonia

Conversely, the distribution of underlying diagnoses among series of patients who present with catatonia may be revealing (Table 2–5). Even among early investigators, catatonia was associated with a diverse range of neuropsychiatric and systemic disorders. Although Kahlbaum proposed catatonia to be a unitary form of insanity, 4 of his patients had neurosyphilis, 1 had peritonitis, 9 had seizures, and 11 had other neurologic findings (Berrios 1981; Carroll 2001; Kahlbaum 1973).

It is obvious from the data in Table 2–5 that catatonic signs are observed in a range of disorders and are not specific to any diagnosis. Catatonia has been associated more or less strongly with schizophrenia or mood disorders in different studies. Organic disorders have been associated with catatonia in about one-quarter of the cases. A smaller percentage of cases

Table 2–5. Percentage distribution of diagnoses among patients with catatonia

Author(s)	Schizophrenia	Mood				Other psychoses	Organic disorders	Personality/ conversion disorders	Unknown
		Total	Depressed	Manic	Mixed				
Joyston-Bechal (1966)	34		27				22	10	9
Abrams and Taylor (1976)	7	71	9	62		5	16		
Barnes et al. (1986)	4		35				36		24
Altshuler et al. (1986)	27		14			14	46		
Bush et al. (1996b)	7	50	11	32	7	4	21	11	4
Rosebush et al. (1990)	16	33				17	25	8	
Pataki et al. (1992)	37	37	5	32			26		
Benegal et al. (1993)[a]	29		25						46
Ungvari et al. (1994)[a]	44	28	17	11		11	6	11	
Fein and McGrath (1990)	33			67					
Lee et al. (2000)	67			17		8	4	4	4

Note. Numbers represent percentage of patients with each disorder as diagnosed by the authors.
[a]Excluded patients with organic disease.

of catatonia have been associated with conversion disorders. Catatonia could not be ascribed to any psychiatric disorder in some studies (Barnes et al. 1986; Benegal et al. 1993; Peralta et al. 1997), lending support to the conceptualization of catatonia in some cases as an independent idiopathic disorder, consistent with the views of Kahlbaum (1973) and the Wernicke-Kleist-Leonhard school (Leonhard 1979).

Discussion

There are several points for discussion that emerge from this review. Studies of the distribution of diagnoses associated with catatonia support the nonspecificity of the syndrome. Catatonic patients are diagnosed with varying frequencies as having schizophrenia (4%–67%) or mood disorders (14%–71%), depending on the population studied and the diagnostic preferences of the investigators. Organic disorders have remained a consistent cause of catatonia in 4%–46% of patients in case series, highlighting the importance of evaluation for organic disease in any patient presenting with catatonic signs. The occurrence of catatonia without classifiable psychiatric disorders may provide support for further study of the concept of idiopathic catatonic disorders (Benegal et al. 1993; Leonhard 1979). Studies of catatonia in association with reactive, personality, or conversion disorders also warrant consideration.

The more challenging question concerns changes in the rate of catatonia over time. Differences in methodology, as discussed next, limit definitive answers. We found that catatonia continues to be reported in 7%–17% of acutely ill patients admitted to psychiatric units. Catatonia has been reported in 13%–31% of depressed or manic patients studied in the last quarter century. By contrast, rates of catatonia among schizophrenic patients have varied widely. Although studies reviewed by Stompe et al. (2002) showed a significant decline in catatonic schizophrenia, we could not demonstrate consistent evidence of a decline across investigations (Table 2–3). However, studies of changes in the rate of catatonic schizophrenia at particular sites (Table 2–4) have demonstrated an average decrease of 57% during the twentieth century.

Methodologic Issues

The methodologic differences among studies of catatonia remain significant and underscore the lack of consensus on the definition of *catatonia*. Investigators have used the DSM, ICD, or Leonhard systems for diagnosing catatonia and underlying disorders, resulting in different rates. Differ-

ences in assessment techniques, definitions of symptoms, and thresholds for diagnosis limit comparisons. Although catatonia has been conceptualized as a syndrome, the clinical significance of even one catatonic sign has yet to be established. There have been few studies separately comparing retarded and excited forms of catatonia in relation to nosology, treatment, and outcome (Morrison 1973), yet these disorders do not necessarily represent the same process.

The issue of diagnostic stability further complicates estimates of the frequency of catatonia. Cross-sectional surveys of the incidence or prevalence of catatonia may provide an incomplete picture leading to underestimates of its occurrence in association with other disorders. For example, Hearst et al. (1971) reported that only 5 of 15 patients presenting with catatonia had been admitted previously with catatonic signs. They concluded that catatonia is a transient state-related phenomenon and that catatonia construed as a subtype of schizophrenia is not clinically meaningful. In the majority of cases, acute catatonic signs are present for less than 2–3 weeks in the context of disorders such as schizophrenia that endure for years (Lee et al. 2000; Ungvari et al. 1994). Guggenheim and Babigian (1974) and Mimica et al. (2001) further documented the inconsistency in the diagnosis of catatonia during the course of schizophrenia. In all studies, the incidence of catatonia increased in proportion to the length of follow-up. In addition, diagnoses of the underlying psychiatric conditions also changed with long-term assessment (Altshuler et al. 1986; Fein and McGrath 1990; Joyston-Bechal 1966).

Significant differences in results also stem from the choice of population studied. For example, there is consistent evidence that catatonia is diagnosed more often in developing nations (Carpenter et al. 1976; Chandrasena 1986; Lee et al. 2000) and in chronic institutional settings (Guggenheim and Babigian 1974). The incidence of new episodes of acute catatonia necessitating hospitalization is different from the prevalence of chronic catatonia in an institutionalized population. Acute and chronic catatonia may have very different etiologies that should be investigated separately (Hearst et al. 1971).

Other methodologic problems include the fact that the size of sample populations is estimated in some studies; data based on hospitalization rates may be biased by admission or referral practices; and reliance on medical records for retrospective detection of catatonic signs predictably underestimates the frequency of catatonia (Bush et al. 1996a, 1996b; Pataki et al. 1992). Finally, sample populations may be affected by treatment. Dosing and choice of antipsychotic drugs, which could induce or worsen catatonia, were specified in only a few studies (Bush et al. 1996a, 1996b; Lee et al. 2000; Rosebush et al. 1990).

Decline in Catatonic Schizophrenia

Although methodologic limitations preclude a definitive answer, the available data suggest that the perception of a decline in catatonia is caused primarily by a reduction in the frequency of catatonic schizophrenia. If this is true, it is interesting to speculate on the reason for this reduction.

First, the decline in catatonic schizophrenia may reflect simply changes in diagnostic practices. Thus, the marked decline in catatonic schizophrenia described by Morrison (1974) and Achte (1961), which is proportional to the decline in hebephrenia and balanced by the increase of paranoid and undifferentiated types, may reflect changes in labeling of subtypes. However, catatonic signs are distinctive, objective, and difficult to overlook, mislabel, or ignore. It is unlikely that a patient presenting with catatonia would be assigned to another subtype. In addition, studies using consistent diagnostic criteria over time (Table 2–4) support a true decrease in the incidence of catatonic schizophrenia.

A related problem concerns misdiagnosis in cases of catatonic patients with mood disorders. Until challenged by Taylor and Abrams (1977) and Morrison (1973), this practice may have artificially inflated estimates of catatonic schizophrenia in earlier studies. As a consequence, one might expect to see a proportional increase in the percentage of manic or depressed patients with catatonia in more recent studies. In fact, this increase has been observed among patients with mood disorders (Table 2–2); but an increase in the frequency of mania or depression among patients with catatonia has not been observed (Table 2–5). Moreover, misdiagnosis of mood disorders as schizophrenia probably occurred equally for patients with and patients without catatonia, so that the percentage of true schizophrenic patients with catatonic schizophrenia would not have changed necessarily, which is contrary to the facts. Finally, there is evidence among patients with catatonic schizophrenia, as defined by Leonhard (1979), that there has been a decline primarily in the chronic and progressive systematic cases without a corresponding decrease in periodic cases that more closely resemble mood disorders (see Astrup 1979; Stompe et al. 2002).

Another reason for the decline in catatonic schizophrenia could be that earlier estimates were inflated by misdiagnosed organic disorders. Indeed, some epidemiologic data support a hypothesis of organic influences on the rate of catatonic schizophrenia. For example, consistent reports of increased rates in developing nations may implicate environmental and public health factors in the occurrence of catatonia (Carpenter et al. 1976; Chandrasena 1986; Lee et al. 2000; Leff 1981). Obstetrical mishaps, head trauma, susceptibility to infections, or the lack of preventive and therapeutic health services could account for geographic differences in the rate

of catatonic schizophrenia (Eagles 1991). Stöber et al. (2002) demonstrated a significant correlation between prenatal infections and systematic catatonia, which is the subtype with the strongest evidence of decline in the recent past.

Encephalitis lethargica is a specific infection that has often been implicated as a confounding factor in historical comparisons of the incidence of catatonic schizophrenia (Mahendra 1981; Marsden 1982; Templer and Veleber 1981). Catatonic symptoms were typical of encephalitis lethargica in both acute and chronic forms (Reid et al. 2001). The epidemic waned in the 1920s in parallel with the early declines reported for catatonic schizophrenia. Postencephalitic cases of catatonia may have contributed to the prevalence of chronic catatonic schizophrenia, which used to be common in institutionalized populations, but new cases are seldom seen today (Achte 1961; Astrup 1979; Guggenheim and Babigian 1974; Hare 1974; Odegard 1967; Stompe et al. 2002).

However, there is no evidence of a decline in encephalitis or other organic conditions in series of catatonic patients (Table 2–5). Although there were probably local outbreaks of encephalitis lethargica before 1915, classical descriptions of catatonic schizophrenia occurred prior to the major epidemic of 1915–1925. Other forms of epidemic encephalitis occur even today, with a rate of catatonia over 30% among patients presenting with behavioral symptoms (Caroff et al. 2001). Postmortem histopathology of brains from patients with catatonic schizophrenia does not resemble the neuropathology specific to encephalitis lethargica (Bogerts et al. 1985; Reid et al. 2001). Finally, Templer and Veleber (1981) and Strömgren (1987) found no correlation between rates of catatonic schizophrenia and epidemics of encephalitis.

The influence of treatment has also been invoked as another possible cause of the decrease in catatonic schizophrenia. The introduction of electroconvulsive therapy in the 1930s and psychotropic drugs in the 1950s could have altered the presentation and outcome of the disorder. This may be true for states of acute catatonic excitement, which have diminished even within the life span of some clinicians (Grinker 1973; Hare 1974). Fish (1964), Hogarty and Gross (1966), Morrison (1973), Astrup (1979), and Stompe et al. (2002) all reported that the acute, periodic forms of catatonia are responsive to treatment and have a favorable outcome. However, several authors (Achte 1961; Astrup 1979; Stompe et al. 2002) emphasized that the chronic and treatment-refractory systematic catatonias appear to have decreased the most. Most important, it is clear that the reduction in cases of catatonic schizophrenia began long before the advent of modern treatment modalities (Morrison 1974; Templer and Veleber 1981).

Another way in which treatment may have affected the incidence of catatonia derives from the cataleptic effects of antipsychotic drugs (Gelenberg and Mandel 1977; Rogers 1985, 1991; Stompe et al. 2002). This line of reasoning suggests that catatonia continues to occur at the same rate but is misconstrued as a drug side effect. However, the distinctive signs of catatonia are reported infrequently as drug side effects (Table 2–5). If catatonia has been obscured by or ascribed erroneously to drug effects, then the recent use of conservative dosing and atypical agents that spare the extrapyramidal system (Caroff et al. 2002) should have unmasked naturally occurring catatonic schizophrenia, with a resulting epidemic of new cases. This has not occurred.

Another intriguing explanation for the decline of catatonic schizophrenia relates to parallel changes in the incidence, manifestations, and course of schizophrenia itself (Eagles 1991; Hare 1983). Changing proportions of diagnostic subtypes among schizophrenic patients may reflect actual changes in the disorder rather than diagnostic fashions. Several investigators have proposed that schizophrenia has diminished in incidence and severity during the last century (Astrup 1979; Der et al. 1990; Eagles 1991; Hare 1974, 1983; Odegard 1967; Strömgren 1987). Because catatonia has been shown to correlate with severity or chronicity in several studies (Achte 1961; Bleuler 1911/1950; Guggenheim and Babigian 1974; Mimica et al. 2001), the decline in catatonic schizophrenia may reflect the evolution of schizophrenia to a less virulent disorder.

The evidence also indicates that catatonia as a subtype of schizophrenia may be misleading. Several studies have shown that catatonia is not consistently diagnosed during episodes in the same patient and that patients with other subtypes of schizophrenia may develop catatonic signs on occasion. Rather than a distinct subtype of schizophrenia, acute catatonia may represent a neurophysiologic reaction to the stress of severe psychotic states, which are less common among patients with schizophrenia than in the past. This view of catatonia as a state-related reaction to stress regardless of diagnosis affords an opportunity to integrate clinical catatonia with animal models of immobility. In addition, the association of catatonia and stress renders understandable descriptions of fear, anxiety, and terror that have been verbalized by patients recovering from catatonia (Achte 1961; Rosebush and Mazurek 1999; Rosebush et al. 1990).

Conclusion

Catatonia continues to be reported in 7%–17% of acute psychiatric patients. The distribution of neuropsychiatric diagnoses in series of catatonic patients supports the nonspecificity of the syndrome. An apparent decline

in the frequency of catatonic schizophrenia has been documented. Possible reasons for this decrease include different diagnostic practices or profoundly important changes in the manifestations and biology of schizophrenia. Among the latter are the influence of infections on the prevalence of chronic catatonia in the past and in the developing world; the efficacy of treatments in preventing and reducing acute catatonic excitement; and the possible evolution of schizophrenia from an inexorable, chronic dementia with prominent motor abnormalities to a less common and less progressive disorder. Finally, the concept of catatonia as a neurophysiologic reaction to the stress of severe psychotic states or as a marker for genetic vulnerability to psychosis may reconcile clinical and basic research findings.

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CHAPTER 3

NOSOLOGY

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Skeptics would argue that ever since Kahlbaum (1874/1973) attempted to construct a disease entity called catatonia, psychiatric research has not moved significantly forward with respect to its nosologic position. Essentially the same fundamental issues have been debated since 1874: the exact definition and specificity of catatonic symptoms, the concept of catatonia as a syndrome or disease entity, its relation to schizophrenia and affective and organic psychoses, and the existence of idiopathic catatonia. In this chapter, we first review psychopathologic and methodologic issues pertaining to the nosology of catatonia and then outline the seminal contributions on the place of catatonia in psychiatric classifications.

Psychopathologic Concept of Catatonia

Catatonia was originally, and still is, devised as a purely empirical, clinical concept. Therefore, to develop a coherent nosology of catatonia, the psychopathologic foundations of the catatonia concept have to be addressed. The first and maybe most fundamental problem—namely, by what psychopathologic principle can a particular motor symptom be categorized as catatonic—has hardly been tackled by modern writers. As a result, the delineation of the clinical concept of catatonia remains arbitrary. None of the current literature on the topic provides a coherent psychopathologic definition of catatonia.

The classical psychopathologic view of catatonia harkens back to Wernicke and Jaspers. Wernicke elaborated the concept of psychomotor dis-

turbances, defining them as abnormalities of motion and speech relatively independent from disturbances of thought or volition (Wernicke 1900). Wernicke described three major groups of motor symptoms—akinesia (psychomotor retardation), hyperkinesia (agitation), and parakinesia (e.g., mannerisms)—thereby introducing the idea of distinguishing between quantitative and qualitative psychomotor disturbances.

Jaspers (1913/1963) further developed Wernicke's ideas. He provided a broad psychopathologic framework for psychomotor disturbances based on his methodologic principles of understanding and explanation. Jaspers defined *catatonia*, "all incomprehensible motor phenomena," as follows: "Somewhere between the neurologic phenomena, seen as disturbances of the motor-apparatus, and the psychological phenomena, seen as sequelae of psychic abnormality with the motor apparatus intact, lie the psychotic motor-phenomena, which we register without being able to comprehend them satisfactorily" (Jaspers 1913/1963, p. 179). Jaspers's definition implies that with the passage of time, the number of catatonic symptoms is decreasing, with the simultaneous increase of neurologic motor symptoms. For example, a depressive stupor or manic exaltation being derived from a mood state is understandable and therefore not called catatonic. Perseveration occurring in a frontal lobe tumor would not qualify as a catatonic symptom either, because it can be explained by well-defined brain damage. The inherent weakness of Jaspers's catatonia definition is that it also implies a subjective judgment concerning the origin of motor symptoms. It is paradoxical that although never tested empirically, because of its seductive logic and clarity, Jaspers's catatonia concept permeated European views and contributed to linkage of catatonia and schizophrenia within Kraepelinian classifications.

Symptoms and Diagnosis of Catatonia

Methodologic issues that hamper research are relevant to the nosology of catatonia. The uncertainty of what signs and symptoms belong to catatonia is reflected in the composition of existing diagnostic criteria. A variety of catatonic symptoms are listed by different authors as making up the catatonic syndrome. The number of symptoms required to establish the cross-sectional diagnosis of catatonic syndrome also varies from study to study (Abrams et al. 1979; American Psychiatric Association 2000; Bräunig et al. 1998; Rosebush et al. 1990). Taylor (1990) opined that the number of catatonic signs has limited diagnostic or treatment significance. Likewise, selecting cardinal or secondary catatonic symptoms lacks any theoretical or even empirical basis (Rosebush et al. 1990).

In addition to the differing number of items on existing diagnostic schedules or catatonia rating scales, a further problem is the lack of agreement with respect to the definition of individual signs and symptoms. Schneider (1914) remarked at the difficulties in distinguishing between stereotypes and mannerisms or between "psychic" and strictly "catatonic" negativism. The distinctions between verbigeration and perseveration (Schneider 1914) and between mannerisms and bizarre behavior (Bostroem 1928) were also subject to debate. Also, there are very limited data on the various types of excitement or what makes an agitation "catatonic" (Bonner and Kent 1936; Kraepelin 1919).

A related methodologic problem is the length of observation (Kraepelin 1919). Most scales essentially measure catatonia cross-sectionally. However, in periodic or chronic cases, catatonic signs simply cannot be reliably assessed at a single point in time because they occur only occasionally. Applying cross-sectional rating scales inevitably leads to loss of significant numbers of catatonic features (Ungvari et al. 1999).

Structure of the Catatonic Syndrome

Following Kraepelin (1919) and Bleuler's (1911/1950) descriptions, most authors distinguished two major catatonic syndromes within the context of schizophrenia—namely, retarded and excited types. This simple division of catatonia, however, did not stand closer scrutiny. Carefully analyzing the charts of 250 patients with catatonic schizophrenia, Morrison (1973) found that a significant minority (29%) displayed a third type, mixed catatonic syndrome. No classical symptoms were confined to any of the three syndromes. Because there were significant differences between retarded and excited patients with respect to the onset, course, and outcome, Morrison suggested that the excited type showing more favorable prognosis would be better categorized as a mood disorder.

A few factor analytic studies attempted to delineate subsyndromes of catatonia. Abrams et al. (1979) extracted two factors. The first factor comprised negativism, mutism, and stupor; the second had mutism, catalepsy, stereotypy, and automatic cooperation and was related to the diagnosis of mania. Oulis et al. (1997) evaluated motor symptoms in consecutively admitted patients with a variety of diagnoses. A retarded factor and an excited factor, together accounting for 39.9% of the variance, were extracted; the catatonic syndrome was nonspecific with respect to diagnosis. In a study of chronic patients with catatonic schizophrenia, Höffler et al. (1998) found seven factors (hyperkinesis, catalepsy, proskinesis, mannerism, impulsiveness, blocking, and repetitive movements) that collectively explained 54.8% of the variance. Northoff et al. (1999) conducted a factor

analysis on acute catatonic patients. Four factors—hypoactive, hyperactive, affective, and behavioral—accounted for 45.6% of the variance. Peralta and Cuesta (2001) assessed the motor symptoms of consecutively admitted psychotic patients. Factor analysis yielded six factors (motor poverty, agitation, stereotypy/mannerism, prokinesia, negativism, and dyskinesia) that collectively explained 59% of the total variance. The conflicting results of factor analytic studies are not surprising in view of the differing patient populations examined, the different rating instruments used, and the lack of universally accepted standardized criteria for catatonia.

Catatonia in Mood Disorders

The concept of catatonia grew out of a particular form of mood disorder, *melancholia attonita* (Kindt 1980). Several of Kahlbaum's cases (*catatonia mitis*) presented with prominent mood symptoms and remissions, raising the possibility that they had primary mood disorders (Kahlbaum 1874/1973). In fact, as early as the 1880s, Krafft-Ebing and Tamburini (cit. Seglas and Chaslin 1890) suggested that Kahlbaum's catatonia was not a separate disease but a form of what we call today bipolar disorder ("folie circulaire"), although they emphasized that individual catatonic symptoms were ubiquitous. Subsequent authors pointed out the close association between catatonic symptoms and mania and depression (Bonner and Kent 1936; Kirby 1913; Lange 1922; Wilmanns 1907). Modern studies using standardized diagnostic assessment and criteria have confirmed the frequent association between catatonia and affective disorders (Abrams et al. 1979; Bräunig et al. 1998; Krüger and Bräunig 2000; Morrison 1973, 1974; Starkstein et al. 1996; Taylor and Abrams 1973, 1977).

When evaluating these studies, one should bear in mind not only the aforementioned methodologic shortcomings of catatonia research but also the uncertainties inherent in current psychiatric classifications. It is still largely an arbitrary decision how to draw the line between different categories, particularly between schizophrenia and mood disorders. Nevertheless, the presence of catatonic features in mood disorders within the context of subsequent editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) now seems to have been firmly established. In view of the conflicting results concerning the significance of catatonia in the course of mania in terms of severity of the illness and its outcome, it is too early to draw the conclusion that mania with catatonic features represents a distinct subtype of bipolar disorder. McKenna (1994) acknowledged the presence of catatonic symptoms in mania and depression while leaving open the question of whether a full, persistent catatonic syndrome could accompany typical bipolar illness.

Catatonia as a Separate Illness

There have been a few recent attempts to reexamine Kahlbaum's claim of catatonia as an independent disease entity. Screening an acute admission unit in India over 1 year, Benegal et al. (1993) found 65 patients who had at least 1 of 10 classical catatonic symptoms; 16 patients had an ICD-9 (World Health Organization 1977) diagnosis of depression, 19 had schizophrenia, and, surprisingly, 30 had only catatonic symptoms and were classified as having idiopathic catatonia. Comparison across a set of clinical and sociodemographic variables failed to find significant differences between idiopathic catatonia and other diagnostic groups. In a study of 112 patients with DSM-III (American Psychiatric Association 1980) schizophrenia, only weak or no correlation was found between catatonic symptoms and 77 psychotic symptoms of schizophrenia and sociodemographic variables (Cernovsky et al. 1998), suggesting the independence of catatonia from schizophrenia. Peralta et al. (1997) approximated Kahlbaum's original descriptions by creating a "Kahlbaum syndrome," defined as the presence of at least one motor symptom out of seven coupled with either depression or mania. Of 567 patients hospitalized for nonorganic psychosis, 45 met the above criteria for Kahlbaum syndrome. Patients with Kahlbaum syndrome were different from patients with schizophrenia and to a lesser degree from mood disorder patients across a range of clinical and sociodemographic variables. The authors concluded that Kahlbaum syndrome is either an independent clinical entity or a variant of mood disorder. In addition to the small number of catatonic symptoms considered, restricting the generalizability of the results, the feasibility of reconstructing a valid syndrome from Kahlbaum's descriptions (Berrios 1996) constitutes the major limitation of this study.

Fink and Taylor (1991) proposed placing catatonia as a separate category in DSM-IV (American Psychiatric Association 1994), mainly on the basis of its unique symptomatology, association with several psychiatric and medical conditions, potentially life-threatening nature, and responsivity to benzodiazepines and electroconvulsive therapy. The American Psychiatric Association opted for the inclusion of catatonia as a modifier of mood disorders and catatonia due to general medical conditions in DSM-IV.

Concept of Catatonia According to the Wernicke-Kleist-Leonhard School

The Kraepelinian catatonic schizophrenia subtype, which is preserved in ICD-10 (World Health Organization 1992) and the successive editions of

Table 3–1. Classification of psychoses with motor symptoms according to Leonhard

I. Motility psychosis (within the group of cycloid psychoses)
II. Catatonic schizophrenias
  A. Unsystematic catatonic schizophrenias; periodic catatonia
  B. Systematic catatonic schizophrenias
    1. Parakinetic
    2. Manneristic
    3. Proskinetic
    4. Negativistic
    5. Speech-prompt
    6. Speech-inactive

Source. Based on Leonhard 1957.

DSM, has not been subjected to systematic research or rigorous validation. The only major attempt to devise an overarching comprehensive nosology of catatonia has been made by the Wernicke-Kleist-Leonhard school of psychiatry (Table 3–1; Kleist 1943; Leonhard 1957, 1999). The catatonia concept of the Wernicke-Kleist-Leonhard school can be summarized as follows: Several neurologic and medical conditions affecting certain areas of the central nervous system can produce individual motor symptoms so a variety of catatonic signs and symptoms occur either persistently (e.g., echolalia in Gilles de la Tourette disease) or occasionally and transiently (e.g., verbigeration in delirium). Loosely formed syndromes (akinetic stupor or excited agitation) can be present in a host of medical and neuropsychiatric disorders (e.g., typhoid fever and epilepsy) and in reactive, depressive, and manic psychoses that may resemble cross-sectionally the different subtypes of catatonic schizophrenia. However, these catatonic syndromes are different from the distinct Kleist-Leonhard catatonic schizophrenia subtypes in several aspects, including the onset, development, and variability of symptomatology; the intensity, frequency, and consistency of symptoms; the presence of other psychiatric symptoms regularly associated with distinct catatonic psychoses; and probably treatment response.

Leonhard's putative disease entities presenting with persistent motor symptoms are divided into two groups on the basis of the nature of motor signs and symptoms: *motility psychosis* with motor symptoms only quantitatively different from normal movements (e.g., marked psychomotor retardation or agitation), and *catatonic schizophrenias* presenting with motor symptoms both quantitatively and qualitatively different from normal movements as defined originally by Wernicke. This latter group is

further subdivided into *unsystematic* and *systematic* catatonic schizophrenias. Periodic catatonia belongs to the group of unsystematic schizophrenias. Each of the six distinct systematic catatonic subtypes meets the general characteristics of systematic schizophrenia. Beyond these general attributes, each subtype has its own highly specific clinical presentation.

The diagnosis of motility psychosis and each catatonia subtype hinges on the presence of a specific symptom highly characteristic of the particular subtype that is, as a rule, accompanied by several other symptoms, forming a distinct clinical syndrome. Leonhard's system uses far more symptoms as building blocks of his catatonia subtypes than other classifications or diagnostic schemes. Another unusual characteristic of Leonhard's system is that motor phenomena are given precedence over paranoid-hallucinatory symptoms; unless the latter symptoms are pathognomonic to a certain subtype of schizophrenia, their presence or absence is regarded as a nonspecific accompanying feature of catatonia. Because of its complex psychopathology, Leonhard's nosology has largely been ignored by mainstream psychiatry (Ungvari 1993).

In the past decade, however, vigorous attempts have been made to validate Leonhard's classification. An excellent interrater reliability (Cohen's κ=0.93–0.97) for the distinction between periodic and systematic catatonias between two experienced raters was found (Beckmann et al. 1996). The stability of clinical picture over a 5-year period was confirmed, although the sample was relatively small (Franzek and Beckmann 1992a). Patients with periodic catatonia responded better to typical antipsychotics than did those with systematic catatonia (see Beckmann et al. 1992).

Season-of-birth data also contribute to the validation of the catatonia subtypes, because in winter–spring births a decrease in periodic catatonia and an increase in systematic catatonia was found (Franzek and Beckmann 1992b, 1993). Mothers of patients with systematic catatonia had significantly more infections in the second trimester than those of patients with periodic catatonia (Stöber 2001), suggesting the role of environmental factors in the pathogenesis of systematic catatonias.

The strongest evidence for the periodic–systematic dichotomy for catatonic schizophrenia comes from genetic studies. Unlike Leonhard's earlier, pioneering investigations, recent genetic studies meet modern methodologic criteria for clinical genetic investigations. In a family study (Beckmann et al. 1996), the morbidity risk for systematic catatonia was 4.6%, whereas the corresponding figure for periodic catatonia was 26.9%. Homogeneity of familial psychoses was found—that is, catatonia subtypes bred true. There were more male probands with systematic catatonia, and they had earlier age at onset than those with periodic catatonia. Unilineal ver-

tical transmission and anticipation of periodic catatonia indicated a major dominant gene effect for this subtype of catatonia (Beckmann et al. 1996; Stöber et al. 1995, 1998). A recent twin study contributed further to the validation of the periodic–systematic dichotomy of catatonic schizophrenia (Franzek and Beckmann 1998). More recently, a genomewide scan found linkage on the 15q15 and 22q13 chromosomes (Stöber et al. 2000). Despite recent advances in validating the Leonhardian groups of catatonia, the question whether the subtle phenomenologic differences between catatonia subtypes have any biological significance remains unanswered.

Conclusion

Although the concept of catatonia spans two centuries, its nosologic validity continues to be debated. Many challenges face clinicians and researchers in this area, as fundamental issues concerning the very concept and descriptive psychopathology of catatonia are still insufficiently elaborated. Future research into catatonia is dependent on a reliable and testable psychopathology and nosology. In our opinion, the study of catatonia will be advanced most successfully by adopting the nosologic approach that identifies catatonia across psychiatric illnesses, rejects the notion that catatonia is a subtype or modifier of another disorder, and postulates it as a relatively separate entity or psychopathologic dimension. In addition, studies focused on catatonia may serve as an innovative and valuable alternative strategy in elucidating mechanisms underlying psychotic disorders in general.

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CHAPTER 4

CLINICAL EXAMINATION

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Motor function assessment is part of every thorough neurologic and psychiatric examination. Neurologists would be remiss if they did not test eye movements, speech, motor strength, gait, and coordination and look for the presence of any abnormal movements. A psychiatric examination is incomplete without an evaluation for the presence of agitation and observations about motor speed and actions. Routine assessment for catatonic features should also be part of these examinations, because 6%–9% of acutely hospitalized adult psychiatric patients have two or more catatonic features (Rosebush et al. 1990), catatonic features reflect dysregulation of motor systems that might accompany life-threatening or treatable neurologic or general medical disease, and catatonic features predispose to increased risk for adverse reactions to drugs that influence the motor system, particularly agents that affect dopamine, serotonin, and γ-aminobutyric acid (Carroll et al. 2001).

The most common error in the evaluation of catatonia is of omission: not doing an assessment because of the mistaken belief that all catatonic patients are mute and immobilized in some rigid strange posture. In fact, most patients with catatonia speak and move about (Abrams and Taylor 1976; Abrams et al. 1979; Taylor and Abrams 1977). Catatonic features may persist throughout the day but may also fluctuate dramatically as in periodic catatonia. Stupor can alternate with excitement. Associated mood, speech, and language disturbances and psychotic features may be so intense that full attention to motor signs is lost. Proactive examination

techniques, rarely taught in residency, may be rudimentary or unknown to the clinician, further reducing sensitivity to catatonia. In this chapter, I address the challenge of identifying patients with catatonia by defining and detailing catatonic features and associated behavior and by describing examination procedures for eliciting these clinical phenomena.

Classic Signs of Catatonia

Catatonic features are listed in Table 4–1. Mutism and stupor are classic signs, but alone they are not pathognomonic. Other motor behaviors should be present, and most patients exhibit four or more signs (Abrams and Taylor 1976). The number of features or their duration required for the diagnosis is not experimentally established.

Mutism and posturing (catalepsy) make up the classic catatonia syndrome. Generalized analgesia is common, sometimes to very painful stimuli. Patients remain in this state for long periods, and if poorly cared for, they develop malnutrition, dehydration, weight loss, disuse muscle atrophy, contractures, and bedsores. They may die as a result of venous thrombosis and pulmonary embolization.

Mutism

The patient is awake and may move about but is silent or has markedly reduced speech. In some patients, the mutism may appear semielective—that is, the patient responds with a few words to some persons but is totally mute with others. At times, the patient may also appear to be in a stupor, and the two states may fluctuate. Akinetic mutism is complete mutism associated with immobility, but the patient appears awake and follows the examiner about the room with his or her eyes. Unlike the locked-in syndrome, these catatonic patients do not cooperate with voluntary blinking signals. Unlike akinetic parkinsonism, akinetic catatonia typically develops over days or several weeks at the most, rather than after years of illness with Parkinson's disease.

Stupor

Patients persist in an unresponsive state for hours, days, or longer. They seem unaware of the events around them. Whereas stuporous patients always have reduced speech output, catatonic mutism is not always accompanied by stupor. Stupor may occur alone, and when there is no clear metabolic, pharmacologic, or neurologic explanation for it, the stupor often reflects the psychomotor retardation of a severe depression. Kahlbaum

Table 4–1. Classic features of catatonia

Feature	Description
Mutism	Patient is verbally unresponsive, but the nonresponsiveness is not always associated with immobility.
Stupor	Patient exhibits unresponsiveness, hypoactivity, and reduced or altered arousal during which he or she fails to respond to questions; when the condition is severe, the patient is mute and immobile and does not withdraw from painful stimuli.
Echophenomena	Echophenomena include *echolalia*, in which the patient repeats the examiner's utterances, and *echopraxia*, in which the patient spontaneously copies the examiner's movements or is unable to refrain from copying the examiner's test movements, despite instructions to the contrary.
Stereotypy	Patient exhibits non-goal-directed, repetitive motor behavior. The repetition of phrases and sentences in an automatic fashion, similar to a scratched record, termed *verbigeration*, is a verbal stereotypy. The neurologic term for similar speech patterns is *palilalia*.
Mannerisms	Patient makes odd, purposeful movements, such as holding hands as if they were handguns, saluting passersby, or making exaggerations or stilted caricatures of mundane movements.
Ambitendency	Patient appears "stuck" in an indecisive, hesitant movement, resulting from the examiner verbally contradicting his or her own strong nonverbal signal, such as offering a hand as if to shake hands while stating, "Don't shake my hand; I don't want you to shake it."
Negativism (gegenhalten)	Patient resists examiner's manipulations, whether light or vigorous, with strength equal to that applied, as if bound to the stimulus of the examiner's actions.
Posturing (catalepsy)	Patient maintains postures for long periods. Posturing includes facial postures, such as grimacing or schnauzkrampf (lips in an exaggerated pucker). Body postures, as *psychological pillow* (patient lying in bed with the head elevated as if on a pillow), lying in a jackknifed position, sitting with upper and lower portions of the body twisted at right angles, holding arms above the head or raised in a prayerlike manner, and holding fingers and hands in odd positions.
Waxy flexibility	Patient initially resists examiner's manipulations before gradually allowing him-/herself to be postured (as in bending a candle).
Automatic obedience	Despite instructions to the contrary, patient permits the examiner's light pressure to move the patient's limbs into a new position (posture), which may then be maintained by the patient despite instructions to the contrary.

used the term *melancholia attonita* to encompass the symptom complex of stupor, mutism, and immobility (Kahlbaum 1874/1973).

Excitement

Patients in stupor may suddenly become energized. The excitement is intense and may last only an hour or two, simulating manic excitement. Catatonic patients may suddenly begin talking incessantly, especially when in "the stage of exaltation." They become impulsive and stereotypic with sudden outbursts of talking, singing, dancing, and tearing at their clothes. They become irritable and may damage objects or injure hospital staff. Catatonic excitement independent of an underlying mood disorder has not been objectively documented (Bleuler 1911/1950; Kahlbaum 1874/1973).

Catatonic excitement seems indistinguishable from delirious mania (see Fink 1999). Delirious mania is the acute onset of excitement, grandiosity, emotional lability, delusions, and insomnia characteristic of severe mania, and the disorientation and altered consciousness characteristic of delirium. These patients are excited, restless, fearful, suspicious, and delusional. Negativism, stereotypy, grimacing, posturing, echolalia, and echopraxia commonly accompany delirious mania. These patients sleep poorly, are unable to recall their recent experiences or the names of objects or numbers given to them, and are disoriented. They confabulate, often with fantastic stories. The onset develops rapidly within a few hours or a few days. Fever, rapid heart rate, tachycardia, hypertension, and rapid breathing are also common associated features. Patients hide in small spaces, close the doors and blinds on windows, or remove their clothes, and run nude from their home. Flights of ideas and garrulous and rambling speech may alternate with mutism.

Echophenomena

Echophenomena involve the spontaneous mimicry of the observer's movements (echopraxia) or repetition of his or her statements (echolalia). Raising your arm over your head is imitated. Or your posture may be mirrored—the patient raises his or her right arm as you raise your left (mirror movements). Patients do not know why they make these movements, and they usually give a silly or inadequate reason for it, denying their illness (anosognosia).

When echolalia is severe, obtaining a history and completing the behavioral examination is difficult because the patient repeats the examiner's questions and answers no further. Administering a low dose of a benzodiazepine or a barbiturate usually resolves such behavior.

Speech-prompt catatonia, a term coined by Leonhard, is a variant of echolalia. The patient typically makes no spontaneous speech but responds to questions by repeating the examiner's questions or by answering with an automatic "I don't know" or with a "yes" or "no," often in contradictory ways. The question "Do you like ice cream?" may be answered, "I don't know." "You do like ice cream, don't you?" may be answered with a "yes." And "You don't like ice cream, do you?" may be answered with a "no." Leonhard (1979) considered this a verbal form of automatic obedience.

Stimulus-Bound Behavior

Patients with echophenomena exhibit other *stimulus-bound* features. They appear compelled to touch, pick up, or use objects, engaging in activities such as turning light switches on or off, pulling fire alarms, taking other patients' possessions left out in the open, or going into another person's room and lying on his or her bed. These behaviors are described as *utilization behavior*. In one test for stimulus-bound behavior, the examiner tells the patient, "When I touch my nose, I want you to touch your chest." Despite understanding the instruction, patients will touch their nose, mirroring the examiner's movement.

Other Disorders of Speech

Catatonic individuals may also have other oddities of speech. *Prosectic speech* is often associated with decreased speech production. It is characterized by utterances of progressively less volume until speech is an almost inaudible mumble. This is the speech form of negativism. Other catatonic individuals have *manneristic speech*, in which they use a foreign accent not typical for them, speaking robotically (like the computer Hal in the movie *2001: A Space Odyssey*) or speaking like a child learning to read and not able to use contractions (e.g., "I cannot do that" rather than "I can't do that"). *Verbigeration* and *palilalia* are speech stereotypies in which the patient automatically repeats words or phrases during conversational speech. An example is "Doctor, I think I can leave now. I'm better. I can leave, can't I? I can leave, doctor. Doctor, I can leave, leave. Doctor, doctor, doctor, I can leave now, can't I?"

Stereotypy

Stereotypy is the term used to describe repetitive movements, often awkward or stiff and apparently senseless. These movements may be complex, taking the form of rituals or compulsive behaviors performed in an

automatic fashion, such as touching objects a certain number of times before using them, or using eating utensils in a certain order unrelated to what is being eaten. Self-mutilation including biting, striking, burning, or gouging the skin may occur. Other examples are rocking, shoulder shrugging, sniffing, wrinkling of the nose, making clicking sounds before or after speaking, automatically tapping or touching objects or body parts, tongue chewing, licking, lip smacking, pouting, teeth clicking, grimacing, frowning, and squeezing eyes shut or opening eyes wide.

Mannerisms

Mannerisms often accompany stereotypies and may be incorporated into a seemingly goal-directed action, but they are carried out in an exaggerated, distinct, or strange way. Catatonic stereotypies and mannerisms should be suspected when obsessive and compulsive features are observed in a psychotic patient. Examples of mannerisms are moving hands or fingers in odd but not typically dyskinetic ways (e.g., "tapping" at the air with index fingers, tiptoe walking, skipping, hopping).

Some catatonic features must be demonstrated during the examination if they are to be observed, as illustrated by the following signs.

Ambitendency

Ambitendency is another stimulus-bound phenomenon. The examiner offers a hand to the patient, as if to shake hands, and simultaneously and firmly tells the patient, "Don't shake my hand. I don't want you to shake it." The two conflicting signals result in the patient raising a hand as if to shake, lightly touching the examiner's hand but not grasping it, or moving the hand back and forth as if the patient cannot make up his or her mind.

Catalepsy

C*atalepsy* refers to the maintenance of postures for long periods without movement. Most often, patients remain in a sitting or standing posture, moving little. Some are dramatic, like *psychological pillow*, in which the supine patient lies with head and shoulders raised as if resting on a pillow and resists any effort to lower the head. Some patients will hold not only their head and shoulders off the bed but their legs as well, doing so for many minutes. *Schnauzkrampf*, in which the lips are puckered in an exaggerated kiss, is another dramatic posture. Other patients have kept the upper and lower parts of the body twisted in opposite directions, squatting on

haunches with arms extended as if doing deep knee-bends, and sitting with arms and legs extended as if falling into the chair. Most cataleptic patients assume relatively mundane postures, such as standing at attention, maintaining a salute, holding arms up as if about to do a bimanual task, or tilting the head in one direction. Any position maintained without obvious functional need for a prolonged period (several minutes or more) is catalepsy. Most cataleptic patients otherwise move about and speak interactively.

Waxy Flexibility

Cataleptic patients can be placed into new postures. The examiner tells the patient what he or she is going to do and then begins by trying to manipulate the patient's arms. Initial resistance soon followed by a slow release, as if bending a candle, is termed *waxy flexibility*.

Automatic Obedience

Some nonposturing patients, instructed to resist the examiner's manipulations, show *automatic obedience*. The patient is asked to tightly grab the arm of a chair or the bedspread and then not to let the examiner lift the patient's arm. With light pressure under the patient's arm, the examiner tries to raise it while telling the patient, "Don't let me do this." The patient with automatic obedience is unable to resist light touch despite understanding instructions to resist. Once the limb is raised, the new posture may be maintained for a long period, or the arm may be lowered slowly. It is useful to test both arms, because unilateral catalepsy and automatic obedience can occur from contralateral brain lesions. Kraepelin described automatic obedience as co-occurring with echophenomena, but this combination is most likely when the catatonia is a feature of mania rather than due to other conditions (Abrams et al. 1979).

Negativism

After testing for automatic obedience, the examiner tests *grasp reflex* and *negativism (gegenhalten)*. The examiner places index and middle fingers firmly on the patient's palm and sees if the patient grasps the fingers tightly. Regardless of whether the patient does so or not, the examiner grasps the patient's hand and moves the patient's arm horizontally back and forth, with varying degrees of strength. A patient with negativism (a stimulus-bound motor response) will resist manipulations with a pressure equal to the examiner's. Other forms of negativism are seen in the ways patients interact with the unit staff or respond to unit rules. Attempts to induce patients to dress, wash, or eat may be met with stubborn resistance and

tensing of every muscle. Such patients refuse any request or do the opposite of what is asked. They lie under their bed, not on it; or they sleep under the mattress, not on it; or they go to another patient's bed. When a staff member attempts to feed them, they clench their teeth like a child in a tantrum. They retain urine and feces and refuse to evacuate bowels and bladder when placed on a toilet, and then soil themselves afterwards. Such behaviors are examples of negativism, not "bad behavior."

Conclusion

Apart from its historical significance, catatonia remains an important syndrome frequently encountered in clinical practice. Unfortunately, training is often inadequate in the clinical skills needed in the examination of phenomenology associated with catatonia. Because of the dramatic response to treatment of most patients with catatonia, it is essential for clinicians to be familiar with the reliably identifiable features of the syndrome reviewed in this chapter. Better recognition of catatonic signs and symptoms and development of standardized assessment examinations and rating instruments (see Chapter 5, "Standardized Instruments," this volume) will directly enhance the understanding of motor regulatory systems and the management of patients with psychotic disorders and manic-depressive illness.

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C H A P T E R 5

STANDARDIZED INSTRUMENTS

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The construction of objective and standardized rating scales to measure psychopathology is a relatively recent development in psychiatric research. Although general psychopathology instruments include sections for the rating of abnormal motor behavior, catatonic symptoms are not rigorously distinguished from less specific behaviors or from extrapyramidal side effects. Recently, several competing rating scales have been proposed to standardize the assessment of catatonia. However, there is no overall consensus on the validity, reliability, sensitivity, and specificity of these instruments. In addition, the differences and similarities between catatonic phenomena and extrapyramidal symptoms remain confusing. In this chapter, I discuss rating scales in terms of their contribution to a more precise definition of *catatonia*, the perspective of their authors, their derivation, and their uses in research and clinical practice.

Rogers's Conflict of Paradigms

Rogers's (1985) seminal work describing the motor disorder of patients with severe psychiatric illnesses was designed to address the contribution of previous treatment, neurologic disorder, and hospitalization. Essentially, Rogers sought evidence to support his argument that a "conflict of paradigms" existed; the same phenomena were being described in terms of neurologic (motor disorder) or psychiatric (catatonia) etiologies. This

could be unhelpful to clinicians, as well as scientifically invalid. Rogers did not construct a scale to quantify catatonic symptoms. To describe motor disorders in long-stay psychiatric patients, he carried out comprehensive examinations of motor disorder in these patients and noted that its manifestations fell into 10 categories (Rogers 1992). He found abnormalities in posture; tone; purposive movement (including echophenomena); speech; facial movement and expression; head, trunk, and limb movement; general activity; gait; eye movements; and blinking. His nonprejudicial approach included phenomena that could be considered extrapyramidal, those that could be considered psychiatric if not frankly catatonic, and those not easily assigned to either category (Lund et al. 1991).

Scrutiny of case notes prior to 1955, the year of initial neuroleptic availability, revealed that almost all patients had similar motor disorders before exposure to neuroleptics. In the vast majority, the disorder was noted within 5 years of their admission. Specific neurologic diagnoses in individual patients could not be supported. Rogers (1985) concluded that severe psychiatric illness was in itself neurological, hence the nature of the motor disorder in the worst-affected patients seen in long-stay wards.

The assessment of catatonia has been further complicated by extrapyramidal side effects of antipsychotic drugs. The intrinsic nature of motor disorder in schizophrenia is well illustrated by work on parkinsonism in drug-naïve first-episode patients and by work on tardive dyskinesia–like abnormal involuntary movements in untreated chronic patients. At least 15% of drug-naïve patients have clinically recognizable parkinsonian symptoms already, and with special equipment such symptoms can be detected in nearly 40% (Caliguiri et al. 1993; Kopala et al. 1997; McCreadie et al. 1996). Dyskinesias were clearly described prior to the neuroleptic era (Farran-Ridge 1926) and continue to be reported in patients who have never been treated with antipsychotics (Brandon et al. 1971; Demars 1966; McCreadie et al. 1982; Owens et al. 1982; Rogers 1985). The most parsimonious explanation for such phenomena is that motor disorder, reflecting an underlying pathophysiology, is intrinsic to schizophrenia. Antipsychotic drugs modify this pathophysiology through their affinities, particularly regarding striatal dopaminergic systems. As a result, a rigid separation of the motor disorder of patients treated with antipsychotics into extrapyramidal versus catatonic does not seem possible (Rogers 1985), and therefore a nonprejudicial approach to the assessment of these disorders is justified. It has been suggested that attempts to devise clinical rating scales based on distinguishing intrinsic from drug-induced motor disorders are doomed to failure (Liddle 1991).

Modified Rogers Scale

McKenna et al. (Lund et al. 1991; McKenna et al. 1991) reviewed the range of catatonic symptoms in the classical literature and felt that they could be subsumed under four categories. These categories are simple disorders of movement, complex disorders of volition, very complex disorders of overall behavior, and disorders of speech. Taking Rogers's methodology as a baseline, McKenna et al. attempted to refine the assessment of motor phenomena. A 0–1–2 scoring for severity was incorporated, items were further specified within categories, and classically described catatonic phenomena were added. A means of examining patients was derived from extrapyramidal side-effect schedules. The resulting instrument was refined through piloting on long-stay inpatients with schizophrenia. Validity of some items was enhanced by including ratings reported by nurses.

This process resulted in the Modified Rogers Scale, which could rate extrapyramidal symptoms, catatonic abnormalities, and phenomena that could be classified as either. The authors attempted to isolate a catatonic subscale by excluding items that could possibly be extrapyramidal in origin or be confused with tardive dyskinesia or parkinsonism. The final scale comprised 36 items grouped into 10 categories of related items. Six categories were felt to represent purely catatonic phenomena.

The scale was examined for interrater reliability, and the catatonic subscale was assessed for test–retest reliability, with satisfactory results. Concurrent validity was assessed by comparing scores with those on independently rated measures of behavior felt to correspond reasonably closely to abnormalities that could be rated on the Modified Rogers Scale (Atakan and Cooper 1989; Wykes and Sturt 1986). Criterion validity was supported by correlating total scores on catatonic categories with the catatonic subscale total and by intercorrelating all the category totals with each other.

The authors were interested in the degree to which extrapyramidal and catatonic symptoms were associated with each other. The conflict-of-paradigms hypothesis would predict such an association on the grounds of a common etiology, or at least an interaction between intrinsic disease processes and drug treatment. Earlier work (Abrams and Taylor 1976; Abrams et al. 1979; Mortimer et al. 1990) had indicated that catatonic symptoms, like other schizophrenic symptoms, could be divided into positive and negative categories according to whether there was an added abnormality of function or a loss of a normal function. Similarly, it was hypothesized that parkinsonism and tardive dyskinesia represent, respectively, negative and

positive aspects of extrapyramidal disorder in schizophrenia. Modified Rogers Scale data, along with independently rated extrapyramidal scores, demonstrated that parkinsonism was associated with negative catatonic scores, whereas tardive dyskinesia was associated with positive catatonic scores. A factor analysis of Modified Rogers Scale scores on both presumed catatonic and extrapyramidal items produced two factors accounting for nearly 50% of the variance. One was interpretable as a hyperkinetic (positive) factor, and the other appeared to represent a hypokinetic (negative) factor. The authors concluded that there was indeed a clinical association between extrapyramidal side effects and catatonic symptoms in schizophrenia, and the conflict-of-paradigms hypothesis was supported. The authors offered a possible explanation for the association in terms of anatomical closeness and functional overlap between the basal ganglia and the ventral striatal-pallidal complex.

The Modified Rogers Scale is comprehensive and well validated. Its length and the extensive guidance on rating catatonic symptoms make it suitable for research rather than routine clinical use. There is no cutoff for *caseness*, or clinically significant catatonia. Its use in this form may be limited to patients with chronic schizophrenia, rather than patients with other underlying, chronic disorders or patients presenting with acute catatonia. It is above all a scale for the nonprejudicial rating of motor disorder, and it does not make assumptions about the origin or classification of symptoms beyond the productive–deficit phenomena dichotomy.

Rogers Catatonia Scale

Starkstein et al. (1996) were interested in the clinical correlates of catatonia in depression. Because the validity and reliability of the Modified Rogers Scale had been assessed with schizophrenic patients, its usefulness with other diagnostic groups was unknown. Starkstein et al. also questioned the ability of the DSM-IV (American Psychiatric Association 1994) criteria to distinguish depressed patients with catatonia from patients with phenomenologically similar disorders such as parkinsonism.

Starkstein et al. (1996), using the Modified Rogers Scale and several other clinical scales, compared depressed patients with and without catatonia with nondepressed Parkinson's disease patients. Catatonia was diagnosed in accordance with DSM-IV from Present State Examination findings. Twenty percent of the depressed patients met criteria for DSM-IV catatonia; no Parkinson's disease patient did so. As expected, total Modified Rogers Scale scores of the catatonic depressed patients were significantly higher than those of the noncatatonic depressed patients and the

Parkinson's patients. Individual Modified Rogers Scale items were examined for their ability to distinguish depressed catatonic patients from the other groups. Successful items were retained, along with items representing DSM-IV criteria. The resulting scale of 22 items was renamed the Rogers Catatonia Scale. Interrater reliability, test–retest reliability, and internal reliability were shown to be satisfactory. Validity was demonstrated by the scale's ability to distinguish depressed catatonic patients from Parkinson's patients with the same degree of motor disorder and from depressed noncatatonic patients with the same degree of depression. Factor analysis confirmed hypokinetic and hyperkinetic factors, together accounting for 64% of the variance. Unlike the results from the schizophrenic sample of McKenna et al. (1991), the hypokinetic factor accounted for a greater percentage of the variance among depressed patients.

Advantages of the Rogers Catatonia Scale include its brevity and derivation from an instrument already validated on a large number of patients. Its only disadvantage is that it may be diagnostically specific and valid in patients with mood disorders but not in patients with other underlying diagnoses.

Bush-Francis Catatonia Rating Scale

Bush et al. (1996) identified 40 motor signs of catatonia from the literature. They selected 23 items to compose a scale but did not explain how these items were chosen. A 0- to 3-point scale was appended to each item, scored according to its frequency or specific anchor points. The authors selected 14 more commonly reported items to form a screening instrument. Two or more items indicated *caseness*—that is, a diagnosis of catatonia. Items were also excluded from the screening version on the grounds of possible nonspecificity to catatonia (e.g., combativeness).

Perusal of the 23 items indicates that quite a few still lack specificity. No attempt was made to exclude possible drug-induced extrapyramidal phenomena, although the item definition for rigidity excludes cogwheeling. The definitions of *perseveration* and *verbigeration* depart from those in at least one other scale (Lund et al. 1991). Grasp reflex is included despite only a single mention in the literature on catatonia, because of a hypothesized frontal lobe etiology of catatonia (Taylor 1990).

The authors screened 228 consecutively admitted inpatients with acute symptoms and identified 28 cases of catatonia, according to the screening instrument. This 28-patient sample had mixed underlying comorbid disorders. The authors demonstrated that their scale was sensitive to change as the patients were treated, but severity did not predict response.

Both screening and full versions demonstrated excellent interrater reliability overall and for each item. Regarding validity, all 28 patients were assessed for catatonia according to three existing sets of diagnostic criteria (Barnes et al. 1986; Lohr and Wisniewski 1987; Rosebush et al. 1990), as well as the DSM/ICD diagnostic systems. No patient fulfilled any of these criteria while failing to reach caseness on the screening instrument. However, up to a quarter of the 28 patients were not catatonic according to at least one set of criteria. The authors argued that their instrument was capable of picking up milder but nevertheless valid cases.

Validity was further examined by assessing the frequency of scale items in the literature from which they were drawn and in comparison to samples of patients described by Kahlbaum (1874/1973), Rosebush et al. (1990), and Morrison (1973). However, there are intrinsic problems in the presumed similarity of items and patients across samples, particularly going back to 1874. Any resemblance is surely remarkable rather than to be expected. However, the same authors (Francis et al. 1997) were able to demonstrate consistency of motor symptoms during recurrent episodes of catatonia with their scale, supporting the possibility of catatonia as a distinct syndrome rather than an epiphenomenon, at least in some patients.

A further study by the same authors (Bush et al. 1997) examined catatonic and motor syndromes in 42 patients with catatonic schizophrenia. Unfortunately, previous work by McKenna et al. (1991) and Lund et al. (1991) was not cited, despite a similar methodology. Only 29 of the 42 patients had cases of catatonia according to the Bush-Francis Catatonia Rating Scale (BFCRS). There were no correlations between the BFCRS total and the various motor disorder scale scores, because the BFCRS rates both positive and negative catatonic symptoms, whereas motor scales rate productive or deficit phenomena but not both. The authors went on to state that the distribution of catatonic phenomena in the chronic group is similar to that in the acute group in which the scale was validated, but they did not give any statistical justification. Overall, the authors claimed that their scale can distinguish catatonia from motor disorder in chronic patients; however, a perusal of their data indicates that of the 42 patients, 9 had isolated catatonia, 20 had catatonia and motor disorder, and 11 did not have catatonia at all. Thus, nearly half of the patients exhibited both catatonia and motor disorder, a finding that begs the question of whether the motor disorder and catatonia ratings were ascertaining the same phenomena: if the 11 noncatatonic patients are excluded, over two-thirds had both motor disorder and catatonia. This supports Liddle's argument on the inseparability of catatonic from other motor phenomena (Liddle 1991).

The advantage of the BFCRS is that it is brief and sensitive, despite some shortcomings of individual items. Its major drawbacks include a lack of demonstrable validity in patients with nonacute symptoms, together with further shortcomings regarding its validation—for example, the rather small number of cases in the studied samples.

Northoff Catatonia Scale

Northoff et al. (1999) invoked Kahlbaum's perspective of catatonia as a psychomotor disease with motor, behavioral, and affective symptoms. They commented that the relationship between neuroleptic-induced extrapyramidal motor features and catatonic symptoms remains unclear but did not address existing evidence for an association in terms of productive versus deficit phenomena (McKenna et al. 1991). They stated that no existing scale considers extrapyramidal hyperkinesias, although the three scales described previously do include productive items to various degrees.

The Northoff Catatonia Scale was derived from both the historical and recent literature. Like Bush et al. (1996), Northoff et al. (1999) identified 40 items divided among motor, affective, and behavioral categories. *Caseness* was defined as the presence of at least one symptom from each category. Some items were defined more rigorously than in other scales. The inclusion of relatively nonspecific affective items—for example, anxiety—could be questioned on the grounds that catatonia ought to be defined in motor terms (Lohr and Wisniewski 1987), whereas others—for example, staring—are questionably affective in nature.

The authors compared a sample of acute catatonic patients with matched control patients followed for 3 weeks. Patients were assessed with the Rosebush criteria (Rosebush et al. 1990), DSM-IV criteria, the Modified Rogers Scale and catatonic subscale, and the Northoff Catatonia Scale. Hypokinetic extrapyramidal phenomena were assessed with a modified Simpson-Angus Scale, and hyperkinetic phenomena were assessed with the Abnormal Involuntary Movement Scale (AIMS). General psychopathology ratings were also completed.

The authors reported 100% diagnostic concordance between their scale and the other scales and sets of diagnostic criteria. Catatonic patients scored high on the affective subscale as well as on the other two subscales, and the distribution of total scores across all patients was bimodal, with a clear separation of catatonic patients from controls. Total scores on the scales were significantly intercorrelated, but the Northoff affective subscale total was not correlated with other scale totals. General psychopathology was not significantly correlated with scale totals. Interrater

reliability, intrarater reliability, and internal consistency were highly satisfactory. A factor analysis demonstrated four factors accounting for 58% of the variance. The most important factor was affective. The others were not as clear but appeared to represent hyperactive, hypoactive, and behavioral groups of symptoms. There were strong relationships between catatonia ratings and AIMS scores, thus partly replicating the findings of McKenna et al. (1991). Affective scores on the Northoff Catatonia Scale were not related to affective scores on general psychopathology scales, suggesting that these items indeed represented different phenomena. The authors did not report the sensitivity to treatment effects of their scale, despite 3 weeks of treatment.

The main criticisms of the Northoff Catatonia Scale regard its length, the status of the items within it, and the grouping of the items. However, its comprehensiveness and its correspondence with other instruments suggest that it may be a useful research tool for further investigations of catatonia.

Catatonia Rating Scale

Bräunig et al. (2000) set out to develop a specific, comprehensive, and quantifiable measure of symptoms that could function as a diagnostic tool and also as a tool to assess treatment efficacy. As in the reports by Bush et al. (1996) and Northoff et al. (1999), the literature was searched for descriptions of catatonic symptoms and behaviors, along with diagnostic criteria. Detailed information from longitudinal studies of catatonic patients was also available to supplement this material. Initially, 61 items were incorporated into the Catatonia Rating Scale, but during a 2-year pilot period, they were reduced to 21. Items thought to reflect independent motor disorder were excluded, with no mention of the intrinsic occurrence of parkinsonian or dyskinetic symptoms in schizophrenia or the influence of antipsychotic drugs.

Of the final 21 items, 16 are motor symptoms and 5 are behavioral. The authors recognized the problem of item nonspecificity (e.g., excitement) by according these items diagnostic validity only if they were accompanied by more specific items (e.g., gegenhalten). Some items are rated by presence or absence, whereas others are subject to a 0- to 4-point scale with defined anchor points. Some definitions (e.g., gegenhalten) are broader than generally accepted. The authors recognized positive and negative features of motor and behavioral symptoms, but this does not quite accord with the productive–deficit phenomena distinction. The authors argued that, on review of the literature, there is overall support for a diagnosis of catatonia in the presence of four symptoms, and this is the threshold for caseness in the Catatonia Rating Scale.

The final version of the Catatonia Rating Scale was assessed with psychiatric inpatients by means of a semistructured interview lasting 45 minutes. Interrater reliability and internal consistency were satisfactory. An incidence study of consecutive inpatient admissions revealed that 12% fulfilled criteria for catatonia in accordance with previous estimates of the incidence of acute catatonia.

The authors felt that their scale, like the scale of Bush et al. (1996), could be useful in identifying milder cases of catatonia. However, they did not provide any evidence of validity apart from the incidence study or any evidence of the validity of categories, such as motor positivism, which remain theoretical. A factor analysis would have confirmed the existence of such subsyndromes, but the two scales that were subjected to this method of validation supported hypo- and hyperkinetic subsyndromes overall (McKenna et al. 1991; Starkstein et al. 1996).

Conclusion

Several diagnostic systems and rating scales for catatonia are now available. Comparisons of these instruments raise important problems and assumptions. For instance, there appears to be not only a conflict of paradigms between neurologic and psychological perceptions of motor disorders but also conflicts between perceptions of how catatonic symptoms relate to each other in terms of individuality, categorization into subtypes, and correlation with the severity of underlying disorders. It is easy to make assumptions about how catatonic phenomena are distributed, but the only concept with replicated empirical validation remains the positive (productive) versus negative (deficit) dichotomy. Despite this finding, the validity of some scales has been evaluated only with measures of internal consistency, a problematic approach if catatonic phenomena do indeed cluster into positive and negative factors.

Furthermore, collaborations and cross-fertilization between investigators are limited, resulting in needless duplication of effort. Nevertheless, the variety of assumptions and approaches has produced a useful range of instruments that may suit different purposes very well. Moreover, reliability and validity are generally satisfactory.

Because catatonia itself is so variable, it may not be possible to develop a scale of global usefulness. No appraisal of rating scales for catatonia would be adequate without an evaluation of their fitness for a specific purpose. But the purpose of these instruments depends on the perceived status of catatonia as a specific entity, a presentation of an underlying disorder, or an incidental finding related to a very wide variety of disorders. The acute–chronic distinction adds further complications. There is limited consensus

on the relative importance of these possibilities and their implications for rating scale development (Rogers 1985, 1992; Taylor 1990).

Clinically, these scales may be useful for teaching recognition of the signs of catatonia, detecting catatonia in comorbid disorders, defining *caseness*, and monitoring the effectiveness of treatment. In research, scales may clarify subtypes and the significance of catatonic signs, delineate treatment strategies and outcomes, and facilitate studies of pathophysiology.

Clinically, there is a potential danger in clinicians focusing on catatonia interventions, based on scale scores, at the expense of treatment for an underlying condition. However, this is a caveat regarding any clinical scale; none can be immune from improper use. Given the inherent dangers of neuroleptic medication in catatonic states (Clark and Richards 1999; Gelenberg 1976), the detection of mild cases may inform medical management and enhance safety. It has been demonstrated that a simple combination of three or more catatonic signs discriminates catatonic patients with a very high degree of accuracy (Peralta and Cuesta 2001). It may be that a diagnostic checklist approach may have more utility, because of simplicity and brevity, than a lengthy and complex rating scale evaluation.

Associating varieties of catatonia with natural history and prognosis has been possible with a short, unvalidated symptom list in one study (Morrison 1973) and a general psychopathology scale in another (Hutchinson et al. 1999), but these approaches were not productive in similar circumstances (Abrams and Taylor 1976; Taylor and Abrams 1977). It may be that more comprehensive and highly developed instruments will be more powerful in this respect. Certainly, no study has compared and contrasted standardized catatonic measurements across the range of physical, mental, and drug-induced disorders. One partial attempt using seven diagnostic checklist symptoms failed to find differences in the pattern of phenomena (Benegal et al. 1993). Such an exercise could cast considerable light on the pathophysiology of catatonic symptoms, especially if enhanced by physiologic measures such as neuroimaging. The evaluation of catatonic symptoms would be difficult to carry out in enough detail without a research-oriented, comprehensive rating scale.

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C H A P T E R 6

LABORATORY FINDINGS

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There is no specific laboratory diagnostic test for catatonia. Catatonia is essentially a clinical diagnosis. The pathophysiology of this neuropsychiatric syndrome of diverse etiology remains unclear. It is associated with a wide range of psychiatric, medical, neurological, and substance-induced disorders. A number of medical complications, including dehydration, pneumonia, and thromboembolism, may develop during the course of catatonia. Laboratory investigations are of importance in the differential diagnosis of the catatonic syndrome and in the diagnosis and monitoring of medical complications. Instead of reviewing laboratory tests used to exclude associated conditions or medical complications, in this chapter I focus on biochemical findings related, directly or indirectly, to the catatonic process and analyze the literature, supplemented with unpublished observations.

Various laboratory findings of potential clinical and pathophysiologic significance have been reported in the literature. Of particular interest are the reported changes in nitrogen balance in periodic catatonia and changes in neurochemistry, leukocyte count, serum creatine phosphokinase (CPK), and serum iron. In this chapter, I review how these simple blood tests have potential value in helping to diagnose catatonia and its subtypes, in predicting treatment responses, and in understanding the pathophysiology of catatonia and its relationship to neuroleptic malignant syndrome (NMS).

Periodic Catatonia and Nitrogen Balance

For several decades, starting in the 1920s, Gjessing and Gjessing (1961) meticulously studied clinical and physiologic findings in periodic catatonia, an intriguing form of catatonia regarded as a subtype of schizophrenia (see Chapter 8, "Periodic Catatonia," this volume). They found a regular, periodic shift in nitrogen balance from gradual nitrogen retention (positive nitrogen balance) to rapid nitrogen overexcretion (negative nitrogen balance). Nitrogen balance was measured by determining levels of blood urea nitrogen and urine ammonia and urea. The observed nitrogen balance shift showed a fixed time relationship to the periodic rhythm of catatonic relapses unique to each individual. Speculating that retention of an endogenous noxious metabolic substance in the hypothalamus may explain the strict periodicity, the investigators used thyroxine to deplete body nitrogen storage in order to stop the nitrogen balance shift and the periodic catatonic relapses. Although this was effective in some patients, the subsequent successful use of neuroleptics, lithium, or antidepressants for the condition made thyroxine therapy mostly unnecessary.

During the *interval phase*, the pulse rate, oxygen consumption, and basal metabolic rate were low (Gjessing 1974; Gjessing and Gjessing 1961). Such a hypometabolic state would shift to a hypermetabolic state with high pulse rate and increased oxygen consumption, basal metabolic rate, and fasting blood sugar in the *reactive phase* of either stupor or excitement. In the reactive phase, the temperature might be moderately elevated up to 38°C and the leukocyte count might be moderately or markedly elevated.

The significance of these findings is difficult to evaluate. The expense, time, and cooperation required in Gjessing's procedures rule out general clinical applications. It is unclear if the laboratory findings in periodic catatonia apply to other catatonic conditions in general. Periodic catatonia with regular periodicity, as described by the Gjessings, is rare and may not constitute a homogenous condition. Although several groups attempted to replicate their findings, relatively sparse results were obtained (Minde 1966).

Neurochemical Findings

Few neurochemical studies of catatonia have been reported in the literature. Gjessing et al. (Gjessing 1974; Takahashi and Gjessing 1972) found a remarkable increase in urinary catecholamines during the reactive phase of periodic catatonia, with normal values during the interval phase. Gjessing (1974) suggested that there is a dysfunction or dysregulation of norepinephrine synthesis in the brain stem to account for the changes observed.

Wheeler et al. (1985) described a patient experiencing recurrent catatonic episodes with tachycardia and hypertension. The plasma epinephrine and norepinephrine levels were elevated in support of a hyperadrenergic state. Linkowski et al. (1984) reported a case of catatonia associated with major depression. They found low cerebrospinal fluid levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid, and low urinary levels of 3-methoxy-4-hydroxyphenylglycol, suggestive of dopamine, norepinephrine, and serotonin hypofunction consistent with that expected in depression. Their findings show that in interpreting laboratory findings in catatonia, the confounding primary condition needs to be taken into consideration.

Northoff et al. (1996a) compared plasma HVA levels in 37 patients in catatonic episodes with levels in 17 healthy control subjects. HVA levels in the catatonic patients were significantly higher than in the control subjects, confirming Gjessing's finding of increased urinary dopamine and HVA and implying increased central dopamine release and turnover. Northoff et al. postulated a co-occurrence of increased and decreased function in different dopaminergic pathways in catatonia. They suggested that there is an increase in mesolimbic dopaminergic function, resulting secondarily in downregulation of nigrostriatal dopamine.

Kish et al. (1990) examined the autopsied brains from three patients—two diagnosed with lethal catatonia and one diagnosed with NMS—for neurotransmitter changes. In the two cases of lethal catatonia, there was an apparent lack of upregulation of striatal dopamine activity. In all three, marked reductions of norepinephrine in the hypothalamus and of choline acetyltransferase activity in the striatum and cerebral cortex were noted. The authors suggested that striatal dopamine dysfunction accompanied by cholinergic hypoactivity may be one of the factors predisposing individuals to developing lethal catatonia or NMS. Their findings provide neurochemical evidence in support of the argument that lethal catatonia and NMS are closely related and share similar pathophysiology (Fink 1996).

Other neurotransmitters, particularly γ-aminobutyric acid, glutamate, and serotonin, have attracted interest (Carroll 2000). Neurochemical studies, coupled with advanced electrophysiologic and neuroimaging measures, would help unravel the complexities of the pathophysiology of catatonia (see Chapter 7, "Neuroimaging and Neurophysiology," this volume).

NMS and Catatonia

There is considerable overlap in phenomenology, treatment response, and possibly pathophysiology between NMS and catatonia (Carroll 2000;

Francis et al. 2000; Koch et al. 2000). It has been argued that NMS is a malignant variant of catatonia and that the two are one entity (Fink 1996; White 1992), as opposed to the view that NMS is a toxic extrapyramidal reaction to neuroleptics that is noncatatonic in nature (Castillo et al. 1989). Although NMS is frequently accompanied by catatonic symptoms, such an association is not reported in many single case reports and case series of NMS (Addonizio et al. 1987). It has been suggested that NMS is a heterogeneous condition that includes catatonic variants and noncatatonic pathologic reactions to neuroleptics (Chandler 1991; Lee 1998, 2000).

The similarity in phenomenology is particularly striking between NMS and lethal catatonia. Controversies remain whether lethal catatonia and NMS are clinically indistinguishable (Caroff 1980; Castillo et al. 1989; Lee and Robertson 1997). Mann et al. (1986) reviewed 292 cases of lethal catatonia reported in the literature. In 65 cases (22%), the phenomenology was equally consistent with the diagnosis of NMS. Lethal catatonia is characterized by relentless excitement, delirium, hyperpyrexia, and autonomic dysfunction leading to stuporous exhaustion (see Chapter 9, "Malignant Catatonia," this volume). Less frequently, the disorder follows primarily a stuporous course. A new name, "malignant catatonia," has been suggested, as opposed to "simple" or "nonmalignant catatonia" without fever and autonomic disturbances (Philbrick and Rummans 1994).

Does the phenomenologic similarity extend to laboratory findings? Leukocytosis, elevated serum CPK, and low serum iron levels are prevalent findings reported in NMS. Do they occur to the same extent in catatonia—malignant or nonmalignant? These issues will be examined in the following sections.

Leukocytosis

Leukocytosis is a common but nonspecific finding in NMS. It occurs in a number of medical and physiologic conditions, including infection, lithium therapy, stress, excitement, and vigorous exercise. Many case studies do not explicitly report the leukocyte count. Levenson (1985), in his review study, found that in only 24 of 53 cases of NMS was the leukocyte count reported, and leukocytosis occurred in 19 of the 24 (79%). Another review found elevated leukocyte counts (10,000–40,000/mm^3) in 78% of NMS episodes (Addonizio et al. 1987).

Does leukocytosis occur to the same extent in malignant catatonia? Mann and Caroff (1987) found that among 134 case reports of malignant catatonia that included a leukocyte count, 66 of them (44%) had leukocytosis. More recently, Singerman and Raheja (1994) reviewed 35 cases of malignant catatonia. In 16 of the cases, leukocyte counts were reported,

and mostly mild leukocytosis was found in 12 of the cases (75%), a figure very close to that reported for NMS.

Does leukocytosis occur in simple catatonia? There have been no systematically conducted studies reported. In a review of 46 case reports of simple catatonia reported in the literature from 1971 to 1997, 33 described the laboratory findings as normal or unremarkable, and 9 did not mention laboratory investigations (unpublished data). In only 3 cases was the leukocyte count reported. Two of these patients had leukocytosis: one had urinary retention, and the other had pneumonia, to explain the leukocytosis. In another review (unpublished data) of leukocyte counts in 24 episodes of acute catatonia included in a prospective study (Lee et al. 2000), 20 episodes of simple catatonia due to a psychiatric cause were identified, and in 3 of them (15%) the leukocytosis was mild and not explainable by concurrent medical conditions. Of note, all 3 episodes were catatonic excitement. It appears that the laboratory similarity in leukocytosis between NMS and malignant catatonia does not extend to simple catatonia.

Creatine Phosphokinase

Elevated serum levels of CPK from skeletal muscle is a frequent finding in NMS. Two reviews reported that elevated CPK levels occurred in 97% of the NMS episodes for which CPK values were reported (Addonizio et al. 1987; Levenson 1985). The increase varies from slight to greater than 100,000 U/L (82% with levels greater than 300 U/L, and levels often greater than 1,000 U/L) (Caroff 1980). It has been demonstrated that CPK levels show no correlation with the degree or duration of muscle rigidity or with temperature elevations (Harsch 1987). In general, CPK levels fall as an NMS episode resolves. Elevated CPK is useful as an adjunct in diagnosing NMS, in monitoring improvement and relapse, and as a marker for risk of renal failure. A major limitation is its lack of specificity. Elevated CPK levels may result from trauma, intramuscular injection, acute psychoses, exposure to neuroleptics, and various neurologic and muscular disorders (Meltzer et al. 1996).

Does elevated CPK occur in malignant catatonia to the same extent as in NMS? Earlier case studies often failed to report CPK values. Mann and Caroff (1987) found only 3 explicitly reported cases with CPK findings, and 2 of the 3 had increased CPK levels. Philbrick and Rummans (1994) reviewed 18 cases of malignant catatonia. CPK levels were reported in 14 cases and elevated in 13 (93%) (10–160 times the maximum normal value). Singerman and Raheja (1994) found elevated CPK values in 16 (94%) of 17 cases of malignant catatonia. The figures show that elevated CPK is equally prevalent in malignant catatonia and NMS.

Does increased CPK occur in simple catatonia? Case reports of simple catatonia often do not provide details of laboratory investigations. In several single case studies, CPK levels were reported to be moderately elevated (Chandler 1991; Craddock et al. 1991; Domken and Farquharson 1992). It was also noted that CPK levels fell and rose, mirroring the severity of catatonia, and that the levels returned to normal when the catatonic episodes resolved.

Northoff et al. (1996b) measured serum CPK in 32 acute catatonic episodes. Patients were assessed for dyskinetic and parkinsonian movements with the Abnormal Involuntary Movement Scale (AIMS) and the Scale for the Assessment of Extrapyramidal Side Effects (SAEPS). The catatonic patient group was compared with noncatatonic dyskinetic psychiatric patients, noncatatonic and nondyskinetic acute patients, and healthy control subjects. In 72% of the catatonic episodes, CPK was elevated mostly to a moderate level.

A number of other findings of the Northoff et al. (1996b) study are of interest. CPK levels in catatonic and noncatatonic dyskinetic patients did not differ significantly. There was a significant correlation between increased CPK and AIMS scores. Northoff and colleagues suggested that the increase of CPK in catatonia might be related to dyskinetic movements. Moreover, they found a negative correlation between raised CPK levels and parkinsonian scores. They also showed that catatonic patients with good responses to benzodiazepines had significantly higher CPK levels and higher AIMS scores. Based on their findings, they were able to distinguish two subtypes of catatonia: "dyskinetic," with high CPK levels, high AIMS scores, low SAEPS scores, and benzodiazepine responsivity; and "parkinsonic," with low CPK levels, low AIMS scores, high SAEPS scores, and less benzodiazepine responsivity.

The findings of Northoff et al. (1996a, 1996b) need replication, and a number of related issues remain to be addressed. The pathogenesis of elevated CPK in catatonia, simple or malignant, is unclear. No studies of CPK in chronic catatonia and no studies with serial CPK measurements, other than single case studies, have been reported. The use of CPK in monitoring progress and relapse of catatonia merits further investigation.

Serum Iron

Rosebush and Mazurek (1991) reported their finding of low serum iron levels in almost all the cases of NMS in their series (96%). The serum iron levels returned to normal on resolution of NMS. Serial measurements of serum iron were done in some cases, showing an inverse relation with serum CPK levels and a correlation with the severity of NMS. They suggested

that low serum iron can be a potential biological marker and a useful adjunct in the diagnosis of NMS.

Does low serum iron occur in catatonia, malignant or simple? White (1992) reported on a patient who had recurrent episodes of malignant catatonia. Serum iron was measured in one episode and found to be low. In some episodes when neuroleptics were used, the patient became profoundly stuporous, with rigidity, exacerbated fever, and autonomic disturbances—a state resembling NMS. Several other authors have also reported the conversion of catatonia to NMS following exposure to neuroleptics (Lee and Robertson 1997; Raja et al. 1994; Singerman and Raheja 1994). Raja et al. (1994) reported three cases of NMS with preceding catatonia. Low serum iron levels were found in all three of the nonmalignant antecedent catatonic episodes.

Carroll and Goforth (1995) found reduced serum iron levels in 3 of 12 episodes of acute catatonia. NMS subsequently developed in 2 of the 3 episodes. In the remaining episode, no neuroleptics had been administered and there was no progression to NMS. The authors suggested that decreased serum iron levels in catatonia predict the progression of catatonia to NMS.

Lee (1998, 2000) examined the predictive value of low serum iron levels in the conversion of catatonia to NMS and explored the potential significance of serum iron in catatonia. Fifty episodes of acute catatonia were prospectively identified. Serum iron was measured in 39 episodes. Seventeen (44%) showed low serum iron levels. The serum iron levels returned to normal on resolution of the catatonia. In comparing the low serum iron group with the normal serum iron group, Lee found that low serum iron levels were associated with malignant catatonia, excited catatonia, and poor responses to benzodiazepines. Seven episodes of malignant catatonia were reported. In all of these cases, the serum iron level was low. Neuroleptics were used in five of these cases, and in all five the malignant catatonia evolved into NMS. No such NMS conversion was noted in those with normal serum iron and in nonmalignant catatonia with low serum iron. The findings suggest that malignant catatonia, associated with low serum iron, is a high risk for NMS; they also provide support for the hypothesis that NMS (or some cases of NMS) is a form of malignant catatonia and that the two conditions share similar pathophysiology.

The association of low serum iron with excited catatonia and unfavorable benzodiazepine responses in Lee's (1998, 2000) study is of interest. Excited catatonia is not well studied. Its nosologic status as a catatonic subtype remains unclear. The response to benzodiazepines of excited catatonia in the study was not as robust as that of retarded catatonia. Excited catatonia was more likely than retarded or mixed catatonia to have low serum iron. The findings suggest that excited catatonia differs from re-

tarded catatonia not only in symptomatology but also in response to treatment and possibly pathophysiology.

Peralta et al. (1999) measured serum iron levels in 40 episodes of acute catatonia and compared the catatonic patient group with a group of noncatatonic psychotic patients. Low serum iron occurred in 35% of the patients with catatonia as compared with 7% of the noncatatonic patients. The mean serum iron level in the acute catatonia patients was significantly lower than in the noncatatonic patients, and the severity of catatonia was inversely correlated with serum iron levels. There was, however, no NMS episode in this sample. Peralta et al. (1999) also studied serum iron in two catatonia subdimensions: negative and positive. Positive catatonic symptoms included agitation, mannerisms, waxy flexibility, echophenomena, and catalepsy; and negative catatonic symptoms included stupor, mutism, and negativism. They found that low serum iron was likely to be related to negative catatonic symptoms.

Although low serum iron is highly prevalent in NMS (96%) (Rosebush and Mazurek 1991) and malignant catatonia (100%) (Lee 1998), it occurs significantly less frequently in simple catatonia (34%–35%) (Lee 1998, 2000; Peralta et al. 1999), consistent with the findings for leukocytosis and elevated CPK. Figure 6–1 summarizes the frequency of occurrence of leukocytosis, raised serum CPK levels, and low serum iron levels in NMS, malignant catatonia, and simple catatonia. There have been few studies of serum iron levels in chronic catatonia. In a review of serum iron levels in eight cases of chronic catatonia, none had low serum iron levels (J.W.Y. Lee, unpublished data).

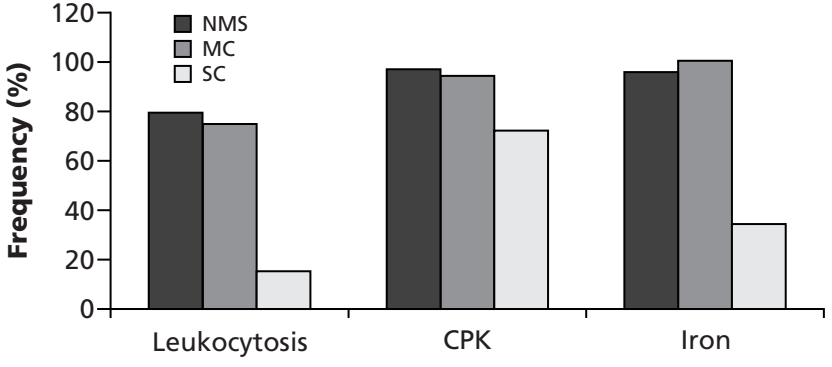


Figure 6–1. Leukocytosis, elevated serum creatine phosphokinase (CPK), and low serum iron in catatonia and neuroleptic malignant syndrome (NMS).

Note. MC=malignant catatonia; SC=simple catatonia.

It should be noted that serum iron values are nonspecific and variable with diurnal changes, and caution needs to be exercised in their interpretation. Low serum iron occurs in various conditions, including infection, inflammation, tissue damage, stress, and strenuous exercise. It has been suggested that low serum iron levels in catatonia reflect central hypodopaminergia. There has been evidence that iron plays an important part in the normal function and structure of dopamine D_2 receptors and that iron-deficiency anemia produces a reduction in the number of D_2 receptors in the basal ganglia. However, brain iron metabolism is complex, and peripheral iron measures correlate poorly with central iron (Sachdev 1993). The mechanism underlying low serum iron in catatonia and NMS remains obscure.

Conclusion

There is no specific diagnostic test for catatonia. Leukocytosis, elevated serum CPK levels, and low serum iron levels may be used as an adjunct in the diagnosis of malignant catatonia and NMS. Although nonspecific, all three laboratory findings are frequently found in both NMS and malignant catatonia. No laboratory findings differentiate between malignant catatonia and NMS. Leukocyte count, serum CPK, and serum iron levels are of use in monitoring progress and relapse of NMS and malignant catatonia. The potential use of serum CPK and serum iron in monitoring the progress of nonmalignant catatonia deserves further investigation.

Laboratory studies provide insight into the pathogenesis of catatonia and the relationship between catatonia and NMS. The similarity in symptomatology between NMS and malignant catatonia extends to laboratory findings, and this supports the hypothesis that NMS (or some cases of NMS) represents a malignant variant of catatonia and that the two conditions probably share similar pathophysiology. The laboratory similarity, however, does not extend to simple catatonia. Leukocytosis is not a common finding in simple catatonia. Elevated CPK and low serum iron levels occur less frequently in simple catatonia than in malignant catatonia and NMS.

Serum CPK and serum iron studies in acute catatonia have potential clinical applications in predicting responses to benzodiazepines and in grouping catatonia into subtypes. The subtypes suggested by Northoff et al. (1996b) and Peralta et al. (1999) remain to be validated. The observation of the progression of catatonia, malignant or simple, into NMS following exposure to neuroleptics and the predictive value of low serum iron in this NMS conversion merit further studies.

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CHAPTER 7

NEUROIMAGING AND NEUROPHYSIOLOGY

Georg Northoff, M.D., Ph.D.

Early neuropathologic studies of catatonia concerned the basal ganglia because subcortical structures are involved in the generation of movements. In contrast, cortical structures were relatively neglected. In the last 10–20 years, however, advanced methods for imaging brain function in general and cortical structures in particular have been developed. Such techniques, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG), allow for investigation of functional activity in cortical structures during generation of movements or experience of emotions. In this chapter, I review the main findings in catatonia obtained by neuroimaging. On the basis of these findings, a pathophysiologic model of catatonia as a psychomotor syndrome will be developed in which catatonia is characterized predominantly by cortical rather than by subcortical dysfunction (see Figure 7–1).

Recently, interest in catatonia and the relationship between catatonia and neuroleptic malignant syndrome (NMS) has increased (Fink 1996; Fricchione et al. 2000). Both catatonia and NMS are characterized by rigidity and akinesia. However, catatonia and NMS differ with regard to the presence of other motor symptoms (cerea flexibilitas in catatonia, tremors in NMS), motor anosognosia (catatonia), and involvement of affective and behavioral alterations (catatonia) (Northoff et al. 1996). Considering motor similarities and psychological differences, one may therefore characterize catatonia as a psychomotor disorder and NMS primarily

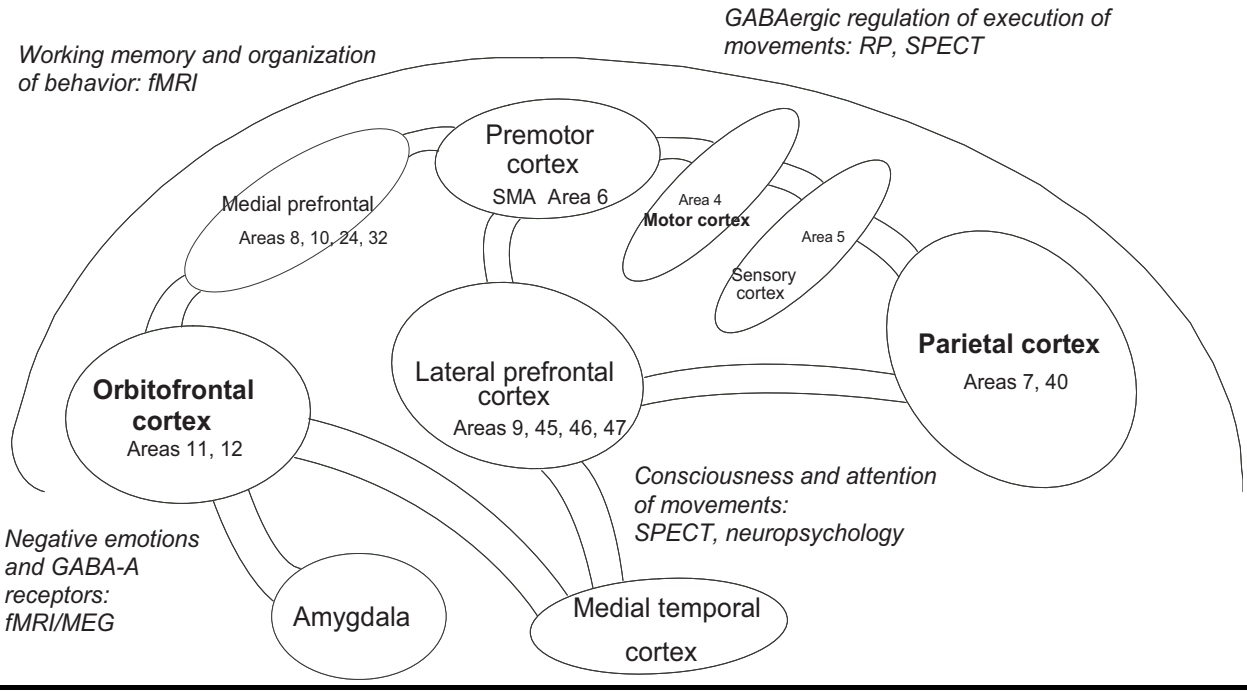


Figure 7–1. Pathophysiologic model of catatonia.

fMRI=functional magnetic resonance imaging; GABA=γ-aminobutyric acid; MEG = magnetoencephalography; RP=readiness potential; SMA= supplementary motor area; SPECT=single photon emission computed tomography.

Source. Adapted from Northoff G: "Brain Imaging in Catatonia: Current Findings and a Pathophysiologic Model." *CNS Spectrums* 5:34–46, 2000. Used with permission.

as a motor disorder. They share some motor symptoms but differ in affective, behavioral, and cognitive states. Phenomenologic contrasts may be reflected in pathophysiologic mechanisms underlying catatonia and NMS. Neural networks responsible for generation of movements may be altered in both disorders, but underlying differences in mechanisms may account for psychological findings. Therefore, a second purpose of this chapter is to contrast catatonia and NMS, relying on findings from brain imaging studies.

Pathophysiologic Findings in Catatonia and Neuroleptic Malignant Syndrome

Neuropathologic Findings

Early postmortem studies of brains from patients with catatonic schizophrenia revealed inconsistent alterations in the basal ganglia (Dom et al. 1981; Northoff et al. 1997, 2000a). It remains unclear whether these alterations were specifically related to catatonia or schizophrenia. Most of these studies were performed on brains of patients prior to the neuroleptic era, so alterations in basal ganglia cannot be related to neuroleptic modulation. Nevertheless, findings should be considered cautiously because the methods and techniques available at that time were limited. Postmortem reports of brain pathology in NMS patients have been nonspecific and inconsistent (Horn et al. 1988; Jones and Dawson 1989).

Neurochemical Findings

Dopamine has been the neurotransmitter of primary interest in studies of catatonia and NMS. In early studies, Gjessing (1974) found increased catecholamine metabolites in the urine of acute catatonic patients, which correlated with vegetative alterations (see Chapter 6, "Laboratory Findings," and Chapter 8, "Periodic Catatonia," this volume). He suggested a close relationship between catatonia and alterations in posterior hypothalamic nuclei.

Investigations of the dopamine metabolite homovanillic acid (HVA) in plasma showed increased levels in the acute catatonic state (Northoff et al. 1996) and particularly in those catatonic patients responding well to lorazepam (Northoff et al. 1995a, 1995b). However, the dopamine agonist apomorphine exerted no therapeutic effect in acute catatonic patients (Starkstein et al. 1996). Thus, these data suggest that the dopaminergic system may be hyperactive in acute catatonia. However, hyperactivity of the dopaminergic system contradicts observations of induction

of catatonia by neuroleptics that block dopamine receptors. This contradiction implies that alterations in dopamine metabolism may be complex in catatonia.

In contrast to catatonia, there is compelling evidence for the role of striatal dopamine D_2 receptor blockade in NMS (Mann et al. 2000). First, typical neuroleptics with high affinity for striatal D_2 blockade cause NMS significantly more often than atypical neuroleptics with low affinity (Caroff et al. 2000). Second, systematic studies have reported significantly decreased levels of HVA in patients with NMS (Nisijima and Ishiguro 1990, 1995). Third, a case report of a patient with NMS noted significant D_2 blockade on single photon emission computed tomography (SPECT) imaging (Jauss et al. 1996). There is also evidence for the efficacy of dopamine agonists in treating NMS (Davis et al. 2000).

Interest in neurochemical alterations in catatonia has focused on γ-aminobutyric acid–A (GABA-A) receptors because lorazepam is efficacious in 60%–80% of acute catatonic patients (Bush et al. 1996; Northoff et al. 1995a; Rosebush et al. 1990). One study using iomazenil binding with SPECT imaging showed that catatonic patients had significantly lower GABA-A receptor binding and altered right-left relations in left sensorimotor cortex compared with psychiatric and healthy control subjects (Northoff et al. 1999c). In addition, catatonic patients could be characterized by significantly lower GABA-A binding in right lateral orbitofrontal and right posterior parietal cortex, correlating significantly with motor and affective symptoms. Furthermore, movement-related cortical potentials, investigated in catatonic patients before and after lorazepam, showed abnormal and inverse electrophysiologic reactivity (Northoff et al. 2000b). In addition, all catatonic patients, even those in a postacute state, showed a paradoxical reaction to lorazepam, reacting with agitation rather than with sedation. These studies indicate that there may be abnormalities in the GABAergic system—and in particular GABA-A receptors (Carroll 1999)—that may be central to the pathophysiology of catatonia.

In NMS, GABA may play a role as well, but not as significant a role as in catatonia because the effects of lorazepam are not as dramatic as in catatonia (Mann et al. 2000). In addition to GABA-A receptors, GABA-B receptors may be involved in both catatonia and NMS (see Lauterbach 1998).

The glutamatergic system—in particular the NMDA receptors—may also be relevant. Some catatonic patients, whose symptoms were refractory to lorazepam, have been successfully treated with the NMDA antagonist amantadine. Therapeutic recovery occurred gradually (Northoff et al. 1997), suggesting that NMDA receptors may be involved secondarily in catatonia, whereas GABA-A receptors seem to be primarily altered. This

assumption is speculative because neither the NMDA receptors nor their interactions with GABA-A receptors have been investigated in catatonia.

As in some cases of catatonia, amantadine is effective in NMS, implying that NMDA receptors may be involved as well (Davis et al. 2000; Fricchione et al. 2000).

Although catatonia has been characterized by a disequilibrium in the serotonergic system, with upregulated serotonin$_{1A}$ (5-HT$_{1A}$) receptors and downregulated serotonin$_{2A}$ (5-HT$_{2A}$) receptors (Carroll 1999), there are no imaging studies of the serotonergic system in catatonia or NMS. In summary, neurochemical investigations suggest a central role for GABA-A receptors in catatonia, affecting the right orbitofrontal, right parietal, and right sensorimotor cortex. In contrast, NMS is characterized by primary dysfunction of dopamine in the striatum.

Structural and Functional Imaging Studies

A computed tomography investigation of patients with catatonic schizophrenia showed a diffuse enlargement in almost all cortical areas, particularly in frontal cortical regions, compared with hebephrenic and paranoid schizophrenic patients (Northoff et al. 1999d). A significant correlation of left frontotemporal areas with illness duration could be found in catatonic patients. Wilcox (1991) observed cerebellar atrophy in catatonic patients.

Investigations of regional cerebral blood flow (rCBF) in catatonia have shown right-left asymmetry in basal ganglia, with hyperperfusion of the left side (Luchins et al. 1989), hypoperfusion in left medial temporal structures (Ebert et al. 1992), alteration in right parietal and caudal perfusion (Liddle 1994), decreased perfusion in right parietal cortex (Satoh et al. 1993), and decreased perfusion in parietal cortex, with improvement after electroconvulsive therapy (Galynker et al. 1997). A systematic investigation of rCBF and SPECT in catatonic patients showed decreased perfusion in right posterior parietal and right inferior lateral prefrontal cortex compared with control subjects (Northoff et al. 2000c). In addition, decreased perfusion in right parietal cortex correlated significantly with motor and affective symptoms, as well as correlating abnormally with visuospatial and attentional neuropsychologic abilities.

Only three functional imaging studies in catatonia have been performed. Two catatonic patients were investigated with fMRI and a motor activation paradigm (Northoff et al. 1999a). Immediately after receiving lorazepam, both patients were imaged while exhibiting posturing during performance of a motor task. They showed an atypical pattern of lateralization, with alterations predominantly in the right motor cortex. This dif-

fers from Parkinson's disease, because no alterations in the supplementary motor area (SMA) were observed.

An activation paradigm for affective-motor interactions was developed and investigated using fMRI and MEG in postacute catatonic patients and control subjects (Northoff et al. 2000b). Catatonic patients showed alterations in right medial orbitofrontal/lateral orbitofrontal-prefrontal activation/deactivation patterns and early magnetic fields, which could be localized in medial prefrontal cortex, during negative emotional stimulation. Behavioral and affective catatonic symptoms correlated significantly with reduced orbitofrontal cortical activity, whereas motor symptoms correlated with premotor/motor activity. Negative emotional processing in right medial orbitofrontal cortex may be particularly altered in catatonia, with an abnormal functional connectivity to premotor/motor cortex.

Another study investigated auditory working memory with fMRI in catatonic patients compared with control subjects (A. Leschinger, F. Baumgart, A. Richter, et al., unpublished data). Catatonic patients showed significantly worse performance in working memory and significantly decreased activity in lateral orbitofrontal and premotor cortex compared with control subjects. Behavioral catatonic symptoms correlated significantly with orbitofrontal and premotor cortical activity, whereas motor symptoms were related to left lateral prefrontal cortical activity.

In summary, imaging studies demonstrate that the parietal cortex and particularly the right parietal cortex may be involved in catatonia. In addition, as demonstrated by fMRI, during working memory and emotional-motor activation, the orbitofrontal cortex may be altered as well. In contrast to the systematic studies using functional imaging in patients with catatonia, no such studies in patients with NMS have been reported so far.

Electrophysiologic Findings

Because catatonic symptoms are observed in patients with seizures, a relation between catatonia and epilepsy has been postulated (Louis and Pflaster 1995). A "non-ictal paroxysmal subcortical dysrhythmia" and an alteration in alpha rhythm have been postulated in catatonia. However, descriptive observations of electroencephalogram (EEG) in systematic studies did not yield any abnormalities in catatonic patients (Northoff et al. 1995b; Rosebush et al. 1990).

Because catatonia shows impressive motor features, movement-related cortical potentials (MRCPs) have been investigated in catatonia (Northoff et al. 2000a). Catatonic patients showed a significantly delayed onset

of late readiness and movement potential in central electrodes compared with control subjects. This delayed onset correlated significantly with catatonic motor symptoms and movement duration. In addition, lorazepam led to significantly stronger delays of late readiness potential in frontoparietal electrodes in catatonic patients than in control subjects. Whereas Parkinson's disease patients show distinct alterations in MRCPs, reflecting their difficulty in initiating movements (Jahanshahi et al. 1995), catatonic patients show alterations in MRCPs that reflect their inability to fully execute and terminate movements. In catatonia, the primary deficit seems to be one of termination rather than of initiation as in Parkinson's disease. There are no reports of investigation of MRCPs in patients with NMS. However, because of similarities in motor symptoms between NMS and Parkinson's disease, one would expect similar alterations in MRCPs (i.e., in early MRCPs), because this seems to be predominantly determined by dopamine, whereas later parts of MRCPs seem to be primarily modulated by GABA (Northoff et al. 2000a).

In summary, electrophysiologic findings do not indicate any consistent EEG abnormalities in catatonia. Investigations of cortical potentials underlying the initiation and termination of movements showed a differential pattern in catatonia compared with Parkinson's disease. Because MRCPs in catatonic patients showed abnormal, strong reactivity to lorazepam, GABA-A receptors may be central in the pathophysiology of motor symptoms in catatonia. In contrast, one would expect NMS to show alterations in MRCPs similar to those in Parkinson's disease, because both disorders can be characterized by striatal dopamine deficiency.

Catatonia as a Psychomotor Syndrome

Pathophysiologic findings in catatonia and NMS show both similarities and differences. In both diseases, striatal D_2 receptors and the basal ganglia may be involved, though to different degrees. In contrast to the importance of striatal dopamine receptor blockade in NMS, alterations in GABA transmission are apparently central in catatonia. Furthermore, there is evidence for involvement of cortical areas, such as right posterior parietal cortex and orbitofrontal cortex, in catatonia, but no findings have yet been reported in these areas in NMS.

How can one account for both pathophysiologic similarities and differences between catatonia and NMS? In the following, I present a unifying model in which I characterize catatonia as a psychomotor disorder, focusing primarily on functional effects of cortical alterations on subcortical regions, and NMS as a motor disorder, focusing on functional effects of subcortical regions on cortical areas (Figure 7–1).

Pathophysiology of Motor Symptoms

Catatonic patients are able to initiate movements but are apparently unable to terminate them appropriately (Northoff 1997; Northoff et al. 1995b). Neural networks underlying *termination* of movements, in contrast to those underlying initiation, have been neglected. In healthy subjects, termination of movements involves the right posterior parietal cortex because the registration and monitoring of the spatial position of movement may be of central importance for termination (Northoff et al. 2000c). Because findings in imaging and neuropsychology indicate a relationship between deficits in visual-constructive functions and decreased rCBF in right posterior parietal cortex (Northoff 2000; Northoff et al. 2000b), alterations in right posterior parietal cortical function may account for the deficit in termination of movements in catatonia. This assumption is further supported by our findings with late MRCPs and fMRI reflecting alterations in termination rather than in initiation. In addition, there are reports of posturing in patients with lesions in right posterior parietal cortex, which provides further support for involvement of the right posterior parietal cortex in monitoring of spatial position of movements and thus in termination. A deficiency in registration and monitoring of movements in catatonia, such as the one proposed, should lead to unawareness of the respective spatial position. This is indeed the case because catatonic patients, unlike Parkinson's disease patients, show anosognosia of posturing (Northoff et al. 1998), which I will call *motor anosognosia*.

In contrast, patients with NMS show neither posturing nor motor anosognosia but rather, like patients with Parkinson's disease, deficits in initiation of movements of which they are fully aware. Consequently, one may assume that motor symptoms in NMS, which resemble parkinsonian signs much more than catatonic symptoms, may be closely related to alterations in dopamine in striatum, as is strongly supported by pathophysiologic findings.

In summary, motor symptoms in catatonia may be primarily of (right posterior parietal) cortical origin, whereas in NMS they may be primarily of subcortical origin. Distinct cortical and subcortical origins may account for differences in motor symptoms between catatonia and NMS. Therefore, one may assume secondary downregulation of striatal dopamine and basal ganglia by primary cortical alterations in catatonia, which may then account for motor similarities between NMS and catatonia.

Pathophysiology of Affective Symptoms

There are strong affective alterations in catatonia that cannot entirely be associated with an underlying affective psychosis (Kahlbaum 1874). This

observation is supported by the therapeutic effectiveness of the anxiolytic lorazepam as well as by subjective experiences in patients who report intense anxieties (Northoff et al. 1998; Rosebush et al. 1990). Consequently, the affective dimension should be included as an important symptom category in catatonia (Northoff et al. 1999b).

An emotional-motor activation paradigm was developed to investigate the interrelation between affective and motor symptoms. Catatonic patients showed an abnormal activation/deactivation pattern in medial orbitofrontal and lateral orbitofrontal/prefrontal cortex during negative emotional stimulation, with deactivation in medial orbitofrontal cortex and activation in lateral orbitofrontal/prefrontal cortex, which is the inverse of the pattern seen in healthy control subjects. Because the medial orbitofrontal cortex is reciprocally connected with the amygdala, it is strongly involved in negative emotional processing (Drevets and Raichle 1998; Northoff et al. 2000b). Reduced and altered activation in orbitofrontal cortex may account for affective alterations in catatonia.

In addition, we found alterations in functional connectivity between medial orbitofrontal and premotor/motor cortex in catatonia compared with control subjects (Northoff et al. 2000b). These findings suggest that disturbed functional connectivity between orbitofrontal and premotor/motor cortex may be closely related to generation of motor symptoms. The lateral orbitofrontal cortex is strongly connected with the ventromedial caudate as part of the striatum, thereby being part of the orbitofrontal loop as a reentrant circuit between lateral orbitofrontal cortex, caudate, pallidum, thalamus, and orbitofrontal cortex (Mann et al. 2000; Mastermann and Cummings 1997). Consequently, alterations in orbitofrontal cortex may modulate both cortical and subcortical motor structures via direct functional connections, leading to downregulation of striatal dopamine and thus to parkinsonian symptoms in catatonia. Such an assumption of cortical-subcortical "top-down modulation" in catatonia corresponds with the early characterization of catatonia as a psychomotor disease by Homburger (1932) and with the subjective experiences of these patients.

The activation/deactivation pattern in medial and lateral orbitofrontal cortex during emotional stimulation seems to be modulated by GABA, because application of lorazepam in control subjects led to a reversal of the activation/deactivation pattern exactly as observed in catatonic patients without use of lorazepam (Northoff et al. 2000b). Alterations in the activation/deactivation pattern in medial and lateral orbitofrontal cortex in catatonia may be related to GABA dysfunction, in accordance with findings from SPECT imaging of benzodiazepine receptors showing reductions in right inferior prefrontal cortex. In catatonia, decreased inhibition

by GABA renders the orbitofrontal cortex unable to exert its gating function on prefrontal and frontal cortical areas, so that prefrontal activity becomes dysregulated. This could account for alterations in orbitofrontal-premotor/motor cortical connectivity. In addition, decreased orbitofrontal activation may lead to functional imbalance of the direct and indirect orbitofrontal loop, with downregulation of the former and upregulation of the latter, thereby reinforcing inhibitory impulses on motor areas in anterior cingulate SMA, leading to akinesia in catatonia. One may assume that altered cortical GABA transmission downregulates subcortical dopamine transmission, which may then account for rigidity in catatonia. Such mechanisms may account also for neuroleptic-induced catatonia (Fricchione et al. 2000). Both orbitofrontal and motor loops may be downregulated and thus vulnerable in the precatatonic state, and this vulnerability may be reinforced further by neuroleptics, resulting in the development of full-blown catatonia.

Motor symptoms in NMS, characterized by primary subcortical origins, may be directly related to striatal D_2 receptor blockade. However, patients with NMS may also show anxiety that, unlike catatonia, may be interpreted as reactive to awareness of motor alterations (Northoff et al. 1998). Blockade of striatal D_2 may modulate not only the motor loop to the SMA but also the orbitofrontal loop, which then may account for both anxiety and the partial therapeutic efficacy of lorazepam in patients with NMS (Davis et al. 2000). In contrast to cortical-subcortical top-down modulation in catatonia, one may speak of subcortical-cortical "bottom-up modulation" in NMS, both taking place via the same orbitofrontal and motor loops. This functional overlap with regard to the loops may account for similarities between catatonia and NMS, whereas the distinct kinds of modulation—that is, bottom-up and top-down—may account for differences between them. One may characterize catatonia as psychomotor, indicating top-down modulation, and NMS as motor, indicating bottom-up modulation.

In summary, affective symptoms in catatonia may be related to orbitofrontal alterations, which then downregulate striatal dopamine, leading to motor symptoms similar to those of NMS and Parkinson's disease. NMS, in contrast, may be characterized by subcortical alterations modulating cortical areas, which may account for affective alterations observed in such patients.

Pathophysiology of Behavioral Symptoms

Catatonic individuals often show bizarre behavioral signs, including repetitive phenomena (echolalia, stereotypies, perseverations), and distur-

bances of will (automatic obedience, negativisms). Such phenomena imply that catatonic patients are unable to control their behavior in an appropriate way. Control of behavior requires online monitoring, which is regarded as part of working memory. Investigations of working memory have shown severe deficits in catatonia that cannot be related to reduced ability of storage but rather are related to severe deficits in monitoring.

In addition, fMRI has shown that catatonic patients can be characterized by significantly decreased activation in lateral orbitofrontal and premotor cortex predominantly on the right side, which correlated significantly with behavioral symptoms (Northoff et al. 2000b). Behavioral alterations in catatonia may be related to dysfunction in lateral orbitofrontal cortex. Lesion studies in this area show repetitive phenomena and disturbances of will similar to catatonia. Medial and lateral orbitofrontal cortex could be characterized by inverse and reciprocal kinds of activity, which seem to be mutually dependent on each other (Drevets and Raichle 1998). Dysfunction in lateral orbitofrontal cortex may be closely related to alteration in negative emotional processing in medial orbitofrontal cortex, accounting for the close relationship between behavioral and affective symptoms in catatonia. Furthermore, lateral orbitofrontal cortex is reciprocally connected with posterior parietal cortex via long association fibers. This relation between lateral orbitofrontal and posterior parietal cortex may account for the deficit in monitoring of the spatial position of movements, which may be central to the pathophysiology of posturing as an inability to terminate movements. In a working memory study, the lateral orbitofrontal function was related to online monitoring, whereas the posterior parietal cortex accounted for spatial registration (A. Leschinger, F. Baumgart, A. Richter, et al., unpublished data). Consecutive tasks requiring both monitoring and spatial registration led to coactivation in both right lateral orbitofrontal/lower lateral prefrontal cortex and right posterior parietal cortex (Jueptner et al. 1997).

Our findings in catatonia indicate that alterations predominantly in right medial, lateral orbitofrontal cortex and right posterior parietal cortex cause dysfunction in the right medial/lateral orbitofrontal-posterior parietal cortical neural network during online monitoring of the spatial position of movements. This hypothesis remains speculative because both orbitofrontal and parietal regions have not been investigated within the same session using functional imaging or during termination of movements.

Unlike catatonia, NMS has been characterized neither by behavioral abnormalities nor by primary alterations in orbitofrontal cortex. Because the orbitofrontal cortex is only secondarily modulated by bottom-up modulation from the basal ganglia, this modulation may not be sufficient to elicit behavioral symptoms found in catatonia. If bottom-up modulation

in NMS is strong enough to affect lateral orbitofrontal cortex, such patients may develop behavioral signs, implying that in such cases one may speak of neuroleptic-induced catatonia.

Conclusion

Catatonia was originally described by Kahlbaum (1874) as a psychomotor disease with motor, affective, and behavioral symptoms. Early in the twentieth century, catatonia research focused on subcortical structures. More recent developments of new brain imaging techniques have revealed predominantly cortical rather than subcortical anomalies in catatonia. As a primarily cortical disorder, catatonia may be contrasted with NMS, which can be characterized as a disorder of the basal ganglia, with secondary involvement of cortical motor structures. Both catatonia and NMS may nevertheless be regarded as variants of the same disorder (see Fink 1996; Fricchione et al. 2000; Mann et al. 2000), implying both similarities and differences. Catatonia and NMS involve the same loops (orbitofrontal and motor). However, catatonia and NMS may differ in terms of distinct kinds of modulation—that is, cortical-subcortical top-down versus subcortical-cortical bottom-up predominately involving GABAergic, dopaminergic, and glutamatergic transmission. On this basis, catatonia may be regarded as a psychomotor disorder, whereas NMS may be described as a motor disorder.

Because similar loops are involved in both, there may be overlap in clinical phenomenology and treatment. Consideration of the pathophysiology of both disorders may reveal the nature of integration of motor function within affective, cognitive, and behavioral contexts, which may further enhance our understanding of brain function in general. Further research could focus on investigations of modulation underlying NMS and catatonia. Finally, differential characterization of catatonia as a psychomotor disorder and NMS as a motor disorder may potentially guide clinical investigations with regard to differential diagnostic symptoms, the search for diagnostic markers in brain imaging, and the development of pharmacologic and nonpharmacologic treatment strategies.

Catatonia may be specifically characterized by affective and behavioral alterations accompanying motor symptoms with right orbitofronto-parietal cortical GABA alterations as a diagnostic marker and GABA/glutamatergic and anxiolytic desensitization treatment strategies. NMS, in contrast, may be characterized by motor symptoms without accompanying affective and behavioral alterations, with striatal dopamine alterations as a diagnostic marker and dopamine enhancement as the predominant treatment strategy.

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CHAPTER 8

PERIODIC CATATONIA

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Periodic catatonia is a fascinating and underrecognized clinical entity that has been recognized mostly in the European literature. It was formally defined in the theoretical system of the Wernicke-Kleist-Leonhard school (Leonhard 1979, 1995; Ungvari 1993). The disorder is characterized by catatonic episodes occurring in a cyclic pattern, with clinical features of combined stupor and excitement, remissions to an interval state, and an autosomal dominant pattern of transmission (Meyer et al. 2001; Stöber et al. 1995).

An ongoing debate has addressed whether catatonic symptoms are associated more often with mood disorders than with schizophrenic illnesses. Because of the prevailing nosology of periodic catatonia, this disorder is presently viewed as a subtype of schizophrenia (Leonhard 1995). This may change as our understanding of the syndrome of catatonia evolves.

Recent research has identified in one extended family a gene associated with periodic catatonia, distinguishing this condition as the first psychiatric disorder to be connected with a specific genetic defect (Meyer et al. 2001). Its periodic nature is potentially linked to the etiology and treatment of other periodic disorders. An improved understanding of the features of this illness will allow better recognition and treatment.

Epidemiology

Limited information is available regarding the epidemiology of periodic catatonia. Gjessing (1974) put forth incidence and prevalence rates of the disorder among schizophrenic patients of 2%–3%. In a more recent series, Leonhard's criteria for periodic catatonia were met in 59.7% of patients with catatonic schizophrenia defined by DSM-III (American Psychiatric Association 1980) criteria (Beckmann et al. 1996; Stöber et al. 1995). This suggests that many patients diagnosed with catatonic schizophrenia may instead have periodic catatonia. Although present rates of catatonic schizophrenia appear significantly lower than those found in the early twentieth century, there is little published information and no clear consensus on the subject (see Chapter 2, "Epidemiology," this volume; also see Morrison 1973, 1974). Confusion about the present rate of catatonic schizophrenia thus makes it difficult to accurately estimate the current incidence of periodic catatonia.

Periodic catatonia has been described across a wide range of ages, including children as young as age 7 (Gjessing 1974). However, most patients present with symptoms between 15 and 35 years of age (Gjessing and Gjessing 1961). There appear to be no significant gender differences in its distribution (Gjessing 1974).

Nosology

In modern literature, periodic catatonia is not recognized in the DSM-IV (American Psychiatric Association 1994, 2000) or ICD-10 (World Health Organization 1992) systems. It is most formally defined in the classification system of Leonhard (1979). Research suggests that the categories in this system have substantial clinical reliability and validity (Ban 1990; Beckmann and Franzek 2000; Strik et al. 1993; Tolna et al. 2001; Ungvari 1985). Although Leonhard's system is complex (Ungvari 1985), recent articles have clarified it, allowing for operationalized diagnosis (Ban 1982; Fritze and Lanczik 1990; Perris 1990). However, because of widespread unfamiliarity with this work, the diagnosis of periodic catatonia may be unknown to many clinicians.

Periodic catatonia falls under Leonhard's class of "unsystematic schizophrenias," sharing this category with his diagnoses of "affective paraphrenia" and "cataphasia" (Leonhard 1995). The common thread unifying these three unsystematic schizophrenias is their similarity in onset, course, and prognosis. Illnesses of this class share the features of frequently abrupt onset and an indistinct clinical picture. They are characterized by a more stable course, frequent periodicity, and favorable outcome (Leonhard 1995).

In contrast, the "systematic schizophrenias" correlate closely with more severe cases meeting DSM and ICD criteria for schizophrenia. These illnesses are characterized by relatively insidious onset, fairly typical presentation, chronic course, and poorer outcome (Leonhard 1995).

Clinical Features

The clinical hallmark of periodic catatonia is the presence of repeated catatonic phases, often occurring with regular periodicity. After the catatonia remits, patients often show some degree of thought, motor, or affective impairment. Importantly, in the catatonic phase, features of both stupor and excitement often coexist, although one pole is generally predominant (Leonhard 1995). Gjessing (1974) suggested that the character of the catatonia is more distinctly polarized, and that the excited variety is far more common than the stuporous. Some patients appear to cycle into either primarily stuporous or excited states, whereas others experience both types of episodes. The duration of the cycles may vary from days to months, but it is usually regular in individual patients. The disorder may persist for decades or may remit spontaneously (Gjessing 1974). Remissions may be interrupted by exacerbations of repeated cycling.

The movements of patients with periodic catatonia lose their natural quality and purposefulness and are performed in jerky, unnatural ways. The meaning of expressive and reactive movements becomes unclear, in terms of both gross limb movements and facial expressions, as the original movements are distorted. Apparently random limb movements, stereotyped postures, and rigidity are common features. Impulsive acts may occur as well, and patients can become aggressive. Negativism is common.

The concurrence of akinetic and hyperkinetic traits is the feature of periodic catatonia that made it dramatic and distinct to Leonhard (1979). In the akinetic phase, patients may sit stiffly but repeatedly strike out with an arm, or they may exhibit facial grimacing as a manifestation of hyperkinesis. In the hyperkinetic phase, akinesis appears to limit the execution of the excited movements, making them jerky and stiff.

Gjessing (1974) described the clinical features of periodic catatonia in terms of the interval phase, the transition into catatonia, and the fully developed catatonic phase. In the *interval phase*, patients may have no obvious deficits but frequently experience limitations in judgment and insight into their illness. Other residual symptoms from repeated cycling may be present, including generalized body weakness, affective impairment, indifference, and irritability, which may lead to aggressive episodes. Residual symptoms in the interval state tend to worsen with increasing numbers of cycles. In cases of poorer outcomes, residual symptoms may

include persistence of some unnatural movements, as well as impulsivity of actions and speech and affective impairment. Recurrences of stuporous states are more likely to be associated with greater residual symptomatology, as compared with repeated excited phases. In the *transition phase*, patients have subtle, recognizable symptoms as they near the catatonic state. Patients going into an excited catatonia become more seclusive and stuporous, whereas those approaching a stuporous catatonia become more excited and restless. Physiologic features include variability in pulse rate and pupillary diameter. Within 1–2 days, patients stabilize into the *catatonic phase*, either excited or stuporous. The stuporous variety is commonly more abrupt in development than the excited.

Patients with catatonic excitement display the characteristic hyperkinetic motor symptoms, along with a decreased level of consciousness, poor concentration, and thought incoherence. However, orientation is often preserved to a surprising degree. Somatic features include tachycardia, mild hypertension, and pupillary dilation. Furthermore, leukocytosis, relative hyperglycemia, and diuresis commonly occur.

In a state of catatonic stupor, the typical akinetic motor features are similarly combined with poor awareness of the environment and very limited ability to comprehend or react to the surroundings. Patients may suddenly awake from their stupor in a state of mild euphoria. Somatic symptoms include tachycardia, hypertension, excessive salivation, and pupillary dilation. Sleep and appetite are limited. Constipation and urinary retention are common. Leukocytosis and hyperglycemia are also noted.

Additional psychotic features and affective disturbances are also found in periodic catatonia but are not essential features. Symptoms of hallucinations, delusions, paranoia, and ideas of reference may accompany both the excited and stuporous episodes. These are sometimes present before the catatonic and periodic features of the illness appear and may represent a prodrome. Although affective disturbances have been readily recognized in other catatonic states, the literature on periodic catatonia reveals little on the subject. Numerous published cases have described maniclike behavior, but explicit references to elevated mood in periodic catatonia are few (Gjessing 1974; Leonhard 1995). Depressed mood is not specifically identified but is apparent in accounts of stuporous patients, in both the interval and catatonic phases (Leonhard 1995). However, there are no data at this time supporting the presence of affective symptoms as a principle finding in periodic catatonia.

As reviewed in Chapter 6 ("Laboratory Findings") in this volume, metabolic studies have revealed a high basal metabolic rate, and elevation of free fatty acids, glucose, and catecholamines during the catatonic phase compared with the interval phase, suggesting increased sympathetic tone

associated with stupor or excitement (Gjessing 1974). Gjessing (1974) also described marked periodicity in total blood nitrogen that paralleled, but did not temporally coincide with, the periodicity of patients' symptoms.

Electroencephalographic patterns show lower voltage and higher frequency of alpha waves during the catatonic phase, as compared with the interval phase (Gjessing 1967). Sleep studies reveal increased rapid eye movement (REM) time at the end of the interval period, followed by prolonged REM latency and decreased REM time during the catatonic phase (Takahashi and Gjessing 1973). Paradoxical bradycardia during REM sleep, which is known to occur in other catatonic states, has also been described during the later part of the catatonic phase, when symptoms are improving, in periodic catatonia (Takahashi and Gjessing 1973).

Etiology

Periodic catatonia has the distinction of being a highly genetically linked illness (see Chapter 15, "Genetics," this volume). Leonhard (1980) considered this an essential feature when he defined the diagnosis in his classification system. Periodic catatonia is now recognized as an autosomal dominant condition (Meyer et al. 2001; Stöber et al. 1995). Stöber et al. found that the relative risk of periodic catatonia among first-degree relatives of affected patients was 26.9%, compared with 4.6% among relatives of patients with other forms of catatonic schizophrenia (Beckmann et al. 1996; Stöber et al. 1995).

In families with periodic catatonia, more parents than siblings were affected, consistent with a major gene effect. In 93% of the families, affected children developed the illness at a younger age than their parents, demonstrating the phenomenon of anticipation (Stöber et al. 1995). Trinucleotide repeats have been investigated in relation to periodic catatonia, as this genetic pattern is associated with genetic anticipation (Bengel et al. 1998; Lesch et al. 1994; Mandel 1993).

Stöber et al. (2000b) determined through linkage analysis that in multiple families, the disease locus maps to chromosome 15q15. In one family, linkage was found to chromosome 22q13, suggesting genetic heterogeneity in periodic catatonia (Stöber et al. 2000a). Research in this family has identified an associated gene on locus 22q13.33 as *WKL1*, which codes for a protein thought to function as a nonselective cation channel found only in the brain (Meyer et al. 2001). A Leu309Met mutation is believed to alter the conformation and function of this suspected transmembrane protein. The gene was expressed at highest concentrations in the amygdala, caudate nucleus, thalamus, and hippocampus. The authors posit that restricted channel function in nigrostriatal motor and mesolimbic systems

may account for the motor, cognitive, and affective signs of periodic catatonia (Meyer et al. 2001).

Decades before detailed genetic analysis could be employed, early researchers investigated pathophysiologic mechanisms of periodic catatonia based on clinical features, laboratory findings, and treatment results. The capacity of high-dose thyroid hormone to ameliorate symptoms and inhibit cycling pointed to the possibility of thyroid dysfunction in periodic catatonia (Gjessing 1975). Abnormal levels of catecholamines suggested that adrenal cortical dysfunction might be involved. Thyroid and catecholamine abnormalities also supported hypothalamic dysfunction as a possible mechanism. The variation in nitrogen balance was also seen as indicative of a hormonal process. The periodicity has been attributed to the buildup of a putative neurotoxic substance, which is then depleted during the catatonic phase, only to regularly build up again (Gjessing 1974, 1975).

Course

Because most patients with psychotic symptoms receive prompt treatment, the natural course of periodic catatonia is rarely seen. It is likely that most cases are diagnosed as other psychotic disorders and only partially treated. In these cases, variability in the patient's course is likely influenced by the periodicity of the illness. Understanding the natural course of periodic catatonia provides insight into the presentation of partially treated patients.

Periodic catatonia may present in an acute fashion, although the pattern often emerges after a lengthy period of a schizophrenic illness (Gjessing and Gjessing 1961). Remissions to the interval state follow acute phases of the illness. Patients may continue to cycle between the interval state and active catatonic psychosis, with regularity, until the course of the illness is interrupted by treatment. Others, particularly young people with brief illnesses, have their illness spontaneously remit (Gjessing and Gjessing 1961). Patients with the hyperkinetic form are said to have a better prognosis, often having little in the way of residual symptoms even after several episodes (Leonhard 1995). However, those with the akinetic form are more likely to experience long-term sequelae.

The rate of cycling in periodic catatonia is highly variable and can range from days to months. Children inheriting the condition are at risk for an earlier onset and more severe course with potential for greater residual effects (Stöber et al. 1995). With proper treatment, some cases may be arrested with a good outcome. This involves control of the catatonic phases, as well as an arrest of the cycling and attenuation of the residua of the interval states. In poorer outcomes, patients may become fixed in the interval state, with chronic residual symptoms of varying severity.

In partially treated patients, antipsychotic medications likely alter the course of the illness and may have the potential to limit catatonic phases. In such cases, the patient may be left in the interval phase, with varying degrees of residual symptoms. Alternatively, antipsychotics may exacerbate catatonic symptoms, further complicating the picture (Philbrick and Rummans 1994). Changes in treatment, such as adjustments in medication dosing, may leave the patient vulnerable to exacerbations of catatonic and other psychotic symptoms. This may present as a course of recurrent catatonia. Although a recurrent course of catatonia may develop in association with other illnesses, it may be a manifestation of partially treated periodic catatonia. In such cases, the periodic quality is not appreciated, and the diagnosis is usually not considered.

Diagnosis

Periodic catatonia is primarily a clinical diagnosis. The presence of regularly cycling periods of catatonic stupor or excitement, alternating with intervals of clearing of catatonic symptoms, defines the diagnosis of periodic catatonia. Multiple laboratory correlates, as well as genetic factors, are associated with the illness. However, these are unlikely to be pursued should the clinical features remain unrecognized.

Two principal barriers limit the recognition and diagnosis of this illness. First, the unfamiliarity of psychiatrists with the existence of this clinical entity obviously limits its recognition. Second, in our age of improved access to mental health care and aggressive treatment of psychotic symptoms with antipsychotic medications, clinicians are unlikely to see the cyclic quality in the natural course of periodic catatonia.

Only European researchers have widely embraced the diagnosis, and it is practically unknown in the United States. Patients with periodic catatonia meet criteria for, and are commonly diagnosed with, catatonic schizophrenia (American Psychiatric Association 1994; Stöber et al. 1995). Periodic catatonia may also be mistaken for the acute mania of bipolar disorder, because they share the cardinal features of hyperkinesia and thought disorder. The diagnosis of periodic catatonia should also be considered in patients appearing to have stuporous depression with psychotic features as part of bipolar disorder.

Because the partially treated patient presents an unclear picture, the clinician should consider periodic catatonia in the differential diagnosis of catatonic schizophrenia and bipolar disorder. The careful gathering of family histories in these cases is crucial. Patients with periodic catatonia will demonstrate a strong unilinear pattern of psychotic disorders in their families. The course of the illness may be clearer in previous generations,

when patients were less likely to be treated. This effort is certainly worthwhile, given the likelihood that a large percentage of patients diagnosed with catatonic schizophrenia, and perhaps bipolar disorder, in fact have periodic catatonia (Beckmann et al. 1996; Stöber et al. 1995). Proper diagnosis is vital to ensure appropriate and adequate treatment of not only the active catatonic phases but the cycling course as well. This also allows clinicians to offer a more accurate prognosis to patients and families.

Relationship to Other Periodic Disorders

The periodicity in periodic catatonia has raised questions regarding its relationship to other cyclic illnesses. The most obvious of these is bipolar disorder. The frequent presence of catatonic symptoms in mood disorders is well recognized (Abrams and Taylor 1976; Fein and McGrath 1990; Perris 1990). Patients with severe psychotic symptoms in the manic or depressive stages of bipolar disorder may indeed resemble the periodically cycling catatonic patient.

Debate on the subject has further considered whether catatonic symptoms may be associated more often with mood disorders than with schizophrenia. The paucity of patients diagnosed with catatonic schizophrenia in our day has likely contributed to this outlook. A review by Abrams and Taylor (1976) suggests that catatonic signs are indeed most commonly associated with mood disorders. The relationship between catatonic symptoms and mood disorders, coupled with the periodicity shared by periodic catatonia and bipolar disorder, paints an intriguing picture of the possible association between these illnesses.

More distant associations may exist between periodic catatonia and other periodic disorders. For example, a recent study of the gene *WKL1* in periodic catatonia noted its similarity to *KCNA1* on chromosome 12p (Meyer et al. 2001). *KCNA1* is associated with episodic ataxia type 1, which also is a periodic, autosomal dominant neurologic condition associated with a cation channel abnormality (Benatar 2000). The implications of an association between these two periodic illnesses, which both involve motor symptoms and appear to be associated with autosomal dominant cation channel abnormalities, are unknown.

Treatment

Current treatments for the psychotic phase of periodic catatonia parallel those for other catatonic syndromes and include benzodiazepines and electroconvulsive therapy. The issue of neuroleptics poses a particular problem.

Although these medications can sometimes arrest catatonic symptoms, concerns arise about the possibility of neuroleptics worsening catatonic syndromes (Philbrick and Rummans 1994).

The general syndrome of catatonia may lie along a continuum that includes catatonic schizophrenia as well as malignant catatonia, of which neuroleptic malignant syndrome is a drug-induced subtype (Philbrick and Rummans 1994). Where periodic catatonia may lie in this theoretical construct is not clear. If periodic catatonia lies near the malignant end of this continuum, neuroleptics may potentially exacerbate symptoms (Clark and Rickards 1999; Philbrick and Rummans 1994).

Early in periodic catatonia research, clinicians recognized the need to treat both the active catatonic phases and the periodicity of the illness. Gjessing (1974) was the first to report the efficacy of high-dose thyroid hormone in the treatment of periodic catatonia. Doses of up to several hundred milligrams daily have been reported to extinguish the active phase of the illness and prevent cycling (Komori et al. 1997). One study cited a high rate of thyroid disorders among patients with bipolar disorder and suggested a mechanism for thyroid hormone in periodic disorders (Cowdery et al. 1983). Komori et al. (1997) suggested that the cyclic nature of both of these illnesses points to a role of thyroid hormone in controlling biological periodicity via a stabilizing effect on the hypothalamus.

Reserpine has been used as an adjunctive agent to thyroid hormone in treating periodic catatonia. Its potential benefit may lie in its antiadrenergic effect as well as its capacity to potentiate the effect of thyroid hormone therapy by interfering with thyroid-stimulating hormone release and action (Komori et al. 1997).

Although lithium is primarily prescribed for bipolar disorder, it has also been proposed in case reports as an anticycling agent for patients with periodic catatonia. It appears to have the potential to offer significant benefit in slowing or arresting the periodicity of the illness (Gjessing 1967; Hanna et al. 1972; Petursson 1976; Wald and Lerner 1978). Although anticonvulsants are commonly used to limit the cycling of bipolar disorder, no reports have investigated the potential of these drugs in treating periodic catatonia.

Conclusion

Periodic catatonia is a well-characterized, discrete psychiatric entity. Its validity is supported by clinical findings as well as genetics. A unique picture of catatonic symptoms coupled with a periodic course occurs in this disorder. The apparently autosomal dominant transmission of the disorder suggests a role in research on the genetic basis of psychotic disorders.

The obscurity of this illness likely leads to many missed diagnoses. Familiarity with the clinical features, heritability, and proper therapeutic approach to periodic catatonia has the potential to greatly improve its recognition and treatment.

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CHAPTER 9

MALIGNANT CATATONIA

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In 1934, Stauder described "lethal catatonia," characterized by extreme motor excitement followed by stuporous exhaustion, cardiovascular collapse, coma, and death. The entire course involved progressive hyperthermia, autonomic dysfunction, clouding of consciousness, and prominent catatonic features. In fact, this disorder had been discussed previously by Calmeil (1832) and Bell (1849) and was the subject of numerous publications throughout the pre–antipsychotic drug era (Mann et al. 1986; Philbrick and Rummans 1994).

Although the incidence of lethal catatonia, or malignant catatonia (MC), appears to have declined following the introduction of modern psychopharmacologic agents, it remains the subject of frequent case reports. From a review of the literature, we propose that MC continues to occur and represents a syndrome rather than a specific disease. Although most often an outgrowth of the major psychoses, MC also occurs in association with diverse neurologic and medical conditions. From this perspective, neuroleptic malignant syndrome (NMS), a potentially fatal complication of antipsychotic drug treatment (Caroff 1980; Caroff and Mann 1993), may be viewed as a

drug-induced form of MC. Our review also supports a conceptualization of catatonia as a continuum, with milder forms at one end and more severe forms involving hyperthermia (i.e., MC) at the other end. In addition, findings from our review suggest that MC, simple catatonia, and NMS share a common pathophysiology involving reduced dopaminergic neurotransmission within the basal ganglia thalamocortical circuits.

Clinical Presentation

Pre–Antipsychotic Drug Era

Despite the diversity of nomenclature, there is considerable consistency to early accounts of MC. A prodromal phase was noted in most cases, characterized by lability of mood, with deterioration of sleep and appetite. In roughly 90% of cases, the disease proper began with a phase of extreme motor excitement. Features of this excited phase included refusal of food and fluids, clouding of consciousness, tachycardia, tachypnea, labile or elevated blood pressure, and profuse perspiration. Acrocyanosis and spontaneous hematomas of the skin were frequently noted. At times, excitement might be interrupted by periods of catatonic stupor and rigidity. Other catatonic signs, such as mutism, catalepsy, staring, posturing, echolalia, and echopraxia, were often present. Thought processes became increasingly disorganized and speech grew progressively incoherent. Auditory and visual hallucinations accompanied by bizarre delusions were often prominent.

In this "classic" excited form of MC, excitement was always associated with hyperthermia, which could attain levels approaching 43.3°C prior to the final stuporous phase of the disorder. This presentation differs phenomenologically from NMS in that although NMS is often preceded by a period of hyperactivity, hyperthermia first emerges concomitantly with, or shortly after, the onset of stupor and rigidity. The excited phase of MC was noted to vary in duration but lasted an average of 8 days (Arnold and Stepan 1952).

In the final phase, excitement gave way to stuporous exhaustion with extreme hyperthermia, coma, cardiovascular collapse, and death. In all of Stauder's (1934) 27 cases, a rigidity of the skeletal musculature was described during this terminal stupor, similar to that seen in NMS. Although other accounts of MC echoed the findings of Stauder, some reports described flaccid muscles in contrast to NMS (Arnold and Stepan 1952). About 10% of cases reported during the pre–antipsychotic drug era involved hyperthermia and a primarily stuporous course unassociated with a preceding hyperactive phase.

MC was fatal in 75% (Bell 1849) to 100% (Lingjaerde 1963) of cases. Most reports were in agreement with Scheideggar's (1929) observation that MC occurred predominantly in young adults between the ages of 18 and 35 and involved women roughly seven times more often than men. MC was estimated to account for 0.25% (Ladame 1919) to 3.5% (Derby 1933) of admissions to psychiatric hospitals and occurred with equal frequency throughout the seasons. Stauder (1934) and Arnold and Stepan (1952) reported findings consistent with a familial occurrence of MC.

Kraepelin (1905), who called this disorder *delirium acutum*, considered it a nonspecific syndrome that could occur as an outgrowth of neuromedical illnesses as well as the major psychoses. In contrast, most early French authors viewed MC as a form of encephalitis involving the hypothalamus (Ladame 1919). Subsequent to Stauder's (1934) publication, however, MC was increasingly seen as confined to the major psychoses, although Stauder himself never fully dismissed the possibility that some or all of his patients may have had encephalitis. The majority of German authors came to link MC with schizophrenia, whereas in the American literature it was associated with mood disorders (Kraines 1934), schizophrenia (Billig and Freeman 1944), or both conditions (Shulack 1946). Autopsy findings were negative in most cases. Central nervous system abnormalities reported by the French were either unconfirmed or deemed trivial. Bronchopneumonia and other infections were considered "opportunistic" because they occurred in an already exhausted and compromised host.

Contemporary Literature

In 1986, we identified a series of 292 cases of MC reported between 1960 and 1985. Most patients had received antipsychotic drug treatment (Mann et al. 1986). Since then, we identified 77 additional MC cases reported in the world literature between 1986 and 2002, thus extending our series to 369 total cases (Lazarus et al. 1989; Mann and Caroff 1990; Mann et al. 1986, 1990, 2001, 2003).

Gender was specified in 322 of the full series of 369 MC cases; in 212 (66%) of the cases, the patient was female. This indicates that women continue to be more commonly affected than men, although the trend may now be somewhat reduced. The mean age at occurrence was 33, compared with 25 during the pre–antipsychotic drug era. Of the 369 cases, 183 (50%) ended in death, representing a modest reduction from the pre–antipsychotic drug era. However, among the 77 cases reported since 1986, only 7 (9%) ended in death. This apparent decline in mortality is striking and presumably reflects greater awareness of MC, early diagnosis, and the rapid institution of appropriate management strategies. Nevertheless, MC

continues to represent a potentially lethal disorder. Similar to findings from the pre–antipsychotic drug era, a uniform seasonal distribution was evident. Among cases reported since 1960, MC was estimated to occur in 0.07% of psychiatric admissions (Koziel-Schminda 1973) or annually in 0.0004% of community adults (Hafner and Kasper 1982).

In addition to catatonic hyperactivity and stupor, the clinical features of MC described in this more recent literature remain hyperthermia, altered consciousness, and autonomic instability as manifested by diaphoresis, tachycardia, labile or elevated blood pressure, and varying degrees of cyanosis. Catatonic signs aside from stupor and excitement continue to be noted. In one large series, Singerman and Raheja (1994) identified 62 patients with psychogenic MC and reported that each exhibited at least three catatonic features. Among the 77 most recent cases, muscle rigidity was reported in 27 (79%) of 34 cases in which muscle tone was characterized.

Among the 77 recent MC cases, creatine phosphokinase was elevated in 24 (96%) of 25 patients in whom it was tested. Leukocytosis was reported in 17 (71%) of 24 patients, and serum transaminases were elevated in 10 (50%) of 20 patients. Serum iron levels were obtained in only 7 patients, but were decreased in all 7. Less consistent findings among the 77 recent cases included nonfocal generalized slowing on electroencephalograms, mild hyperglycemia, elevated serum creatinine, hyponatremia, hypernatremia, and dehydration. Philbrick and Rummans (1994) found that 3 of 5 MC cases treated at their facility had evidence of frontal atrophy on computed tomography (CT) scans of the head. Furthermore, 1 patient with a normal head CT had decreased frontal perfusion on posttreatment single-photon emission computed tomography imaging.

In 49 (13%) of the 369 contemporary MC cases, a preexisting neuromedical illness initiated the full syndromal picture. Infectious causes predominated—in particular, acute and postinfectious viral encephalitis and bacterial septicemia—with cerebrovascular disorders, normal-pressure hydrocephalus, and various metabolic and toxic disorders accounting for additional cases (Mann et al. 1986, 2003).

Of the 369 cases, 320 (87%) were associated with a major psychotic disorder, diagnosed as schizophrenia in 126 cases, mania in 13 cases, major depression in 22 cases, psychosis not otherwise specified in 22 cases, and periodic catatonia in 10 cases. In the remaining 127 cases of psychogenic origin, a specific diagnosis was not given. In this series, the frequent association of MC with schizophrenia may be spurious, resulting from a continued misconception that catatonic signs imply catatonic schizophrenia. Of the 320 MC cases attributed to the major psychoses, 163 (51%) ended in death. Autopsy data were available for 99. Of these 99, 79

(80%) proved autopsy negative and as such were considered "genuine" psychogenic MC cases. In the remaining 20 cases, however, death could be attributed to complications of catatonic immobility, such as deep venous thrombosis with pulmonary embolism. Such cases of benign catatonia rendered fatal by severe intercurrent medical complications were differentiated from genuine psychogenic MC.

Catatonia, Malignant Catatonia, and Neuroleptic Malignant Syndrome

Our review of the modern literature supports Kraepelin's (1905) conceptualization of MC as a nonspecific syndrome. Consistent with this view, it is appropriate to consider the relationship between MC, simple catatonia, and NMS. Among the 369 contemporary MC cases, the "classic" excited form involving extreme hyperactivity and progressive hyperthermia prior to the onset of stupor continued to predominate, with 67% of cases presenting in this fashion. However, 33% of patients exhibited a primarily stuporous course. This represents a change from the pre–antipsychotic drug era, when only about 10% of patients presented in this fashion. Furthermore, a selective analysis of the 77 MC cases reported since 1986 indicates that this trend has continued, with only 57% exhibiting excitement and 43% now presenting as stuporous.

In many of these cases involving a stuporous course, stupor and hyperthermia developed only following the initiation of antipsychotic drug treatment, giving rise to questions concerning the differentiation of MC from NMS. Furthermore, the clinical features of the presentation of classic excited MC, once stupor emerges, appear equally difficult to distinguish from NMS. Viewing MC as a syndrome, we suggested that NMS represents an antipsychotic drug–induced form of MC. Accordingly, the emergence of NMS as a subtype of MC could help explain the increased percentage of primarily stuporous MC cases reported in the contemporary literature.

Along these lines, Philbrick and Rummans (1994) view catatonia as a continuum with milder forms at one end (simple catatonia) and more severe forms, involving hyperthermia and autonomic dysfunction (MC), at the other. They also conceptualize NMS as a drug-induced form of MC, and thus a variant of the larger catatonic syndrome. Fricchione et al. (1997, 2000) suggested a close relationship between catatonic states triggered by antipsychotics and those that are not, and they proposed that antipsychotic drug–induced catatonia is to simple catatonia what NMS is to MC.

Koch et al. (2000) provided further evidence for overlap among catatonia, MC, and NMS. Among 16 patients with NMS, 15 met simultaneous clinical and research criteria for catatonia. Furthermore, in each of their cases, there was a strong positive correlation between the severity of NMS and the number of catatonic signs, strengthening the argument for a relationship between these two disorders. Fink (1996) also contended that NMS and catatonia are variants of the same disorder.

In 1991, Rosebush and Mazurek found decreased serum iron levels in NMS and suggested a role for lowered iron stores in impairing dopamine receptor function in that disorder. In support of the hypothesis that NMS is a severe variant of catatonia, Carroll and Goforth (1995) reported that catatonic patients with low serum iron levels were at risk for developing NMS on exposure to antipsychotics. Furthermore, Lee (1998) found low serum iron levels in all seven MC episodes drawn from his series of 50 prospectively identified patients with catatonia. Of note, Lee (1998) distinguished MC from NMS based on the absence of extrapyramidal features in the former. Similar to Carroll and Goforth (1995), Lee reported that when antipsychotic drug treatment was initiated in five MC episodes, all progressed to NMS. In addition, by describing 17 consecutive cases of NMS in which catatonia had been the presenting picture prior to the administration of antipsychotics, White and Robins (2000) provided further evidence that NMS represents an intensification of a preexisting catatonic state rather than a separate entity.

In contrast, some authors consider simple catatonia, MC, and NMS to be distinct clinical syndromes. Both Castillo et al. (1989) and Fleischhacker et al. (1990) proposed that excited or agitated behavior points to a diagnosis of MC. However, agitation is commonly a feature of the psychosis preceding NMS for which antipsychotics were originally used (Levenson 1989). Castillo et al. (1989) also maintained that prominent muscle rigidity might be a distinguishing feature. Similarly, Lee (1998) differentiated NMS from "non-NMS MC" on the basis of extrapyramidal rigidity. However, as Levenson (1989) underscored, patients with agitated catatonia usually receive antipsychotics early in treatment. As such, if rigidity is present, it may be difficult to know whether this represents NMS or antipsychotic drug–induced extrapyramidal symptoms superimposed on MC. In our most recent series of 77 MC cases, muscle rigidity was identified in 79% of cases in which its presence or absence was specified.

Others have argued that case reports and case series of NMS do not consistently mention catatonic features. Pearlman (2000) reviewed roughly 700 reports on NMS between 1989 and 1999 and found that catatonic features were mentioned in only about 25%. However, he underscored that incomplete reporting of clinical data compromised attempts to assess the

actual prevalence of catatonic features. This contrasts with the work of Koch et al. (2000), in which catatonic signs were consistently identified in NMS patients through systematic screening with specific catatonia rating scales. We concur with Fricchione et al. (1997, 2000) that despite a few differences in presentation, catatonia, MC, and NMS appear to be part of a unitary syndrome.

Pathogenesis

A consideration of the pathogenesis of MC with a particular focus on dopamine further supports a view of simple catatonia, MC, and NMS as variants of a unitary syndrome. A number of authors have posited a key role for dopamine hypoactivity in triggering both simple catatonia and MC (Fricchione et al. 1997, 2000; Lohr and Wisniewski 1987; Taylor 1990). Furthermore, there is compelling clinical evidence implicating antipsychotic drug–induced dopamine receptor blockade in the pathogenesis of NMS (Mann et al. 2000). Fricchione et al. (1997, 2000) along with our group (Mann et al. 2000, 2003) proposed that the onset of catatonia coincides with a reduction in dopamine activity within the basal ganglia thalamocortical circuits. As elucidated by Alexander et al. (1986, 1990), these circuits represent one of the brain's principal organizational networks underlying brain-behavior relationships. Five circuits connecting the basal ganglia with their associated areas in the cortex and thalamus have been identified and are named according to their function or cortical site of origin (Figure 9–1). They include the motor circuit, the oculomotor circuit, the dorsolateral prefrontal circuit, the lateral orbitofrontal circuit, and the anterior cingulate–medial orbitofrontal circuit. Each circuit involves the same member structures, including an origin in a specific area of the frontal cortex; projections to the striatum (putamen, caudate, and ventral striatum); connections to the globus pallidus interna and the substantia nigra pars reticulata, which, in turn, project to specific thalamic nuclei; and a final link back to the frontal area from which the circuits originated, thus creating a feedback loop.

Dopamine is in a key position to influence activity in each of the circuits. Mesocortical dopamine pathways project directly to circuit origin sites in the supplementary motor area, frontal eye fields, and the three prefrontal cortical areas. Additionally, dopamine modulates each circuit through its projections to the striatum (Cummings 1993). The motor, anterior cingulate–medial orbitofrontal, and lateral orbitofrontal circuits represent the most likely candidates for involvement in the pathogenesis of simple catatonia, MC, and NMS.

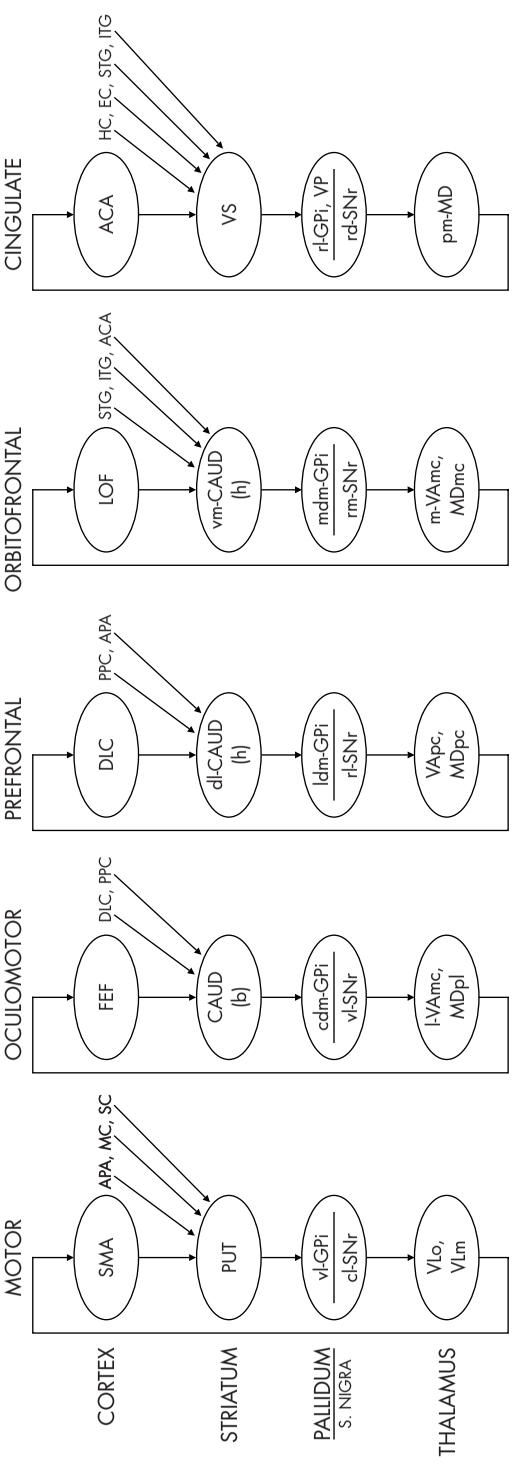

MOTOR
OCULOMOTOR
DORSOLATERAL PREFRONTAL
LATERAL ORBITOFRONTAL
ANTERIOR CINGULATE
CORTEX
STRIATUM
PALLIDUM
S. NIGRA
THALAMUS
SMA
APA, MC, SC
FEF
DLC, PPC
DLC
PPC, APA
LOF
STG, ITG, ACA
ACA
HC, EC, STG, ITG
PUT
CAUD (b)
dl-CAUD (h)
vm-CAUD (h)
VS
vl-GPi
cl-SNr
cdm-GPi
vl-SNr
ldm-GPi
rl-SNr
mdm-GPi
rm-SNr
rl-GPi, VP
rd-SNr
VLo, VLm
l-VAmc, MDpl
VApc, MDpc
m-VAmc, MDmc
pm-MD

Figure 9–1. Proposed basal ganglia thalamocortical circuits.

Parallel organization of the five basal ganglia thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra, and thalamus.

ACA=anterior cingulate area; APA=arcuate premotor area; CAUD=caudate [(b)=body; (h)=head]; DLC=dorsolateral prefrontal cortex; EC=entorhinal cortex; FEF=frontal eye fields; GPi=internal segment of globus pallidus; HC=hippocampal cortex; ITG=inferior temporal gyrus; LOF=lateral orbitofrontal cortex; MC=motor cortex; MD=medialis dorsalis; MDmc=medialis dorsalis pars magnocellularis; MDpc=medialis dorsalis pars parvocellularis; MDpl= medialis dorsalis pars paralamellaris; PPC=posterior parietal cortex; PUT=putamen; SC=somatosensory cortex; SMA=supplementary motor area; SNr=substantia nigra pars reticulata; STG=superior temporal gyrus; VAmc=ventralis anterior pars magnocellularis; VApc=ventralis anterior pars parvocellularis; VLm= ventralis lateralis pars medialis; VLo=ventralis lateralis pars oralis; VP=ventral pallidum; VS=ventral striatum.

cdm=caudal dorsomedial; cl=caudolateral; dl=dorsolateral; l=lateral; ldm=lateral dorsomedial; m=medial; mdm=medial dorsomedial; pm=posteromedial; rd=rostrodorsal; rl=rostrolateral; rm=rostromedial; vl=ventrolateral; vm=ventromedial.

Source. Adapted from Alexander GE, DeLong MR, Strick PL: "Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex." *Annual Review of Neuroscience* 9:357–381, 1986. Used with permission.

Specifically, the onset of hypodopaminergia in the motor circuit may underlie muscle rigidity (Mann et al. 2000, 2003). In addition, hypodopaminergia involving the anterior cingulate–medial orbitofrontal circuit could participate in causing diminished arousal, mutism, and akinesia and contribute to hyperthermia and autonomic dysfunction. Lesions of this circuit have been associated with the neurologic condition akinetic mutism, which involves severe hypomotility, diminished arousal, and mutism and has been mistaken for simple psychogenic catatonia. Furthermore, certain cases of akinetic mutism have presented with hyperthermia and autonomic dysfunction, making them difficult to distinguish from MC and NMS. In this regard, it is of considerable interest that the anterior cingulate–medial orbitofrontal circuit contains a spur from the ventral pallidum to the lateral hypothalamus. This suggests that reduced dopamine activity could cause hyperthermia and autonomic dysfunction in MC and NMS by disrupting anterior cingulate–medial orbitofrontal transmission to the lateral hypothalamus.

Lastly, hypodopaminergia involving the lateral orbitofrontal circuit may mediate selected catatonic features observed in simple catatonia, MC, and NMS. Dysfunction in the lateral orbitofrontal circuit has been associated with use and imitation behaviors (Cummings 1993). These behaviors involve automatic imitation of gestures and actions of others or automatic and inappropriate use of objects such as tools or utensils. Use and imitation behaviors reflect enslavement to environmental cues (Cummings 1993) and share striking similarities with catatonic features such as echopraxia, echolalia, and gegenhalten, all of which are viewed as stimulus-bound or motor-perseverative phenomena consistent with frontal lobe dysfunction (Taylor 1990).

Recently, we proposed that in addition to dopamine D_2 receptor blockade, NMS is the product of preexisting central dopamine hypoactivity that represents a trait vulnerability marker for this disorder, coupled with state-related downward adjustments occurring in the dopaminergic system in response to acute or repeated exposure to stress (Mann et al. 2000, 2003). Here we suggest that such trait- and state-related factors are also critical in causing hypodopaminergia in the basal ganglia thalamocortical circuits in simple catatonia and MC. A number of lines of evidence indicate that certain individuals may exhibit baseline hypodopaminergia, including reduced cerebrospinal fluid homovanillic acid (HVA) levels in post-NMS patients; reduced striatal HVA levels or lack of elevated HVA-to-dopamine ratios in patients who died from MC or NMS; lower cerebrospinal fluid HVA levels and more severe baseline parkinsonian symptoms in patients with Parkinson's disease following recovery from NMS; and reports of abnormalities in the dopamine D_2 receptor gene in NMS (Mann et al. 2000, 2003).

Furthermore, the enhanced responsiveness of the dopaminergic system to stress may be implicated as a state-related cofactor predisposing to simple catatonia, MC, and NMS. The dopamine innervation of the medial prefrontal cortex in the rat is unique in that it is activated by very mild stressors (Thierry et al. 1976). In addition, considerable data indicate a functional interdependence of dopaminergic systems innervating the medial prefrontal cortex and subcortical dopaminergic systems; in particular, changes in the medial prefrontal cortex dopaminergic system appear to have an inverse relationship with dopamine turnover in the dorsal and ventral striatum (Louilot et al. 1989; Pycock et al. 1980). Accordingly, if stress activates the stress-sensitive mesocortical dopamine pathway to the medial prefrontal cortex, it will have direct feedback effects in both dorsal and ventral striatum, rendering those areas hypodopaminergic and predisposing to simple catatonia, MC, and NMS in individuals with preexisting central dopamine hypoactivity. This discussion is, of course, simplistic, as other neurotransmitters, including serotonin, γ-aminobutyric acid, and glutamate, could be directly or indirectly involved in the pathogenesis of these disorders.

Treatment

Effective management of MC depends on early recognition and the prompt institution of supportive medical care. Careful monitoring for medical complications is essential. The bulk of evidence indicates that the dopamine receptor blocking effects of antipsychotics drugs are likely to aggravate episodes of MC as in NMS and that antipsychotics should be withheld whenever MC is suspected.

Philbrick and Rummans (1994) observed that the benefits of benzodiazepines in MC appeared less uniform than in simple catatonia but were nonetheless impressive at times. They asserted that even a partial response might be beneficial and retard progression of MC until more definitive treatment can be instituted. Fricchione et al. (1997, 2000) suggested that if simple catatonia proves unresponsive to benzodiazepines after 5 days of treatment, electroconvulsive therapy (ECT) should be considered as a definitive measure. In cases of MC, however, these authors argued against a 5-day delay and urged that ECT be started if benzodiazepines do not briskly reverse the MC process.

Indeed, ECT has been viewed as a safe and effective treatment for MC when it occurs as an outgrowth of a major psychotic disorder (Mann et al. 1986, 1990, 2001, 2003). Although controlled data are lacking, case reports as well as series of cases have described excellent results with its use. Among 50 patients reported in four large series, 40 of 41 patients treated

with ECT survived (Mann et al. 1986). In contrast, only 5 of 9 patients who received only antipsychotics and supportive care recovered. Similarly, in Philbrick and Rummans's (1994) review of 18 MC cases, 11 of 13 treated with ECT survived, compared with only 1 of 5 who did not receive ECT. However, ECT appears effective only if it is initiated before severe progression of MC symptoms. Sedivic (1981) stressed that the development of a comatose state or a temperature in excess of 41°C augurs poorly for response even to ECT. Arnold and Stepan (1952) found that of 19 patients starting ECT within 5 days of the onset of hyperthermia, 16 survived, whereas in 14 patients who began treatment beyond this point, ECT had no effect in preventing a fatal outcome. Although earlier protocols called for particularly intensive treatment (Arnold and Stepan 1952), more recent trials have indicated that ECT can be successful when given once or twice daily or every other day for a total of 5–15 treatments (usually bilateral) (Mann et al. 1986, 1990). Substantial improvement often becomes evident after 1–4 treatments.

Other data, also anecdotal, suggest that MC due to the major psychoses can be effectively and safely treated with adrenocorticotropic hormone (ACTH) and corticosteroids (Lingjaerde 1963; Mann et al. 2003). However, because severely debilitated patients have tolerated ECT without incident, and because the utility of hormonal therapy is less well documented, ECT appears to be the preferred treatment. ACTH and corticosteroids may be used if ECT proves ineffective. Several authors have suggested that the addition of dantrolene to ECT represents the optimal treatment for MC (Mann et al. 2003), and dantrolene alone has been reported effective in several MC cases. Additional cases have involved successful treatment with bromocriptine, dantrolene, and ECT; bromocriptine and dantrolene; dantrolene and benzodiazepines; calcitonin; and artificial hibernation (Mann et al. 2003). In MC due to neuromedical illnesses, treatment must obviously be directed at the underlying disorder. Nevertheless, anecdotal reports have described ECT as dramatically effective in suppressing the symptoms of severe MC-like states complicating neuromedical conditions (Mann et al. 1986, 1990). Along these lines, ECT has been used effectively in the treatment of NMS.

Conclusion

MC continues to occur and represents a nonspecific syndrome that develops as an outgrowth of neuromedical illnesses as well as the major psychoses. NMS may be conceptualized as a drug-induced form of MC and therefore another subtype of the larger catatonic syndrome. The hypothesis that simple catatonia, MC, and NMS share a common pathophysiology,

involving reduced dopamine functioning within the basal ganglia thalamocortical circuits, provides additional support for a view of these disorders as manifestations of a unitary diagnostic entity. ECT appears to be the preferred treatment for MC stemming from major psychotic disorders, and it may also be effective in cases caused by neuromedical illnesses. Antipsychotic drugs should be withheld whenever MC is suspected.

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C H A P T E R 1 0

MEDICAL CATATONIA

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Etiology

Since the seminal monograph published by Kahlbaum (1874/1973), nonpsychiatric medical conditions have been known to be associated with catatonia and remain a diagnostic challenge for physicians. Two major points have been emphasized about medical catatonias by previous reviewers: catatonia has been ascribed to a long list of medical illnesses, and catatonia due to general medical conditions accounts for a larger percentage of patients presenting with catatonia in psychiatric settings than previously suspected. We wish to address these and a third, more ambitious, point. That is, medical catatonia provides us with a much greater understanding of the anatomical and biochemical mechanisms underlying catatonia in general.

There have been several reviews of catatonia and causative medical illnesses. Gelenberg (1976) identified more than 35 general medical conditions and drugs that have been associated with catatonia and cautioned clinicians to consider these illnesses and medications in catatonic patients. Barnes et al. (1986) reviewed 25 cases of catatonia on a neurology unit and added more illnesses to Gelenberg's list, including familial and idiopathic cases. Lohr and Wisniewski (1987) also reviewed the literature on medical catatonias, proposed criteria to define catatonic syndromes, and observed that neuroleptic-induced catatonias seemed to occur in patients already at risk for the development of catatonia. Accordingly, neuro-

Table 10–1. Most likely etiologies of medical catatonia

Underlying etiology	Focal	Diffuse
CNS structural damage	X	
Encephalitis and other CNS infections	X	X
Seizures or EEG with epileptiform activity	X	X
Metabolic disturbances		X
Phencyclidine exposure		X
Neuroleptic exposure		X
Systemic lupus erythematosus (usually cerebritis)	X	X
Corticosteroids		X
Disulfiram		X
Porphyria and other conditions		X

Note. CNS=central nervous system; EEG=electroencephalogram.

leptic malignant syndrome (NMS) also may be conceptualized as a drug-induced hyperthermic subtype of medical catatonia (Adityanjee et al. 1999; Fricchione et al. 2000). This supports the argument that catatonia and NMS are, in fact, single entities (Fink 1996). This link is further bolstered by the results of several investigations that determined that up to 10% of patients with catatonia who are treated with antipsychotics may develop NMS (Carroll 2001). In summary, several reviews and chapters in neuropsychiatric texts present tables listing 40 or more medical conditions associated with the catatonic syndrome (Barnes et al. 1986).

Catatonia due to a general medical condition was added to DSM-IV (American Psychiatric Association 1994), making the identification and study of medical catatonia easier for clinicians and researchers. In a literature analysis by Carroll et al. (1994), levels of evidence were used to determine the relative strength of the putative association between medical illness and catatonia. In many instances, there was only a weak association between a condition (e.g., diabetes mellitus) and catatonia, or the association was multifactorial (e.g., cerebritis and corticosteroids plus neuroleptics). We have created a hierarchy of medical conditions most likely to cause medical catatonia, which allows the clinician to focus the diagnostic workup on the most likely and fulminant etiologies. For example, encephalitis would be considered before porphyria in the likely causes of medical catatonia (Table 10–1).

However, comorbidity remains a major confounding issue with regard to the assessment and treatment of catatonic syndromes, in that many patients may have coincidental medical conditions or direct medical complications such as deep venous thrombosis resulting from prolonged catatonic immobility. Care must be taken by the clinician to resist the temp-

tation to label these patients as having "medical catatonias" based only on the degree of medical morbidity without the presence of an identified causative factor.

Relative Frequency

It is difficult to determine the frequency of medical catatonias relative to psychiatric catatonias because published reports of catatonia tend to have small numbers and medical catatonias are not always clearly identified. In addition, there may be an ascertainment bias for this literature because reports of medical catatonia with a favorable treatment response are more likely to be published than reports of medical disorders with subtle or refractory catatonia alone. Among the larger studies of catatonia conducted after 1985, the relative percentages of medical-based cases of catatonia range from 20% to 25% (Barnes et al. 1986; Bush et al. 1996a; Hawkins et al. 1995; Rosebush et al. 1990). The setting appears to affect the frequency of medical catatonia, because the relative frequency might be expected to be higher on medical units and consultation-liaison services compared with inpatient psychiatric units. In our neuropsychiatric facility, the frequency of medical catatonias is 30% among all patients with catatonia (B.T. Carroll, H.W Goforth, unpublished data). This may reflect greater awareness and more careful screening for medical catatonia among patients on medical and psychiatric wards.

Psychopathology

On the basis of the literature, a retrospective chart review, and a prospective study, we compared the clinical findings between cases of medical and psychiatric catatonias (Carroll et al. 2000). Although there were differences in some individual catatonic signs in medical catatonias, no consistent pattern emerged that would allow one to distinguish medical from psychiatric catatonias. Because no single catatonic sign or set of signs could be found to differentiate these groups, the importance of Gelenberg's admonition to consider medical etiologies in all patients presenting with catatonia, regardless of ascribed psychiatric diagnosis, was reaffirmed.

Neurobiology

The literature on medical catatonia significantly overlaps with and contributes to the study of NMS, lethal catatonia, and akinetic mutism. Furthermore, it provides additional insights in the understanding of other neuro-

psychiatric illnesses, including autism and abulia (apathy syndrome). The literature on medical catatonias includes a large number of cases with fatal outcome and identifies a variety of neuropathologic mechanisms involved in the production of the catatonic syndrome. Kahlbaum (1874/1973) stressed the importance of the clinico-anatomical study of catatonia and performed autopsies on his patients in an effort to isolate a causative lesion. Both his and subsequent studies failed to identify a single common lesion associated with medical catatonias (Northoff 2000).

In a comprehensive review of frontal lobe syndromes and pathways, Mega and Cummings (1994) concluded that catatonia was due to lesions or dysfunction in the anterior cingulate gyrus and the pathway from the anterior cingulate cortex to the globus pallidus and then to the medial dorsal thalamus. However, these authors did not define catatonia as a syndrome but inferred its presence from studies of akinetic mutism. Further studies of akinetic mutism and catatonia involving autopsies, brain imaging, and neurophysiologic data have disputed the notion of a single responsible lesion. Currently, identified lesions associated with akinetic mutism include those in the bilateral medial frontal lobes, the anterior cingulate gyrus, regions adjacent to the third ventricle, the thalamus, the pons, and the upper brain stem. Similarly, lesions associated with catatonia include those associated with akinetic mutism, plus lesions in the remaining frontal lobes, the parietal lobes, the temporal lobes, the basal ganglia, and the cerebellum. Because focal lesions in these regions only rarely cause catatonia, we might posit that medical catatonias result from dysfunction in *neural pathways* that include these structures.

In contrast to focal lesions, diffuse central nervous system etiologies such as encephalitis and seizures are responsible for a significant number of cases of medical catatonias in the literature. Diffuse disease processes associated with medical catatonia support the hypothesis that medical catatonias are caused by pathway dysfunction, rather than focal, site-specific pathology, and may arise from lesions at one or more points along these pathways. Furthermore, there may be additional diffuse etiologies that adversely and specifically affect these pathways, including neurochemical or neurophysiologic factors. One recently proposed pathway for the development of catatonia involves the medial frontal cortex, inferior orbital frontal cortex, thalamus, and associated neurons projecting to the parietal cortex (see Chapter 7, "Neuroimaging and Neurophysiology," and Chapter 9, "Malignant Catatonia," this volume).

Neurochemical studies supported by functional brain imaging have also provided insight into types of cerebral dysfunction responsible for producing the catatonic syndrome. Possible neurochemical etiologies for medical catatonias include glutaminergic antagonism, γ-aminobutyric acid antago-

nism, serotonergic actions, and dopamine antagonism (Carroll 2000). The relationship among antipsychotic drugs, dopamine D_2 receptor blockade, and NMS has been a focus of more intense study (Mann et al. 2000). Recently, the identification of D_2 blockade in all novel antipsychotics (Caroff et al. 2000; Kapur and Seeman 2001) and identification of the TaqI A polymorphism of the D_2 receptor gene have provided additional support for this dopamine-based hypothesis (Suzuki et al. 2001).

Treatment

The treatment of psychiatric disorders due to medical conditions focuses on treating 1) the presenting psychiatric syndrome in the same way one would treat the idiopathic psychiatric disorder that it most resembles, 2) identified comorbid conditions, and 3) the causative medical condition. Medical catatonias tend to be multifactorial (Carroll et al. 1994), and all three approaches to treatment should be considered in most cases (Bush et al. 1996b).

A review of lorazepam in the treatment of catatonia included several cases of favorable response in medical catatonia as well as catatonia of a purely psychiatric etiology (Salam and Kilzieh 1988). Hawkins et al. (1995) also found favorable treatment responses of medical catatonias to lorazepam, and Fink (1996) demonstrated cases in which medical catatonias responded favorably to electroconvulsive therapy. Overall, both medical and psychiatric catatonias are similar in appearance and treatment response. However, this literature may reflect the ascertainment bias previously discussed—namely, that successfully treated cases may be overrepresented.

Stabilization of comorbid medical conditions and appropriate prophylactic medical care addressing issues such as dehydration, poor nutrition, infection, and thromboembolic prophylaxis are likely to improve treatment response. Caution needs to be exercised, though, because treating the underlying medical condition exclusively in catatonia is usually not a successful approach, given that the medical conditions are frequently irreversible or the catatonia may persist. One notable exception is seizure-induced catatonia, which has been reported to respond to treatment with anticonvulsants and lorazepam when confirmed by electroencephalography.

Conclusion

The study of medical catatonias has provided important insights into the mechanisms of many neuropsychiatric disorders, including NMS. Medical causes are implicated frequently among patients presenting with a catatonic

syndrome, and consequently, any clinician treating patients with catatonia must maintain a high index of suspicion for medical etiologies. This index of suspicion is further supported by evidence demonstrating that medical catatonias are indistinguishable from psychiatric etiologies in the number and type of individual symptoms. Medical causes must be addressed to ensure the best outcome, and the literature on the treatment of medical catatonias suggests that lorazepam and ECT can benefit these patients as well as patients presenting with catatonia with purely psychiatric etiologies.

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CHAPTER 11

DRUG-INDUCED CATATONIA

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Toxic or drug-induced catatonia has been recognized for many years but is reported only sporadically. Much of the literature consists of single cases or small series of patients. However, a renewed interest in catatonia in recent years has led to improved and systematic research methods for descriptive psychopathology and treatment approaches (Carroll 2000). Among these improvements are rating scales providing systematic and operational definitions of specific motor and psychopathologic features of catatonia (see Chapter 5, "Standardized Instruments," this volume; also see Bräunig et al. 2000; Bush et al. 1996a; Northoff et al. 2000). In addition, DSM-IV, and its text revision, DSM-IV-TR (American Psychiatric Association 1994, 2000), recognized organic catatonia and expanded its enumeration of possible catatonic features, although it still lacks the detailed descriptions that are found in research rating scales.

In this chapter, we revisit the literature on drug-induced catatonia, using recent developments in systematic diagnostic criteria to review clinical findings and phenomenology. We screened reported cases of drug-induced catatonia using criteria from DSM-IV and the Bush-Francis Catatonia Rating Scale (BFCRS; Bush et al. 1996a). We examine whether reported cases provide sufficient clinical detail to allow clinical (i.e., DSM-IV) or research (i.e., Bush-Francis) diagnoses of catatonia; whether cases meeting these criteria share common features of catatonia with recent reports of idiopathic cases in psychiatric populations; and whether the treatment response

or outcome of drug-induced catatonia differs from the well-established treatment response of catatonia to benzodiazepines and electroconvulsive therapy (ECT). Finally, because recent reports have addressed neuroleptic malignant syndrome (NMS) as a severe drug-induced catatonic state, we review our previously published data, which support the hypothesis of NMS as a form of drug-induced catatonia.

Methods

We identified published cases of drug-induced catatonia from several computerized database searches. Additional reports were found from citations in the obtained reports. Clinical reports were included for review if they were judged to describe drug-induced catatonia and to contain sufficient clinical information to determine DSM-IV clinical criteria or Bush-Francis research criteria (Bush et al. 1996a). We sought at least four cases for any given drug to include in data analysis. For DSM criteria, we employed "catatonia due to a general medical condition" with motor criteria as delineated for catatonic schizophrenia (American Psychiatric Association 1994); for research criteria, we used at least 2 of 23 items from the full BFCRS. The DSM-IV (and DSM-IV-TR) criteria include 11 motor signs of catatonia, for which prominence of 1 sign is sufficient for the diagnosis. We also used the definitions of catatonic signs from the BFCRS. The BFCRS is a 23-item rating instrument that was used in several previous prospective (Bush et al. 1996a, 1996b; Lee et al. 2000; Ungvari 1999) and retrospective (Koch et al. 2000) studies of catatonia. It includes all 11 signs from DSM-IV as well as 12 additional signs. The first 14 items are used for screening purposes and were adopted for study of phenomenology for this report (Figures 11–1 and 11–2).

We employed a comparison group for analysis of clinical features of catatonia in the drug-induced catatonia literature. Bush et al. (1996a, 1996b) identified 28 patients with acute idiopathic catatonia by prospectively screening consecutive admissions to an acute psychiatric inpatient facility. Detailed initial ratings of the BFCRS were available from these data. These patients represented an acute presentation of catatonic signs, which was generally true for drug-induced catatonia and therefore taken as a reasonable comparison.

We identified an adequate sample of reports of drug-induced catatonia for four drug categories (neuroleptics, steroids, disulfiram, phencyclidine [PCP]) and a small sample of a miscellaneous group. Several additional case reports involving drugs with fewer than four cases are included as illustrative examples. We performed the data analysis by visually comparing the frequency distribution of catatonic signs for each drug-induced cata-

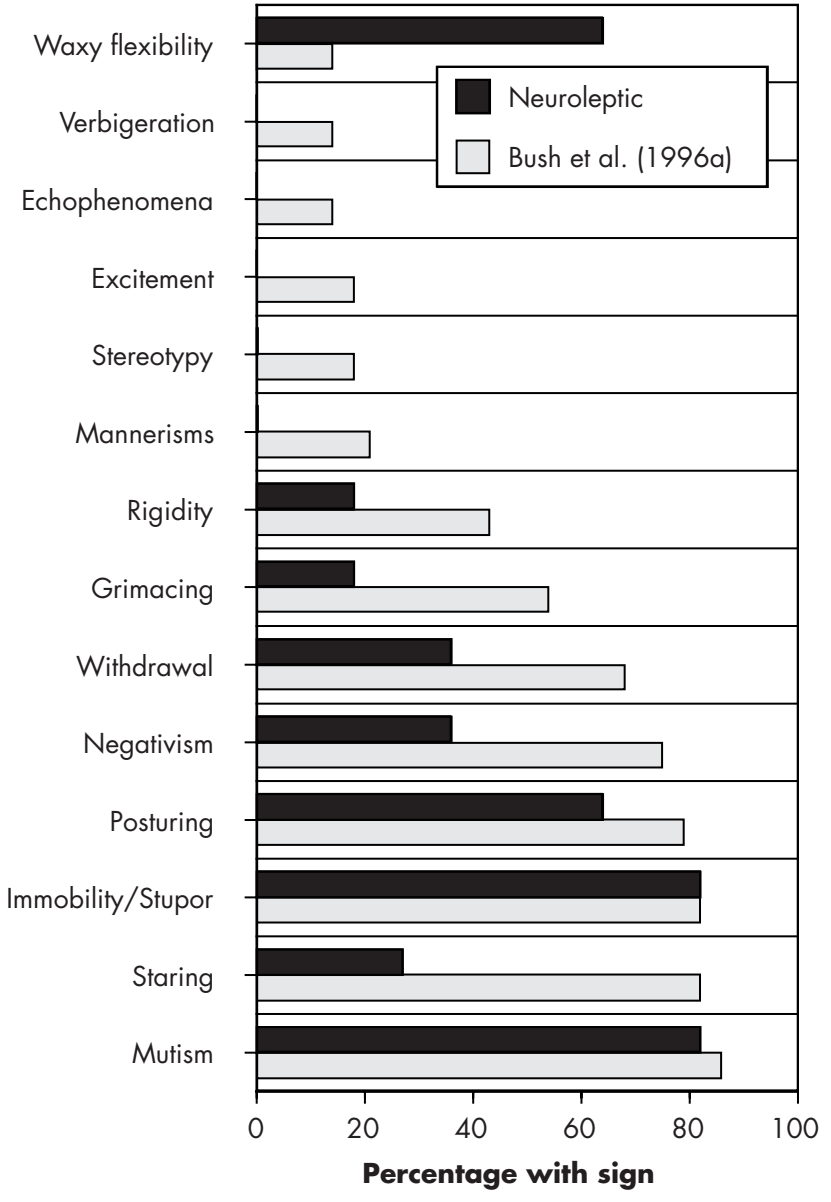


Figure 11–1. Distribution of catatonic signs in cases of neuroleptic-induced catatonia.

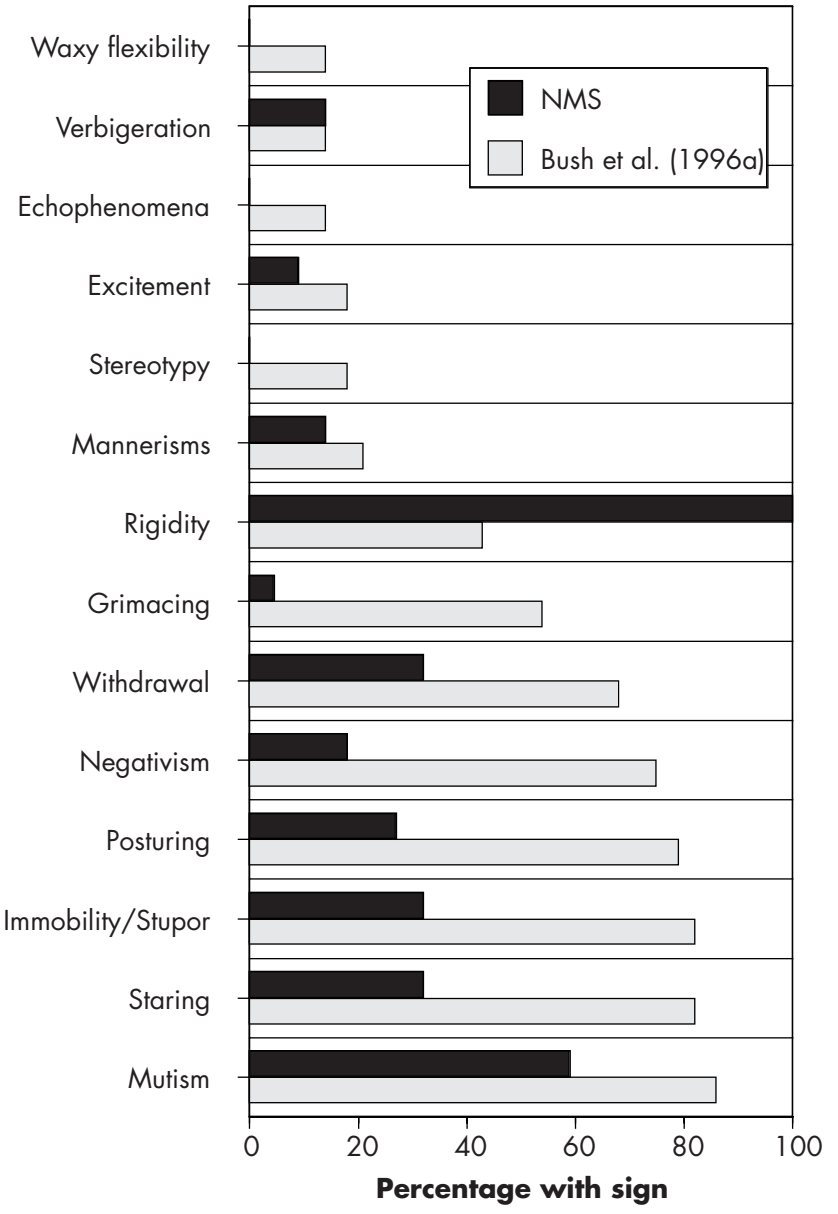


Figure 11–2. Distribution of catatonic signs in cases of neuroleptic malignant syndrome.
NMS=neuroleptic malignant syndrome.

tonia series, using the prospective comparison group data set. In addition to conducting a search of the literature for case reports of drug-induced catatonia, we also reexamined our group's published data that address NMS as a special case of drug-induced catatonia (Koch et al. 2000).

Results

Disulfiram-Induced Catatonia

Disulfiram has been used for the treatment of chronic alcoholism because it interferes with the metabolism of alcohol, leading to elevation of systemic acetaldehyde. This induces a toxic reaction of vasodilation, hypotension, vomiting, headache, tachycardia, and at times death (Knee and Razani 1974). Knee and Razani hypothesized that disulfiram blocks the enzyme dopamine β-hydroxylase, which led to the hypothesis of altered dopamine metabolism to explain the psychoses that have been reported in alcoholic patients taking this medication.

We identified six case reports of patients who had been taking disulfiram for 1–5 months and who developed catatonic symptoms (Fisher 1989; Knee and Razani 1974; Liddon and Satran 1967; Reisberg 1978; Weddington et al. 1980). Out of the six cases, only one was restarted on disulfiram and neuroleptics without recurrence of psychosis or catatonia (Reisberg 1978). None of the patients received benzodiazepines or ECT for treatment of drug-induced catatonia. In most of the cases, the patient improved by either simple discontinuation of the agent or a short course of treatment with neuroleptics, mainly perphenazine.

All of the disulfiram cases met the DSM-IV clinical criteria and the Bush-Francis research criteria for catatonia. Compared with the pattern of signs in our prospectively identified idiopathic cases (Bush et al. 1996a, 1996b), the disulfiram-induced cases showed a lower incidence of reported signs, which may be expected from the retrospective data collection compared to our prospectively identified cases. Both samples showed the familiar pattern of retarded catatonia, in which signs such as mutism, immobility, posturing, and withdrawal are most common, whereas excitement and impulsivity are less common. Many signs that are uncommon even in idiopathic cases (mitgehen, ambitendency, echophenomena) were not recorded in the disulfiram case reports.

PCP-Induced Catatonia

Phencyclidine abuse is associated with hallucinations, violence, and depression of consciousness (Allen and Young 1978; Baldridge and Bessen

1990). McCarron et al. (1981) described the incidence of clinical findings in 1,000 cases of PCP intoxication. Catatonic signs were found in 117 patients, but only 87 had been exposed to PCP alone. We included only these 87 cases in the study. Catatonia lasted for 1 day or less in 85%; most lasted 4–6 hours. However, 13 patients had catatonia for 36 hours to 6 days. Most patients had no history of psychosis and had no psychiatric effects after recovery. An association was found between catatonia and rhabdomyolysis.

In the McCarron et al. (1981) study, the criteria for catatonia included motor signs (posturing, catalepsy, and rigidity), psychosocial withdrawal (mutism, negativism, and staring), excitement (nudism, impulsiveness, agitation, and violence), and stupor. A fifth classification comprised "ancillary" signs that included stereotypy, mannerisms, grimacing, and verbigeration.

Bush et al. (1996a) classified nudism as a form of impulsivity. For data analysis, we added those patients with nudism (3%) to patients who had impulsivity (13%). We also combined patients who had hyperventilation and diaphoresis with patients who had hypertension into the Bush-Francis criteria for autonomic abnormality. Patients who were violent were added to the criteria for combativeness. Negativism was present in 100% of the patients; mutism and staring followed as the second most common signs, at 94%.

Although the data of McCarron et al. (1981) were presented in aggregate form, it is almost certain that all the cases met DSM-IV criteria because all had negativism, and the Bush-Francis research criteria are similarly likely to be met in view of the 94% incidence of both mutism and staring. Again, the pattern is typical for retarded catatonia. As might be expected for PCP, there appeared to be a higher prevalence of autonomic signs and combativeness.

Steroid-Induced Catatonia

Corticosteroids are associated with numerous adverse effects, including mental disturbances ranging from mania to psychoses (Doherty et al. 1991). We reviewed five cases of steroid-induced catatonia (Doherty et al. 1991; Hoffman et al. 1986; Ilbeigi et al. 1998; Perry et al. 1984; Sullivan and Dickerman 1979). None had a prior psychiatric history. The route of administration of the corticosteroids varied from oral to intravenous; in one case, adrenocorticotropic hormone (ACTH) was used intramuscularly after psychosis was noted (Doherty et al. 1991). The dosages of steroid also varied. Only one case report mentioned the DSM criteria for catatonia. In three cases, catatonia was preceded by psychotic symptoms. The management also varied. Only one patient received ECT, with excellent improvement after five sessions.

As to clinical features in these cases, the most common signs described were stupor and mutism. Two cases showed automatic obedience. Again, a pattern of retarded catatonia was found. Several of the less commonly observed signs in the prospective cases were not reported in the steroid cases. All of these cases met DSM-IV clinical criteria as well as Bush-Francis research criteria for catatonia.

Neuroleptic-Induced Catatonia

Neuroleptic-induced catatonia has been identified in patients receiving antipsychotic agents. This syndrome was well described in a classic paper by Gelenberg and Mandel (1977). The existence of this syndrome has led to hypotheses linking the biological basis of catatonia and NMS (Carroll 2000; Fricchione 1985).

We identified 11 case reports of neuroleptic-induced catatonia (Bahro and Strnad 1999; De 1973; Fricchione et al. 1983; Hoffman et al. 1986; Johnson and Manning 1983; Kontaxakis et al. 1990; Leigh et al. 1978; Riley et al. 1976; Stoudemire and Luther 1984). Some of the cases reported involved postoperative management of agitation in patients without a previous psychiatric history (Fricchione et al. 1983). Other cases were reported after medication adjustment of patients with chronic psychiatric illnesses. Four cases were treated mainly with benzodiazepines (Fricchione et al. 1983) and responded well. One patient with a history of schizophrenia and a frontal lobotomy responded well to clozapine.

As to clinical features of neuroleptic-induced catatonia, Figure 11–1 shows that mutism, stupor, and waxy flexibility typical of retarded catatonia were the most common signs noticed in these case reports. Stereotypy, mannerisms, and echophenomena were not reported. It is not clear if these signs were not recognized or not present. All of these cases met DSM-IV clinical criteria as well as Bush-Francis research criteria for catatonia.

Other Drug-Induced Catatonias

Ciprofloxacin is a fluoroquinolone antimicrobial agent used in a case report for the treatment of typhoid fever (Akhtar and Ahmad 1993). The patient was admitted to the hospital with typhoid fever and started on oral ciprofloxacin. After 4 days of treatment, the patient became lethargic and dull, then mute and motionless. He also showed staring, waxy flexibility, and mitgehen characteristic of retarded catatonia. Ciprofloxacin was discontinued, ECT was begun, and the patient improved. The patient met both DSM-IV and Bush-Francis criteria for catatonia.

Cocaine-induced catatonia was reported in a woman with no prior psychiatric history (Gingrich et al. 1998). The patient had been on a binge for 6 days and started to show bizarreness, mutism, staring, negativism, and stereotypy. Haloperidol was given (the patient was presumed to be experiencing cocaine-induced psychosis), but it had no effect. Lorazepam was given intramuscularly, with resolution 2 hours after the dose. The patient reported similar episodes in the past, apparently induced by cocaine.

We identified one case of a woman who developed catatonic symptoms after a methylphenidate challenge (Wiener and Kennedy 1985). She was tapered off triazolam and clomipramine prior to receiving methylphenidate. Within hours, she became immobile, mute, and unresponsive and was staring. She received intravenous diazepam, and her mobility and ability to follow verbal commands improved. This case met both DSM-IV and Bush-Francis criteria for catatonia.

Jackson et al. (1992) described a man who developed mutism, posturing, waxy flexibility, and increased muscle tone on the fifth day of bupropion treatment. He also had withdrawal and refused food. The patient had 4 of 14 signs of catatonia on the BFCRS. Parenteral lorazepam led to a noticeable decrease in catatonic signs. He eventually received 14 bilateral ECTs, with resolution of catatonia.

Cohen et al. (1999) described a case series of adolescents treated with clomipramine who developed catatonic features. Of the cases described, only one boy received clomipramine as monotherapy. After a few months, he showed catalepsy, waxy flexibility, posturing, negativism, rigidity, and stereotypy. He responded well to amisulpride but had incomplete resolution of symptoms. This patient met Bush-Francis and DSM-IV criteria for catatonia.

The features of catatonia associated with these agents are overall those of retarded catatonia, in which mutism, staring, posturing, and withdrawal are the most commonly reported features.

Neuroleptic Malignant Syndrome: A Drug-Induced Catatonia?

Catatonia and NMS share clinical features, biochemical findings, and treatment response (Carroll 2000; Koch et al. 2000). Some authors place them in the same spectrum of illness, on the basis of careful analysis of NMS cases where neuroleptics appear to have precipitated or worsened catatonia (White and Robins 2000). These hypotheses have important treatment implications, because a link between catatonia and NMS might encourage the use of well-established treatments for catatonia such as lorazepam and ECT in NMS.

Our group recently reported the first systematic assessment of catatonic signs in NMS (Koch et al. 2000). Sixteen rigorously defined NMS cases were identified retrospectively. Of these, 11 met the stringent research criteria of Caroff and Mann (1993), and all 16 met NMS criteria according to DSM-IV. Both diagnostic schemes require fever plus rigidity as primary features, and either two (DSM-IV) or five (Caroff-Mann) secondary features. The records of these 16 patients were carefully reviewed for the presence of catatonic signs within 24 hours of the diagnosis of NMS.

Of the 16 NMS patients, 15 met Bush-Francis research criteria and DSM-IV clinical criteria for catatonia. They had a mean of 6.1 of the 23 BFCRS catatonic signs. There was a strong positive correlation ($\rho = 0.71$) between the BFCRS scores and severity of NMS symptoms.

Figure 11–2 shows the distribution of catatonic signs in the 16 NMS cases compared with the prospective cases of catatonia from Bush et al. (1996a). Again, overall fewer signs were detected in the retrospective NMS cases than the prospective cases. The pattern is typical of retarded catatonia. Rigidity was present in all cases, as it is required for the diagnosis of NMS according to both DSM and Caroff-Mann criteria.

All 16 NMS patients were treated with benzodiazepines, and the features of NMS resolved in 24–72 hours (Francis et al. 2000). This resolution appeared to be more prompt than published cases of similar severity in which treatment consisted of supportive measures alone. These observations suggest that benzodiazepines may be useful in the treatment of NMS. A case series of two patients prospectively treated by lorazepam supports this view (Khaldarov 2000).

Conclusion

The literature on drug-induced catatonia is mostly one of sporadic case reports and unsystematic descriptions. We attempted to apply systematic assessment to this literature and found that most published cases are of the typical retarded catatonia type that is commonly seen in acute psychiatric populations, and that the pattern of catatonic signs is very similar across several drugs. The number of signs detected and reported is lower than that seen in a reference sample of prospectively identified psychiatric patients. Insufficient information was available as to specific treatments for drug-induced catatonia, but the syndrome typically resolves without residua. High-potency benzodiazepines remain a reasonable treatment option. Systematic evidence supports the view that NMS is a drug-induced form of catatonia, which may have implications for treatment options such as benzodiazepines or ECT for NMS.

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CHAPTER 12

PHARMACOTHERAPY

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Catatonia is a clinical syndrome characterized by a range of psychomotor abnormalities that occur in the context of a wide variety of both psychiatric and medical conditions. This syndrome is a significant clinical problem because it is associated with considerable mortality and morbidity from pulmonary embolism, intercurrent infection, and dehydration (McCall et al. 1995). The most compelling reason for recognizing and diagnosing catatonia is its exquisite responsiveness to treatment, particularly benzodiazepines (BZDs).

Benzodiazepines—A Safe and Highly Effective Treatment

Beginning in the 1980s, a number of case reports described the effectiveness of low-dose lorazepam (Fricchione et al. 1983) or diazepam (McEvoy and Lohr 1984). Rosebush et al. (1990) prospectively screened 140 consecutive admissions to an acute inpatient psychiatry unit for catatonia. Patients had to display 4 or more of the 11 signs described by Kahlbaum (1874/1973) to be considered catatonic. When these conservative criteria were used, a diagnosis of catatonia was made 15 times. The vast majority of patients had catatonia of the retarded type, and in only 2 of the 15 episodes was excitement intermixed with the features of retardation. Following treatment with lorazepam 1–2 mg orally or intramuscularly, 12 (80%) of the 15 episodes resolved fully and rapidly. Two factors that appeared to predict response were the presence of intense anxiety during the episode

and the clinical constellation of immobility, mutism, and withdrawal with refusal to eat or drink. In our ongoing prospective study of more than 100 patients with catatonia, predominantly of the retarded type (Rosebush and Mazurek 1997a), we have continued to observe a robust response in approximately 85% of patients following treatment with lorazepam.

Yassa et al. (1990) described 10 catatonic patients, all of whom responded to low-dose lorazepam, either by mouth or by intramuscular injection. Seven had dramatic resolution of their catatonic state within hours of receiving BZD treatment. Of note, 9 of the 10 individuals were receiving, and continued to receive, antipsychotic agents during BZD treatment. Ungvari et al. (1994) used low-dose lorazepam to treat 18 patients with catatonia that had been present for 2–22 days. Fifteen (83%) had a marked response or complete resolution of their catatonic state within hours. In a literature review of 72 episodes of catatonia treated with BZDs, a response rate of almost 80% was found (Hawkins et al. 1995).

The ideal treatment is one that is easily administered, produces a rapid response, and has a wide margin of safety. Low-dose BZDs that can be administered orally, intramuscularly, or intravenously satisfy all these conditions. For these reasons, treatment of catatonia with low-dose lorazepam has replaced electroconvulsive therapy (ECT) as a first-line treatment (Rosebush et al. 1992). Low-dose lorazepam offers several advantages over ECT. First, the response is rapid, thereby decreasing the time during which a patient is at risk of the complications from immobility. Second, BZDs have a wide margin of safety even at high doses and do not present the cardiovascular challenge posed by ECT and the required anesthesia. Furthermore, ECT is a more complicated procedure and generally associated with greater stigma. As a result, family members are usually much more willing to give surrogate approval for BZDs. If an initial dose of lorazepam is effective in resolving the catatonia, which it is in 85% of cases, then one is in a position to carry out a full assessment to determine whether or not ECT might be the most appropriate treatment for the primary, underlying condition (Rosebush and Mazurek 1999).

Relation of Treatment Response to Underlying Diagnoses

Catatonia has been reported to occur in the context of a wide spectrum of psychiatric, medical, and neurologic disorders (see Chapter 3, "Nosology," Chapter 10, "Medical Catatonia," and Chapter 11, "Drug-Induced Catatonia," this volume). In our prospective study and follow-up of patients with catatonia, we have found that mood disorder is the most common underlying diagnosis, accounting for almost half of all cases (Rose-

bush and Mazurek 1997a). This is followed in frequency by schizophrenia (20%), primary medical or neurologic disease (20%), BZD withdrawal (8%), and other psychoses (7%). In our ongoing study, we have found that approximately 20%–25% of patients *presenting* with catatonia have an underlying disorder that is not primarily psychiatric in nature (Rosebush and Mazurek 1994, 2000).

The nature of the relationship between catatonia and any particular concurrent medical illness has not been elucidated, and a final common pathway for the disparate array of conditions reported in association with catatonia has not yet been identified. One possible unifying mechanism is the experience of overwhelming anxiety and preoccupation with death during catatonia, reported by many patients (Rosebush et al. 1990) We suspect that many medically ill patients are extremely anxious about their condition, and for some, this may reach a point of intensification that precipitates catatonia. Another possible reason why so many different conditions have been observed to "cause" catatonia is that the withdrawal of BZDs can precipitate catatonia (Glover et al. 1997; Hauser et al. 1989; Rosebush and Mazurek 1996, 1999). Individuals admitted to medical wards, particularly on an emergency basis, may not report or be asked about chronic BZD use. We have wondered whether many of the cases of catatonia seen on medical units might be secondary to BZD withdrawal.

Although the vast majority of patients respond robustly to low-dose BZDs, regardless of their underlying diagnosis, patients with schizophrenia appear to do least well. In our series, catatonic patients with schizophrenia have a response rate of only 20%–30%, compared with an overall response rate of over 90% in all other diagnostic subgroups, including those with underlying medical and neurologic disorders. A similar finding was reported by Ungvari et al. (1999, 2001), who conducted a randomized, double-blind, placebo-controlled, crossover study of lorazepam 6 mg/day for 6 weeks in 17 patients with chronic schizophrenia and chronic catatonia. In contrast to the 83% rate of response to lorazepam they observed in their original study of patients with acute catatonia, the authors found no statistically significant difference between lorazepam and placebo on any clinical measure in the schizophrenic patients with chronic catatonia.

The poor responsiveness to BZDs of catatonic symptoms in patients with schizophrenia may be related to a number of factors. A defining characteristic of schizophrenia is the refractory chronicity of the symptomatology, including, in many cases, the catatonic features themselves. Another possible factor in the poor response to BZDs in schizophrenia is the relative absence of anxiety in these patients, especially compared with the overwhelming anxiety described afterward by many other patients with catatonia. Also, the catatonic features exhibited by the schizophrenic pa-

tients studied by Ungvari et al. (1999) included posturing, grimacing, stereotypy, and waxy flexibility, whereas the characteristic signs in those who respond to BZDs tend to be immobility, mutism, and withdrawal.

The relatively less robust effect of BZDs in schizophrenic patients with chronic catatonia should not, however, discourage the treating physician from a trial of therapy. We reported a therapeutic success in one such case involving a 29-year-old man with schizophrenia and chronic severe catatonia, who responded slowly but completely to monotherapy with low-dose lorazepam (Gaind et al. 1994). He went from a state of prolonged and profound incapacitation requiring continuous hospitalization to semi-independent living, which he has maintained at 8-year follow-up.

The treatment of catatonic states in patients with an underlying psychotic disorder presents a dilemma for the clinician. There is considerable anecdotal evidence that the administration of antipsychotic drugs in the context of catatonia may increase the risk of neuroleptic malignant syndrome (Rosebush and Mazurek 1997b; White and Robins 1991). Given this risk, we suggest administering one to three doses of lorazepam 1–2 mg to catatonic patients known to have a psychotic illness, prior to the administration of antipsychotic drugs. Even if the catatonic symptoms do not respond, we feel it is prudent to continue the BZD as an adjunctive treatment while antipsychotic drugs are being introduced, in the hope that this may reduce the risk of neuroleptic malignant syndrome. A reasonable alternative in this situation might be ECT, which is also the recommended treatment of catatonia when pharmacologic interventions fail (see Chapter 13, "Convulsive Therapy," this volume). It has been proposed that a 3- to 5-day trial of BZDs be attempted prior to considering ECT (Fink et al. 1993).

Potential Mechanisms for Effectiveness of Benzodiazepines in Treating Catatonia

The pharmacologic properties of BZDs result from their relationship to the amino acid γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. BZDs act by binding to an allosteric site on the GABA-A receptor, resulting in the potentiation of GABA-mediated chloride conductance and inhibition of neuronal firing. GABA-A receptors are widely distributed in the central nervous system, allowing multiple potential sites of action for the BZD drugs. It has been suggested that individual BZDs might have differential efficacy in the treatment of catatonia (Scamvougeras and Rosebush 1992). These observations may relate to the fact that GABA-A receptors are made up of varying combinations of 16 different subunits, potentially allowing the various BZDs to exert heterogeneous clinical and pharmacologic effects.

The therapeutic actions of BZDs in catatonia can be understood in a number of ways, depending on how the disorder is conceptualized. They are described in the following subsections.

Catatonia as a Movement Disorder

We previously proposed that catatonia can perhaps be best understood as a movement disorder (Rosebush and Mazurek 1991). The clinical features of catatonia closely parallel those of parkinsonism, which is known to arise from dysfunction of the basal ganglia (Rogers 1991). At least four of the major projection pathways in the basal ganglia use GABA as a neurotransmitter: 1) the so-called direct pathway from the striatum to the internal part of the globus pallidus (GPi) and the reticular part of the substantia nigra (SNr), 2) the indirect pathway from the striatum to the external segment of the globus pallidus (GPe), 3) the projection from the GPe to the subthalamic nucleus, 4) and the projections from the GPi and SNr to the ventral-anterior and ventral-lateral nuclei of the thalamus. BZDs may potentiate GABA signaling in any or all of these pathways, thereby alleviating the immobility, rigidity, and staring that characterizes retarded catatonia. We have had patients with catatonia tell us that they felt better *because* they were able to move following treatment with lorazepam, supporting the notion that the basal ganglia might be one of the primary sites of action of the drug.

Catatonia as an Expression of Extreme Anxiety

In our ongoing study of catatonia, a large majority of the patients reported having felt extremely anxious, to the point that approximately 15% actually believed they were dead or going to die. The experience of anxiety may be an important final common pathway for catatonia given that it can occur in the context of diverse conditions, including medical or neurologic disorders, primary psychiatric illnesses, and BZD withdrawal. The potent anxiolytic properties of BZDs may explain their efficacy in treating catatonia in so many different clinical situations. The relative lack of anxiety in schizophrenic patients with catatonic symptoms may explain the relative ineffectiveness of BZDs in these individuals.

Catatonia as a Type of Seizure Disorder

It has been suggested that BZDs may be effective in some cases of catatonia because they have anticonvulsant properties and the underlying problem is really one of seizures (Menza and Harris 1989). Complex partial seizures and nonconvulsive status epilepticus can be very difficult to dis-

tinguish from catatonia clinically, and in our opinion an electroencephalogram should be obtained on all catatonic patients, at least those with the retarded form, prior to treatment. However, we should note that in our prospective study of more than 100 cases of catatonia, the electroencephalogram has been normal in almost every patient. This would suggest that the therapeutic efficacy of BZDs in most cases of catatonia needs to be explained by something other than the anticonvulsant actions of the drugs.

Catatonia as a State of Extreme Inhibition

The concept of behavioral disinhibition is of interest given that some patients describe their catatonic immobility and mutism as defenses against aggression or other actions that they find unacceptable. Furthermore, the resolution of retarded catatonia with BZDs can be followed by extreme agitation and aggression, albeit rarely. Although there is considerable controversy about whether or not behavioral disinhibition is a real clinical consequence of BZD drug use in humans, studies in animals have repeatedly shown that BZDs have the potential to release suppressed behaviors and reduce the fear of negative consequences that would otherwise be attendant on certain actions. Indeed, BZDs are developed according to whether they induce feeding, drinking, and locomotor behaviors that were decreased in response to punishment (Charney et al. 2001).

Recommended Treatment Regimen With Lorazepam

We recommend that unless there is a contraindication to using the intramuscular route, such as a known bleeding condition, patients with catatonia receive lorazepam 2 mg im initially. The oral route is less reliable given the nature of the condition, characterized as it is by unresponsiveness and negativism. One cannot always be certain the patient has actually taken or swallowed the medication, and it is much more slowly absorbed. Response is typically seen within 1–3 hours. If there is no response after 3 hours, the same dosage should be repeated, and again a 3-hour period should be allowed to elapse. If, once again, there is no response, a third injection may be given. The young, elderly, or medically compromised patient should have the dose reduced to 1 mg each time. Single intravenous doses of a BZD bring about an even more rapid onset of action. Just as rapidly, however, it redistributes throughout the body, ultimately producing a shorter duration of effectiveness than that seen with oral or intramuscular administration, unless given in the form of a continuous intravenous drip.

Duration of Benzodiazepine Treatment After Resolution of the Acute Episode

BZDs not only bring about rapid resolution of the catatonic state but seem to be required for the maintenance of improvement until treatment of the primary disorder has been instituted (Clothier et al. 1989; McEvoy 1986; Vinogradov and Reiss 1986). Failure to continue with BZDs appears to put the patient at high risk of relapse into catatonia. Once the underlying illness has been treated, BZDs can then be tapered and discontinued in most cases. In our experience, there is a subset of patients who relapse whenever BZDs are discontinued and who seem to require long-term maintenance treatment with the drug. This raises the interesting question of whether catatonia should be considered a diagnosis in its own right and not simply a manifestation of another underlying disorder.

Complications Associated With Benzodiazepine Treatment

BZDs have a wide margin of safety. The most common side effect is sedation, but in the case of catatonia these medications have the paradoxical effect of activating patients. Typically, patients who respond begin to move and talk and then ask for food or drink without an intervening period of sleep. After lorazepam treatment, a few patients fall asleep before becoming activated.

Unsteadiness following BZD administration is a concern in the elderly or in anyone with a gait disturbance, especially when the therapeutic goal of treatment is activation. For this reason, lower dosages are recommended in these patients, and precautions—for example, teaching about side effects, using bed side-rails, making a walker available, and providing close supervision when the patient is up and about—are in order.

At high, preoperative dosages, BZDs depress alveolar ventilation and reduce the hypoxic drive. Such effects are more marked in someone with chronic obstructive pulmonary disease (COPD). At lower, but still hypnotic dosages, BZDs may worsen any sleep-related respiratory disorders like obstructive apnea secondary to their effects on upper airway muscles, resulting in reduced ventilatory response to carbon dioxide. For this reason, one should use a lower dosage of lorazepam and carry out more frequent monitoring of vital signs in the catatonic patient who is known to have COPD, sleep apnea, or obesity. Measurement of oxygen saturation is an easy, noninvasive, and readily available tool for monitoring in this situation.

Rarely, in our experience, a patient will change from catatonic immobility to marked psychomotor agitation with the risk of harm to self or

aggression toward others. It is important to be prepared for this eventuality and to maintain close observation during treatment. In the event of psychomotor agitation, we suggest that higher, hypnotic doses of lorazepam be given to bring about sedation.

Other Pharmacotherapies for Catatonia

While there is consensus that BZDs are safe and effective for catatonia, other pharmacologic therapies have also been reported to be useful. Because of the clinical overlap between catatonia and parkinsonism, drugs used to treat Parkinson's disease have been tried in catatonia. Northoff et al. (1997) used intravenous amantadine to successfully treat three patients with acute catatonia, and Neppe (1988) reported the successful treatment of catatonic stupor with levodopa in six patients. In the latter study, however, patients became floridly psychotic and the use of neuroleptic medication was required. Convincing reports of the effectiveness of intramuscular and intravenous anticholinergic agents in the treatment of catatonia have been published (Albucher et al. 1991; Panzer et al. 1990), suggesting an efficacy that might approximate that of BZDs. Given the importance of acetylcholine in striatal neurotransmission, this observation would support the notion that basal ganglia dysfunction plays a major role in the pathophysiology of catatonia (Calabresi et al. 2000). Zolpidem, a selective GABA-A agonist, was used to successfully treat catatonia in one patient, underscoring the therapeutic efficacy of enhancing GABAergic function in catatonic states (Thomas et al. 1997).

The GABA-A receptor complex also has a component that binds barbiturates, and this may explain why sodium amobarbital can also be effective in relieving catatonic states. Unlike BZDs, which potentiate the effects of naturally occurring GABA, barbiturates carry a higher risk of side effects because they act directly on the GABA-A receptor and can therefore have a greater sedative-hypnotic effect as well as a higher potential for respiratory depression.

Conclusion

Based on clinical evidence, benzodiazepines are highly effective and safe as the first-line treatment of catatonia. They are particularly effective in treating the retarded type of acute catatonia regardless of etiology but may be less effective in patients with chronic catatonia associated with schizophrenia. The mechanism of action of BZDs relates to their GABAergic effects and may reflect conceptualization of catatonia as a disorder of movement,

extreme anxiety, seizures, or extreme inhibition. Guidelines for the use of lorazepam were outlined in this chapter. Evidence on the efficacy of other pharmacologic agents is limited but may be worth further investigations.

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C H A P T E R 1 3

CONVULSIVE THERAPY

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Although electroconvulsive therapy (ECT) is an effective treatment for patients with mood and psychotic disorders, it is among patients with catatonia that the most remarkable efficacy is observed (Abrams 2002; Fink 1979, 1990, 1999). The first patients to benefit from convulsive therapy had catatonic symptoms, and the clinical experience of more than six decades has shown that catatonia is the clinical condition with the most rapid, dramatic, and often lifesaving response to ECT.

In 1934, Meduna injected camphor-in-oil intramuscularly in a patient with the catatonic form of dementia praecox and elicited the first iatrogenic seizure intended to treat mental illness (Fink 1984). The patient had been hospitalized for 4 years, in a state of withdrawal, unresponsiveness, and mutism. He was bedridden and required nasogastric tube feeding and total nursing care. He improved dramatically and after a course of 11 treatments was discharged from the hospital, returned to work, and remained well on follow-up 4 years later.

In 1938, Bini and Cerletti induced seizures electrically rather than chemically. This new method was so easy to administer and so much better tolerated that it rapidly replaced chemically induced seizures in clinical practice. Their first patient was a psychotic man with manic and catatonic symptoms. He expressed purposeless excitement and confusion alternat-

ing with mutism and posturing. He responded well to electrically induced seizures after 3 weeks of treatments (Fink 1979). It was fortunate that both subjects in these pioneering applications exhibited catatonia and their response to treatment was dramatic. As a result, ECT quickly became an established treatment for patients with severe mental illnesses.

In selecting treatments for catatonia, physicians are strongly influenced by their diagnostic system (Fink and Taylor 2003). On the basis of historical developments and trends, catatonia was considered only as a type of schizophrenia during much of the twentieth century. This classification discourages the use of ECT as an early treatment option, as ECT is rarely considered a first-line treatment for schizophrenia. In the 1970s, however, catatonia was increasingly recognized as a syndrome among patients with mood disorders and acute neurologic conditions (Abrams and Taylor 1977; Gelenberg 1976; Gelenberg and Mandel 1977; Morrison 1975; Taylor and Abrams 1977). Despite these reports, catatonia remained a subtype of schizophrenia in DSM-III and DSM-III-R (American Psychiatric Association 1980, 1987). Fink and Taylor (2001) called attention to the frequency of catatonia among patients other than those with schizophrenia for the DSM-IV (American Psychiatric Association 1994) commission members. The commission maintained the preeminent position of catatonia in schizophrenia but did recognize catatonia secondary to medical disorders and as a modifier of depressive and bipolar disorder.

The classification of catatonia as schizophrenia encourages clinicians to treat catatonic patients with antipsychotic medications. But in practice, catatonic patients are treated otherwise. Hawkins et al. (1995) reviewed the treatments for catatonia in reports of 178 patients in 270 episodes. Benzodiazepines ($N=104$) were most commonly used, with lorazepam most frequently prescribed ($N=72$). A benzodiazepine alone elicited the resolution of symptoms in 70% of the catatonic patients, whereas use of lorazepam specifically elicited a 76% remission rate. ECT alone, although reported in fewer cases ($N=55$), resulted in the resolution of catatonic symptoms in 85% of the patients. Of the 40 patients treated with antipsychotic medications alone, only 3 (7.5%) responded. When the presence of malignant catatonia was suspected, the response with ECT was 89% (9 of 11), with benzodiazepines 40% (2 of 5), and with antipsychotic drugs 0% (0 of 2). This dissociation among diagnostic classification, clinical practice, and therapeutic response warrants our attention.

Systematic studies of any treatment for catatonia are lacking (Francis et al. 1996). The evidence for efficacy for any treatment comes from retrospective studies and clinical reports of the rapid benefits of a treatment in patients with life-threatening conditions. When catatonia has been rec-

ognized, more than 90% of the patients have responded first to barbiturates and more recently to benzodiazepines (see Chapter 12, "Pharmacotherapy," this volume). When these treatments have failed, ECT has been successful. ECT is effective in catatonia refractory to lorazepam (Bush et al. 1996; Yeung et al. 1996), partially responsive to lorazepam (Ungvari et al. 1994), and refractory to amobarbital (McCall 1992). In patients unresponsive to treatment with other benzodiazepines, ECT is effective (Bush et al. 1996; Malur et al. 2001). The particular efficacy of ECT in relieving catatonia is best seen and reported in the treatment of the more malignant, delirious, and life-threatening forms of the illness.

ECT in the Different Forms of Catatonia

Little attention is paid to how best to identify the syndrome of catatonia (see Chapter 3, "Nosology," this volume). Yet, in systematic studies of adult inpatient populations, using catatonia rating scales, between 8% and 14% of the samples exhibit two or more signs of catatonia for 24 hours or longer (Fink and Taylor 2001, 2003). Many different forms of catatonia are recognized. A retarded motor form with stupor, retardation, and rigidity is labeled a benign stupor. An excited form, often associated with a history of mania, is labeled excited catatonia, manic delirium, delirious mania, or oneiroid state (Fink 1999; Fink and Taylor 2001, 2003). Physicians have been baffled since the nineteenth century by an acute, fulminant, psychotic, febrile, and delirious illness that historically resulted in death in more than half the cases. This illness has been given many names, including pernicious, lethal, or malignant catatonia (MC) (see Chapter 9, "Malignant Catatonia," this volume; Fink and Taylor 2003).

Another form of catatonia is neuroleptic malignant syndrome (NMS). Following the introduction of antipsychotic drugs, an acute, occasionally fatal syndrome marked by fever, rigidity, mutism, and autonomic instability was described. The characteristics of NMS are indistinguishable from those of MC, and treatment may be the same for both (Fink 1996a; Fink and Taylor 2003; Rosebush et al. 1990; White and Robins 1991). A similar syndrome, precipitated by drugs affecting brain serotonergic systems, is identified as the toxic serotonin syndrome (Fink 1996b). Other forms of catatonia include periodic catatonia (see Chapter 8, "Periodic Catatonia," this volume), the rapid cycling of mixed affective states, and primary akinetic mutism (Fink and Taylor 2003).

These descriptive entities constitute a common syndrome by rigorous examination protocols and quantitative rating scales that identify the signs of catatonia (Fink and Taylor 2003). Two or more signs for more than 24 hours and their responsiveness to barbiturates, benzodiazepines, anti-

convulsants, or ECT define the syndrome. ECT is effective in all forms of catatonia, even after pharmacotherapy has failed.

A striking description of the benefits of ECT in the treatment of 34 patients with MC was reported by Arnold and Stepan (1952). ECT was administered daily, occasionally three times in 1 day. Of 18 patients treated within 3 days of the onset of the episode, 15 survived. Of the 16 patients treated on day 5 or later, only 1 survived. Recent literature reviews report mortality rates for MC up to 100% prior to the 1940s (Mann et al. 1986, 1990). In the past half century, Mann et al. identified reports of 292 patients with a mortality rate of 60%. ECT was the most effective, relieving the syndrome in 40 (98%) of 41 patients. The efficacy of ECT in treating MC was confirmed by Philbrick and Rummans (1994). In a literature review of a 5-year period (1986–1991), they identified 13 cases of MC and added 5 of their own. Of the 13 patients who received ECT, 11 recovered (85%) and 2 died. All 5 of the Mayo Clinic patients received ECT and recovered. The beneficial effects of ECT in MC, described by numerous authors since these reports, are summarized by Fink and Taylor (2003). Early intervention with ECT is encouraged to avoid undue deterioration of the patient's medical condition.

Some authors approach NMS and MC as entities with different psychopathologies, reserving barbiturates and ECT for patients with MC and dopamine agonists (L-dopa, bromocriptine) and muscle relaxants (dantrolene) for patients with NMS. But once the identity of the syndromes was recognized, ECT was applied to patients with NMS (Pearlman 1990). Among the first reports was that of Greenberg and Gujavarty (1985), who observed the efficacy of ECT in three patients with NMS. The more recent literature has been summarized by Trollor and Sachdev (1999). In 46 published reports describing experiences with 55 patients, ECT was effective in 40 patients with NMS (73%). It was also effective in relieving psychosis and NMS in 10 (18%) of the patients. Complete recovery of symptoms was reported in 25 (63%) of the cases, and partial recovery was noted in 11 (28%).

Early descriptions of NMS associated it with malignant hyperthermia (MH), a clinically similar pharmacogenetic syndrome of acute muscle rigidity, hypermetabolism, and fever associated with inhalational anesthetics and succinylcholine. Although this association is now questioned, one consequence persists. Some authors argue that ECT is not safe in MH. They then avoid ECT or the use of succinylcholine in patients with NMS. The evidence for the safety of ECT in NMS so far is strong. However, in the event that an anesthesiologist is concerned about the use of succinylcholine, nondepolarizing muscle relaxants, such as mivacurium and atracurium, are effective alternatives.

Emergence of Catatonia During ECT

The emergence of catatonia in a patient with bipolar disorder after two sessions of ECT was described by Pandey and Sharma (1988). When the patient was given a single unmodified ECT 3 weeks later, after complete resolution of symptoms, the catatonia reemerged. Malur and Francis (2001) described the appearance of catatonia in four patients during ECT. Catatonia resolved with benzodiazepines and continuation of ECT. Considering the universal efficacy of ECT in relieving catatonia, reports of the emergence of catatonia during ECT are puzzling. A possible explanation is that the patients experienced recurrence of their catatonic symptoms because of the rapid withdrawal of benzodiazepines prior to ECT. Rapid withdrawal from benzodiazepines evokes catatonia (Deuschle and Lederbogen 2001; Rosebush and Mazurek 1996; Zalsman et al. 1998).

ECT in Patients With Atypical Catatonic Features

An interesting aspect of the role of ECT in catatonia is the rapid response of patients with atypical presentations. We recently reported two examples from our clinical experience. A delirious mania manifested itself as a severe medical illness with stupor and other catatonic features that resolved with ECT (Levin et al. 2002).

> A patient was admitted in a state of excited delirium following intrathecal administration of an analgesic for chronic pain. He exhibited purposeless agitation, rigidity, periods of mutism, negativism, and staring. Vital signs were increased, and his temperature was 100.3°F. He required physical restraint and received intravenous haloperidol, lorazepam, and midazolam with little effect.
>
> As all efforts to reduce the delirium failed, he was paralyzed, intubated, and ventilated in an intensive care unit for 2½ weeks. Attempts to wean him from the ventilator failed because of severe agitation, despite the use of haloperidol and valproate. Cogwheel rigidity and muscle twitches were prominent. On day 17, his temperature spiked to 104°F, right lower lobe pneumonia was diagnosed, and antibiotics were started. Serum creatine phosphokinase was elevated on admission and remained persistently so.
>
> Finally, the patient was treated with bifrontal ECT on a daily basis. On day 21, he was weaned from neuromuscular paralysis. He showed no signs of agitation and was successfully extubated. Postextubation, he was confused and disoriented but not agitated or catatonic. Some dysarthria, ataxia, and involuntary muscle twitches persisted. He described his mood as very anxious, although his affect was flat. He had no recollection of his illness and returned to work 1 month later.

Another example is a patient with catatonia accompanied by Tourette's syndrome in the context of recurrent major depressive disorder. A long list of medicines did not relieve the syndrome, but ECT did (Trivedi et al. 2003).

> A woman with recurrent depression was hospitalized with depressed mood, slow speech, suicidal thoughts, rigidity, and posturing. Her illness progressed despite medications. She developed a deep venous thrombosis and survived an embolus to a lung. In her fifth week of illness, she assumed a fetal position and was mute thereafter except for outbursts of repetitive expletives. The expletives resembled coprolalia associated with Tourette syndrome.
>
> Her treatment was changed to lorazepam 6 mg/day, and bilateral ECT was begun. After the second treatment, she slowly answered questions, stood, walked, ate, and went to the bathroom by herself for the first time in many weeks. After the third treatment, the expletives ceased. She walked and spoke spontaneously, but rigidity and posturing were manifest.
>
> The day after the fifth treatment, all signs of catatonia were gone. She was no longer depressed, smiled spontaneously, and cared for herself. She was discharged on lithium, thiothixene, and olanzapine. Examinations up to 1 year later found her without signs of catatonia or depression.

ECT Technique in Catatonia

The practical aspects of the administration of ECT in catatonic patients do not differ from those in patients with other psychiatric disorders. It is not uncommon, however, that patients present with compromised medical status (Carroll 1996; Fink and Taylor 2003). Every effort should be made to optimize the patient's physical condition before ECT, without unnecessarily prolonging the patient's suffering. Fever, autonomic instability, and rigidity associated with catatonia might be inaccurately perceived as an unrelated or a superimposed condition and lead to extensive medical examinations and undue delays in initiating ECT. More favorable results and reduced morbidity are obtained when ECT is initiated early in the course of catatonia (Hawkins et al. 1995; Philbrick and Rummans 1994).

Almost all reports of successful ECT for severe forms of catatonia report the use of bilateral ECT. Our ECT protocol in catatonia is simple. Bitemporal electrode placement at energies selected by half-age estimates (Petrides and Fink 1996) are monitored by the quality of induced electroencephalographic seizures (Abrams 2002). Daily treatments for up to 5 days are to preferred, with continuation ECT at more conventional frequencies (Fink and Taylor 2003).

Because benzodiazepines are the first choice of treatment in catatonia, patients often come to ECT receiving these medicines. Rapid withdrawal is not recommended, as it may provoke worsening or recurrence of catatonic symptoms (Deuschle and Lederbogen 2001; Rosebush and Mazurek 1996). Continuation of the medicines is recommended. Indeed, a synergistic effect of ECT and benzodiazepines has been reported (Petrides et al. 1997). In continuation treatment after ECT, benzodiazepines are often useful and can be continued for many months after recovery.

Mode of ECT Action in Catatonia

The rapid alleviation of catatonic signs before the alleviation of the underlying illness indicates that the improvement of catatonia does not necessarily depend on the treatment of the psychotic or the affective symptoms. There are no controlled studies designed to answer the question of how ECT works in catatonia. Changes in brain perfusion have been reported before and after ECT treatment of catatonia. In a group of nine patients with catatonia treated with ECT, Escobar et al. (2000) reported an improvement in brain perfusion using single photon emission computed tomography (SPECT) imaging in the parietal, temporal, and occipital areas in patients with mood disorder and catatonia, but no changes in patients with schizophrenia and catatonia. Galynker et al. (1997) reported increased SPECT image perfusion in the left parietal and motor cortices in a patient with schizoaffective disorder and catatonia treated with ECT.

Several theories about the mode of action of ECT offer models for how ECT affects catatonia. Barbiturates, benzodiazepines, and carbamazepine are effective treatments for catatonia, but they affect γ-aminobutyric acid (GABA) (Paul 1995). These compounds impede the passage of currents, so that more energy is needed to stimulate succeeding synapses. The reduced ability of electric currents to elicit motor seizures reflects a rise in seizure thresholds. Seizure thresholds rise during the course of ECT (Abrams 2002). Seizure durations shorten with repeated seizure inductions. ECT has also been used to end an ongoing status epilepticus (Fink et al. 1999). The impact of catatonia or its treatment on brain or serum GABA levels may be worthwhile to investigate.

The dramatic picture of catatonia and its rapid relief by ECT and benzodiazepines suggests that catatonia may be the final common outcome pathway for abnormal brain seizure activity. It is conceivable that ECT relieves catatonia by raising the seizure threshold and inhibiting the propagation of abnormal electrical signals through cerebral synapses. Catatonia is prominent in patients with epilepsy, and nonconvulsive status epilepticus is in-

cluded in the differential diagnosis of catatonia. Against such an association, however, is the absence of electroencephalographic seizure activity in catatonic patients. However, electroencephalograms of catatonic patients are frequently difficult to interpret because of muscle rigidity producing artifacts.

ECT is most effective in those patients with a neuroendocrine abnormality, such as an abnormal dexamethasone suppression test or a diminished thyroid-stimulating hormone response to thyrotropin-releasing hormone (Fink 1979, 2000). These abnormalities disappear with effective treatment. The persistence of neuroendocrine abnormalities, or their recurrence, is the harbinger of a poor clinical outcome or a recurrence of the illness. The most detailed reports of an association between catatonia and thyroid abnormality are those of Gjessing (1976). The efficacy of interventions that affect brain GABAergic systems to relieve catatonia, especially MC, argues for a neuroendocrine view of catatonia and for the mode of action of ECT. Such a view is a useful update on Meduna's hypothesis that led to the development of ECT.

Conclusion

Consistent evidence over the last century supports the high degree of efficacy and safety of ECT in the treatment of all forms of catatonia. ECT is often effective regardless of etiology and, in the special circumstances of MC, NMS, excited catatonia, and atypical forms, even after pharmacotherapy has failed. Early application of ECT may prevent unnecessary morbidity and mortality. Investigations of brain GABA function, seizure pathophysiology, and neuroendocrine abnormalities may shed light on the mechanism of action of ECT in catatonia.

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C H A P T E R 1 4

PROGNOSIS AND COMPLICATIONS

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The long-term prognosis of catatonia varies according to the nature of the underlying disorder. We now recognize catatonia as a syndrome associated with a wide range of disorders, including primary psychiatric disorders, metabolic disorders, neurological disorders and brain injury, and drug-induced disorders. Idiopathic catatonic states such as periodic catatonia and hyperkinetic-akinetic motility psychosis have also been described (see Chapter 3, "Nosology," this volume). Diminished interaction due to dementia, a severe negative symptom or deficit state of schizophrenia, or the effects of prolonged institutionalization may be mistaken for catatonia. Treatment response of a catatonic episode and outcome after multiple episodes are both determined by the nature and severity of the disease state of which catatonia is a manifestation. Classic catatonic signs such as stupor, negativism, and excitement do not by themselves identify the etiology or determine the prognosis.

Historical Outcome Studies

In Kahlbaum's (1874/1973) original study of catatonia, 41% of the patients had a good outcome. He noted that cure is possible and recovery relatively frequent for cases presenting with atonic melancholia (stupor) and those with excited states. The latter were most likely bipolar patients

with manic catatonic excitement. However, Kahlbaum also noted that catatonia can be directly lethal. When viewed as a subtype of schizophrenia, catatonia has a relatively better prognosis than do the other subtypes of schizophrenia. Kraepelin (1913/1971) considered catatonia as a subtype of dementia praecox and found that 59% of catatonic patients progressed to "a state of profound idiocy." However, Kraepelin shared the view that catatonia had a relatively better prognosis. Eugen Bleuler (1916/1951), like Kahlbaum, recognized multiple forms of catatonia, such as depressive, manic, that with religious delusions, cyclical, and so forth, and considered the prognosis to be more variable. He emphasized that only those presenting with a picture of chronic catatonia "are quite hopeless." He also noted a form of catatonia that progressed to "rapid dementia." M. Bleuler (1978), in his landmark studies of long-term outcome in schizophrenia, grouped the various syndromes on the basis of onset, symptoms, and outcome. Out of 208 subjects with schizophrenia studied, about 22% of patients, including those presenting with catatonia, had "a severe end state," but 79% had mild and moderate end states.

Gjessing (1976) meticulously described periodic catatonia and reported a good prognosis for these cases. Even Kraepelin (1913/1971), who believed periodic catatonia was a subtype of schizophrenia, agreed that the prognosis was good for this syndrome. Gjessing noted that only 2%–3% of patients with schizophrenia belong to the periodic catatonia subtype. Many of the cases originally described by Gjessing fit the description of neither schizophrenia, as they do not have thought disorder, nor bipolar disorder, since, despite an episodic course, they do not have a primary mood disturbance. Leonhard (1979) designated recurrent nonschizophrenic, nonaffective psychoses as cycloid psychoses. Within this group, those patients with a catatonic presentation (hyperkinetic-akinetic motility psychoses) have a good prognosis. Leonhard noted that "only a small defect state remains after several attacks" and agreed with Gjessing's postulation of periodic catatonia as an independent disorder with high familial aggregation, rather than a subtype of schizophrenia.

Thus, it is clear that the pioneers in psychiatry recognized catatonia to be a syndrome and the outcome to be variable, from cure to rapid deterioration and even death. Within the functional catatonias, rather than specific catatonic signs, these early authors noted that prognosis depends on factors such as type of onset, associated mood disorder, and family history. Patients with an acute onset, excited state, absence of core schizophrenic symptoms, episodic course, and positive family history had a good prognosis. Those with an insidious onset and chronic catatonic presentation had a very poor outcome. Additionally, three other distinct functional disorders with catatonia were recognized: one with an acute onset

and rapid progression to a deteriorated state or even death; the second with a recurrent or periodic form with a very good prognosis; and the third, a bipolar type—namely, cycloid psychosis. In DSM-IV, and its text revision, DSM-IV-TR (American Psychiatric Association 1994, 2000), catatonia is included under several categories—as a subtype of schizophrenia, as an extended dimension of depression or mania, and as secondary to a medical condition. Prognosis is determined by the nature of the underlying condition. The idiopathic catatonic states such as periodic catatonia and cycloid psychosis are to be classified as atypical or psychosis not otherwise specified in DSM-IV-TR.

Outcome in Psychotic Disorders With Catatonia

In recent years, there has been a dearth of long-term studies of outcome in the catatonic syndromes. This may partly be due to the diminishing frequency of these syndromes or to the availability of treatments such as benzodiazepines, neuroleptics, and electroconvulsive therapy (ECT). Morrison (1974) reviewed the outcome in 214 cases between 1920 and 1971 in which the patient presented in a catatonic state and was diagnosed with schizophrenia. When research criteria were applied, 37% could be rediagnosed with a mood disorder. Eighty-five patients (39.7%) showed a full recovery, a rate similar to the 41% recovery rate first noted by Kahlbaum. The remaining 129 patients (60.3%) either had a partial recovery or were in a chronically ill state. Acute onset, presence of depression, and family history of depression predicted recovery. Of the various catatonic signs examined, only stereotypy had modest predictive value and was associated with good recovery. A gradual onset and presence of auditory hallucinations predicted poor outcome.

Hearst et al. (1971) evaluated 20 cases of catatonic schizophrenia for any relation between the catatonic features and outcome but did not find any. van Os et al. (1996) examined 166 consecutive patients with functional psychoses for symptom patterns, severity, and short-term outcome. They noted three patterns of outcome. The syndrome with bizarre behavior and catatonia was associated with a relatively longer course of illness and poor premorbid social functioning. The group with insidious onset and blunt affect had an even more disabling course, whereas syndromes with positive psychotic symptoms or manic symptoms had a more benign course. Stöber et al. (1995) studied 139 probands with DSM-III-R (American Psychiatric Association 1987) schizophrenia, catatonic subtype, and found that 83 of them met the criteria for periodic catatonia and 56

for systematic catatonia, which is associated with a less favorable course, according to the Leonhard classification. The two syndromes appeared to be distinct in terms of family morbidity risk and age at onset. Barnes et al. (1986) reviewed 25 cases of catatonia: 20% of the patients had an organic disorder, 36% had a mood disorder, and only one (4%) had schizophrenia. Others (40%) had no identifiable cause. Cases with a mood disorder and the idiopathic cases had a high incidence of recurrent episodes, positive family history, and good prognosis. The presentation in the latter subgroup appears very similar to the description of periodic catatonia. Cases presenting acutely with rapid progression had a poor outcome and showed evidence of renal failure. Rigby et al. (1989) studied the significance of stupor in the long-term outcome of schizophrenia. Of the 271 patients reviewed, 12 who presented with stupor had a less favorable course.

Thus, outcome studies in the last 25 years echo historical descriptions. Cases presenting with catatonia are a heterogeneous group with variable outcome (Figure 14–1). Whereas insidious onset, blunted affect, and chronic stupor predict poor outcome, a diagnosis of mood disorder, recurrent catatonia, and strong family history are associated with a better outcome. These studies also confirm that a subgroup of catatonia exists that presents acutely, progresses rapidly, is often complicated by renal failure, and could be fatal.

No established biological indices of prognosis in catatonia are available. Wilcox (1993) studied the ventricular-brain ratio (VBR) in cases of catatonia. Catatonia associated with schizophrenia had the highest VBR. High VBR was associated with a chronic and deteriorating course. Hypometabolism in the frontal and temporal cortex noted by positron emission tomography or single-photon emission computed tomography has been associated with a poor outcome in catatonia. However, these data are anecdotal. Hypermetabolism in the thalamus and hypometabolism in the basal ganglia have also been reported but their relation to outcome has not been studied (Atre-Vaidya 2000; Lauer et al. 2001).

Outcome in Mood Disorders With Catatonia

It is now well accepted that a primary mood disorder may present with catatonic symptoms. The outcome in such cases, in comparison to those with a primary psychotic disorder, is more favorable, as previously noted. There have been several studies of catatonia from the perspective of mood disorders. Abrams and Taylor (1976, 1977) published a series of reports based on cases with one or more signs of catatonia. Two-thirds of the patients qualified for a research diagnosis of mood disorder and only 7% for a diagnosis of schizophrenia. Nonresponders to somatic treatments such as

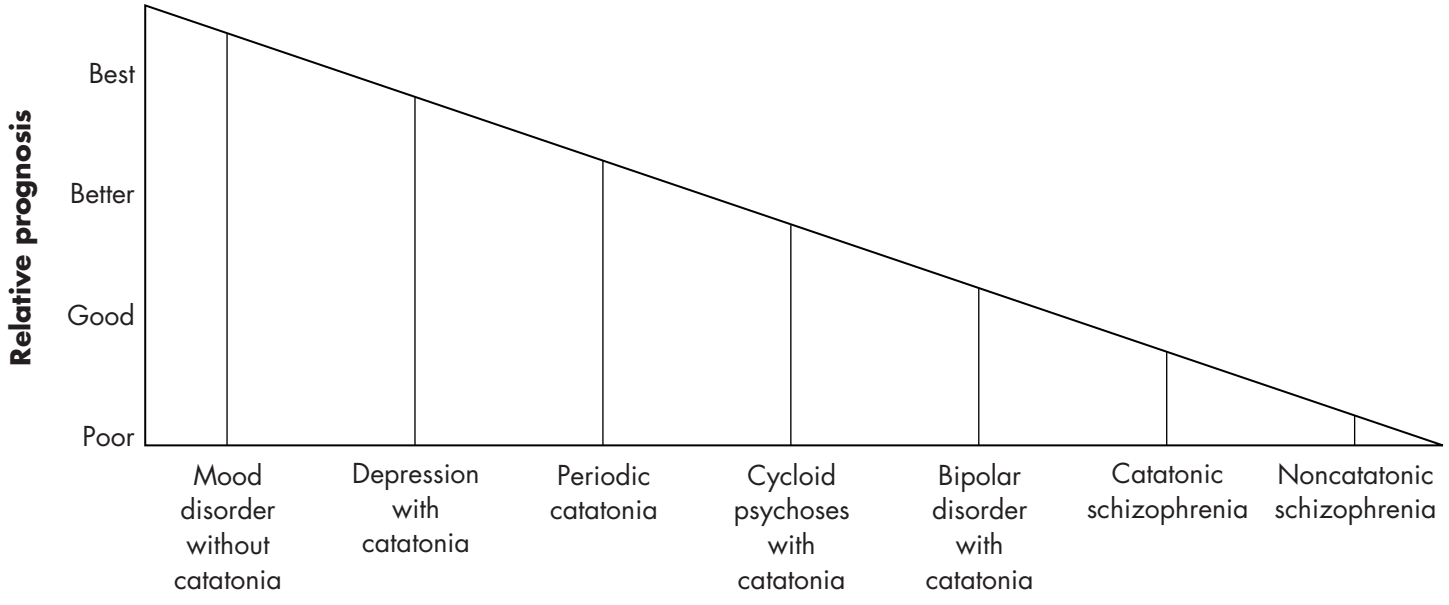


Figure 14–1. Schematic diagram of relative prognosis in psychotic and mood disorders with and without catatonia.

medication and ECT tended to be younger at onset of illness, disoriented, and diagnosed with schizophrenia. Responders had rapid, pressured speech; alcohol abuse; and a mood disorder. By factor analysis, Abrams and Taylor found evidence for two catatonia factors. Factor I consisted of mutism, negativism, and stupor and was unrelated to diagnosis, age at onset, gender, family history, or treatment response. Factor II consisted of mutism, stereotypy, catalepsy, and automatic obedience and was associated with mania and a favorable treatment response (Abrams et al. 1979; Taylor and Abrams 1977). In another series of patients with bipolar disorder, these investigators noted that 28% had one or more signs of catatonia (Taylor and Abrams 1977). Presence of catatonia did not alter the short-term response of mania to treatment.

These studies established that catatonic signs are frequently seen in patients with mood disorder. Whereas the presence of catatonia does not change the short-term treatment response in mania per se, the association with other signs of schizophrenia makes the outcome poorer. The presence of catatonia in depression or psychosis, however, does make the outcome worse than that of depression or psychosis without catatonia (Figure 14–1). Bräunig et al. (1998) reported that catatonic patients with mania had a worse prognosis than noncatatonic manic patients. The catatonic subgroup had a more severe form of illness, as shown by more episodes, more symptoms, longer hospital stay, and lower Global Assessment of Functioning scores.

Swartz et al. (2001) reported on the outcome in 19 cases of depression with catatonia treated with ECT. Three to 7 years after the index course of treatment, 10 of 13 patients discharged on tricyclics, lithium, venlafaxine, or bupropion had done well, but none of the other 6 patients who were discharged on a selective serotonin reuptake inhibitor did well. Neuroleptics are considered by many to be only variably effective for the treatment of catatonia and might possibly cause a worsening of the overall course (Clark and Rickards 1999; Mann et al. 2001).

Although the role of ECT in treating the acute catatonic state is well recognized, its role in chronic catatonia remains to be defined. Malur et al. (2001) reported three cases of medically complicated, prolonged catatonia that improved with ECT. In the last 2 years, the authors of this chapter have given ECT to four patients with chronic catatonia, with modest improvement, including a reduction in core catatonic behaviors such as mutism and posturing. However, relapse in the catatonic condition occurred soon thereafter, and maintenance ECT was needed to sustain the improvement. In some of these cases, the catatonia had remained undiagnosed or neglected for years. The catatonia was associated with immobility and muteness, which led to a drastic reduction in the quality of

life. The immobility caused contractures, constipation, and a need for gastrostomy tubes, all common medical complications in chronic catatonia (discussed further in the next section). Although patients had dramatic improvement with ECT, the benefits were partial and were sustained only with maintenance ECT. With earlier diagnosis and treatment of catatonia, many of the adverse effects experienced might have been prevented.

Complications of Chronic Catatonia

Not all patients with chronic catatonia fit the stereotype of the rigid, stuporous patient in a fixed posture, but it is such patients who are most at risk for medical complications. Chronic catatonic patients are at significant risk because their physicians may fail to diagnose or treat medical complications or coincident medical illnesses. Swartz and Galang (2001) described three cases with long delays in the recognition of serious medical problems because the patients were mislabeled as hopelessly demented, leading to therapeutic nihilism. Even when it is clearly recognized that a patient has catatonia, providers sometimes become passive in the pursuit of treatment and prevention of complications, out of a sense of helplessness. Furthermore, recognition and treatment of medical problems are difficult because of patients' poor communication, inability to cooperate, and prolonged immobility. Chronic catatonic patients typically reside in freestanding psychiatric hospitals where general medical care resources may not be adequate. For all these reasons, those caring for catatonic patients must be vigilant for medical morbidity. We now review the major medical complications that are frequently encountered in chronic catatonic patients.

The most common pulmonary complication is *aspiration*. Although its frequency and contribution to mortality in catatonia have not been quantified, aspiration is the most common cause of death in patients with dysphagia caused by neurologic disorders and the most common cause of death in patients on tube feedings (Marik 2001). Aspiration can result in pneumonitis and/or pneumonia. Prophylactic antibiotics are not recommended in patients who are considered at high risk for aspiration. In patients with symptoms of aspiration pneumonia, broad-spectrum antibiotics that include coverage against gram-negative organisms are recommended (Marik 2001). Although corticosteroids have frequently been prescribed for aspiration pneumonitis, the practice is not supported by the available data (Marik 2001). On the basis of a single case report of fatal aspiration pneumonitis in a patient with catatonia, Bort (1976) recommended prophylactic administration of antacids in catatonia. It is not clear that this is

a good idea. Although antacids neutralize gastric acidity and therefore would be expected to reduce pneumonitis injuries, gastric acidity normally keeps stomach contents sterile. Hence, neutralization with antacids may promote colonization by pathogenic organisms, making aspiration pneumonia more likely and more severe (Marik 2001). The same rationale would argue against routine administration of histamine H_2 blockers or proton pump inhibitors.

Other forms of pneumonia are also common in patients with chronic catatonia. Multiple risk factors include malnutrition, weak cough, poor respiratory effort, atelectasis, and crowded institutional settings; these factors also make infection with an antibiotic-resistant organism more likely.

Pulmonary embolus is another common cause of death in patients with catatonia. Prolonged inactivity promotes venous stasis, which in turn leads to thrombosis. Dehydration is another factor promoting venous thrombosis. In a retrospective study, Carroll (1996) found that about 6% of catatonic patients developed venous thrombosis. Case reports of thrombosis, often leading to pulmonary embolism, have been frequent in catatonia (Barbuto 1983; McCall et al. 1995; Morioka et al. 1997; Regestein et al. 1977; Sukov 1972). McCall et al. (1995) described two new cases and 20 cases previously reported of pulmonary embolism in psychogenic catatonia. They found that death from pulmonary embolus did not occur until after the second week of catatonic symptoms, often without warning. Suggested preventive measures have included hydration, physical therapy, support hose, and prophylactic anticoagulation. Low-dose subcutaneous heparin and low molecular weight heparin are well supported by studies in postsurgical patients at high risk for venous thromboembolism. However, the risk is lower in chronically immobilized patients (Heit et al. 2000) for whom prophylactic anticoagulation is not standard care. Whether prophylactic anticoagulation would reduce morbidity in catatonia is unknown but worthy of study.

Malnutrition and *gastrointestinal complications* are common in chronic catatonia. Reduction of oral intake leads to dehydration and malnutrition. Malnutrition promotes other complications, especially infection and skin breakdown (Thomas 2001). Dehydration also leads to constipation or ileus. For all these reasons, it may become necessary to provide enteral feeding—that is, nasogastric tubes or percutaneous endoscopic gastrostomy (PEG) tubes. Unfortunately, there is a high rate of complications with both. As previously noted, aspiration is the most common cause of death in patients with feeding tubes. Nasogastric tubes can cause esophagitis and, when misplaced, can result in pneumothorax, empyema, or bronchopleural fistula. Feeding tubes are associated with diarrhea, depen-

dent edema, and bacterial colonization of gastric contents (Thomas 2001). Although duodenal placement of a PEG or a jejunostomy may be more effective in providing nutrition, they do not result in any less aspiration (Gustke et al. 1970). There are also potential adverse metabolic consequences of enteral feeding, including hypoglycemia, hypercapnia, and electrolyte abnormalities. Thus, the chronic catatonic patient presents the same ethical dilemma encountered in other patients who may require prolonged nutritional support. Failing to provide hydration and nutrition will lead to morbidity and death, but the complication rate with feedings is high, and the outcome in some patient groups has not necessarily improved (Gillick 2000). However, catatonia is a reversible condition. The difficult decision regarding whether the benefits of enteral feeding outweigh its burdens can be avoided altogether if catatonia is treated early, aggressively, and effectively. Lewis et al. (1989) reported a case in which intravenous amobarbital facilitated food and fluid intake in a patient with catatonia, obviating the need for tube feeding. However, a randomized, double-blind, placebo-controlled crossover study found no such benefit following analogous administration of lorazepam (Ungvari et al. 1999). ECT may be a better alternative in these cases.

Catatonia also results in a number of *adverse oral effects*. Dental caries and gum disease are frequent. Poor oral hygiene leads to colonization with more pathogenic organisms, in turn making aspiration more likely to result in serious pneumonia. Frequent administration of antibiotics to treat infection may result in secondary oral fungal infections.

Skin breakdown is extremely common. Stasis, immobility, and pressure all contribute to the development of *decubitus ulcers*.

Genitourinary tract complications are frequent as well, including urinary retention due to bladder distention (Barbuto 1983; Regestein et al. 1971). Many chronically catatonic patients have urinary incontinence and require catheterization or diapers. Malnutrition, poor hygiene, and an indwelling catheter create a high risk for urinary tract infection. Carroll (1996) found urinary tract infections in 8% of catatonic patients, but this may be an underestimate. Institutionalized patients are more likely to develop infections with resistant organisms. When feasible, intermittent catheterization or other preventive measures may reduce the risk of infection. However, despite precautions, the majority of patients catheterized beyond 2 weeks will eventually develop bacteriuria. Treatment of symptomatic bacteriuria is always appropriate. For the asymptomatic patient, removal of the catheter and a short course of antibiotics is usually a successful approach. However, if the catheter cannot be removed, antibiotic therapy for asymptomatic bacteriuria is unlikely to be successful and may result in infection with a resistant strain.

Menstrual hygiene is another area of frequent neglect in the chronic catatonic patient. Poor menstrual hygiene leads to vaginal infections. Treatment with antibiotics for other infections may result in *Candida* vaginitis.

Finally, *neuromuscular complications* are also common in chronic catatonia, including flexion contractures in immobilized patients and postural nerve palsies. Physical therapy and mobilization should reduce the occurrence of both. Prolonged immobilization is a risk factor for rhabdomyolysis. Although rhabdomyolysis has been recognized as a complication of acute lethal catatonia, neuroleptic malignant syndrome, and severe neuroleptic dystonia, the incidence of rhabdomyolysis in chronic catatonia is unknown.

Conclusion

The long-term prognosis for patients presenting with catatonia is good in nearly half the cases, but a significant minority proceed to a state of deterioration as originally described by Kraepelin. Although the association of catatonia with mood disorder makes its prognosis better than the prognosis for the schizophrenic subtype, the reverse is not true—that is, the association of mood disorder with catatonia makes its outcome worse than without catatonia. In the short term, catatonic syndromes have a good prognosis, particularly when treated with ECT. Organic catatonias vary in their outcome based on the underlying cause. Idiopathic periodic catatonia appears to have a good prognosis, both short- and long-term. The catatonic condition sometimes progresses to a chronic state and may last for years, leading to institutionalization and therapeutic nihilism. Medical comorbidity is wide-ranging and frequent in chronic catatonia. Such patients present complex medical and behavioral challenges requiring an aggressive multidisciplinary approach. Despite newer drugs, ECT both as acute and maintenance treatment offers the best-established therapy for this condition.

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CHAPTER 15

GENETICS

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Catatonia has attracted increasing attention in relation to basic theoretical problems of psychiatry (Pichot 2001). Important strategies in examining genetic factors in catatonia are twin, adoption, and family studies. On the molecular level, mutation scans, association studies, and linkage analyses in combination with positional cloning projects are important in studying the underlying genetic variants predisposing to catatonia. Meticulous clinical and nosologic differentiation is also essential to cope with genetic heterogeneity (McKusick 1969).

Fortunately, the Wernicke-Kleist-Leonhard school has provided operationalized descriptions of psychomotor disturbances within the endogenous psychoses (Kleist 1912; Leonhard 1999; see also Chapter 3, "Nosology," this volume). Cycloid motility psychosis, which exhibits purely quantitative hyperkinetic or akinetic traits in a phasic, remitting course, contrasts with the prognostically less favorable distinct forms of catatonic schizophrenias (i.e., periodic catatonia and systematic catatonias). Periodic catatonia is characterized by qualitatively different hyperkinetic and akinetic motor disturbances occurring during psychotic episodes, giving way to grimacing or masklike faces, iterations, and distorted stiff movements, alternating with akinetic negativism, stereotypies, or negativistic behavior (see Chapter 8, "Periodic Catatonia," this volume). These acute psychotic episodes progress to debilitating residual states with psychomotor weak-

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ness and apathy. The periodic course and polymorphous symptomatology of periodic catatonia are distinct from those of the systematic catatonias. Precisely described symptom combinations permit exact delineation of each form of systematic catatonia, all of which have an unfavorable long-term course (Leonhard 1999).

Incidence of Schizophrenic Psychoses in Families With Chronic Catatonic Schizophrenia

In catatonia, Kallmann (1938) found a high familial incidence of homogeneous psychoses amounting to 18.8% in parent–offspring pairs, and a significantly increased morbidity risk of 9.6% in siblings. These findings were confirmed by Weinberg and Lobstein (1943) and Hallgren and Sjøgren (1959). These authors reported that patients with predominantly catatonic symptoms had an increased familial incidence (8.3% and 8.5%) compared with paranoid schizophrenic patients (3.1% and 4.7%). Scharfetter and Nüsperli's (1980) family study also showed a significantly increased risk in first-degree relatives of catatonic patients (12.8%) compared with patients with paranoid schizophrenia (6.5%) or hebephrenia (8.4%). Furthermore, in catatonia the risk for homogeneous psychoses in relatives was the most prominent compared with other functional psychoses. Recently, Mimica and colleagues (2001) reported on a representative sample of patients with catatonic schizophrenia. Among 402 patients who were followed, the diagnosis of schizophrenia, catatonic type (according to ICD-8; World Health Organization 1967), was made in 59 cases (14.7%) at least once in the course of follow-up. Positive family history of psychosis was found in 44.1% of these patients, a frequency significantly higher than the corresponding figure for all noncatatonic schizophrenic subtypes (20.1%).

Clinical-Genetic Studies in Catatonia Subphenotypes

Twin Studies

In a systematic study of twins who were born after 1930 and hospitalized for psychiatric disease, the index twin had to meet the diagnostic criteria of DSM III-R (American Psychiatric Association 1987) schizophrenia or schizophrenic spectrum disorder (Franzek and Beckmann 1998, 1999). In the total sample of 22 monozygotic twin pairs, periodic catatonia appeared in 6 pairs (27%): 5 monozygotic pairs were concordant and 1 pair was discordant for periodic catatonia. Among the 25 dizygotic twin pairs,

3 pairs (12%) with periodic catatonia were found: 1 pair was concordant, the other 2 were discordant. There were significantly different concordance rates in monozygotic twins (92%) and in dizygotic twins (50%) (Table 15–1). The degree of heritability was estimated to be 0.46 in periodic catatonia, indicating dominance effects of heredity. The median interval until the onset of concordance was 2 years. None of the monozygotic twins had systematic catatonia. Systematic catatonia was observed in 2 dizygotic twin pairs; both were found discordant, with a healthy co-twin. Thus, the concordance rate was zero in systematic catatonia. Leonhard (1999) examined 72 twin pairs (including 45 monozygotic twins) in a non-systematic twin survey. Of 6 monozygotic pairs with periodic catatonia, 5 pairs were found concordant (83%). As was true for all forms of systematic schizophrenia, there were no cases of systematic catatonia among monozygotic twins. Considering the absence of other theories, one speculative explanatory model is that specific psychosocial factors—that is, intensive communication during childhood in monozygotic twins, are preventive factors (Leonhard 1986, 1999).

Family Studies

In a family study of chronic schizophrenia, catatonic symptoms were documented in 24% of the sample population at least once during the illness (Beckmann et al. 1996; Stöber et al. 1995). The final diagnostic group of 139 index cases consisted of 83 patients (42 males) with periodic catatonia and 56 patients (42 males) with systematic catatonia. Each index case represented a single pedigree; multiple ascertainment was strictly avoided. In a subsample, the degree of diagnostic agreement was assessed and reached 0.93 (Cohen's κ), and catamnestic evaluation of the total sample yielded a diagnostic stability of 97% (κ=0.93), indicating sufficient diagnostic reliability and stability of the phenotypes. To obtain reliable data concerning the morbidity risk, the investigators allocated only those relatives with documented psychiatric hospitalization to the group of affected family members. The evaluation of the morbidity risk and the transmission patterns was based on 543 first-degree relatives.

If the frequencies of multiply affected nuclear families were compared, 6 nuclear families (11%) of index case individuals with systematic catatonia had further affected family members, contrasting with 49 nuclear families (59%) of periodic catatonia case individuals. Differences between the two phenotypes in the number of schizophrenic first-degree relatives were impressive (Table 15–2). Seven secondary cases in systematic catatonia contrasted with 59 secondary cases in the nuclear families of index cases with periodic catatonia. In systematic catatonia, the mor-

Table 15–1. Concordance rates of monozygotic and dizygotic twins with periodic catatonia and systematic catatonia

	Periodic catatonia	Systematic catatonia
Monozygotic twins	6	0
Concordant/discordant	5/1	—
Pairwise concordance	83%	—
Probandwise concordance	92%	—
Dizygotic twins	3	2
Concordant/discordant	1/2	0/2
Pairwise concordance	33%	0%
Probandwise concordance	50%	0%

Note. *Pairwise concordance* refers to the calculation of the percentage of the concordant pairs by means of the total number of investigated pairs. The *probandwise concordance* method is based on the number of index twins of the twin survey and is the best choice if the cases are ascertained in a systematic study. In the probandwise method, each ascertained person is included in the calculation.
Source. Based on data from Franzek and Beckmann 1999.

bidity risk was 4.6% for first-degree relatives, whereas in periodic catatonia the morbidity risk reached 26.9%. In systematic catatonia, mothers' morbidity risk was 6.8%, but in periodic catatonia the mothers' risk curve rose to 33.7%. In systematic catatonia, the risk for fathers was 2.0%, contrasting with 15.4% for fathers in the periodic catatonia data set. Among index case individuals with systematic catatonia, the risk for brothers was 5.9% and for sisters 0%. The corresponding rates were 18.1% for brothers and 23.7% for sisters of case individuals with periodic catatonia. In periodic catatonia, a moderate inverse relationship between early-onset index cases (<22 vs. ≥22 years) and an increased risk in siblings (24.1% vs. 17.8%) implies a potential impact of the index case age at onset on the familial risk (Stöber et al. 1998a). The age at onset in periodic catatonia may be partially genetically driven, because the disorder affected both sexes at similar frequency and age, and the mean ages at onset of males (23.2 ± 8.0 years) and females (26.5 ± 10.8 years) in our family study were equivalent to those in Leonhard's (1999) series.

The morbidity risk found in specific catatonia phenotypes was in accordance with Leonhard's (1999) findings in his last series of 1,465 index case individuals with endogenous psychoses. The diagnoses of periodic catatonia and systematic catatonia were formulated in 136 index cases and 232 index cases, respectively. In systematic catatonia, a low morbidity

Table 15–2. Cumulative morbidity risk of first-degree relatives of index cases with periodic catatonia or systematic catatonia (life-table analysis using Kaplan-Meier estimates; log-rank χ^2 statistics)

	Periodic catatonia (*n*=83)			Systematic catatonia (*n*=56)			
First-degree relatives	***n***	**Affected**	**Morbidity risk**	***n***	**Affected**	**Morbidity risk**	***P***
Fathers	78	11	15.4%	53	1	2.0%	0.02
Mothers	83	22	33.7%	56	3	6.8%	0.005
Siblings	162	26	24.4%	111	3	3.9%	0.01
Total	323	59	26.9%	220	7	4.6%	0.001

risk was found (2.7% for parents and 3.5% for siblings). In none of these families did the disease extend through three successive generations. Therefore, systematic catatonia seems to represent sporadic forms of schizophrenic psychoses. In periodic catatonia, an excess of homogeneous psychoses was found, with a morbidity risk of 22.0% for parents and 21.2% for siblings. The increased familial incidence in catatonic psychoses reported in earlier studies seemed to be confined to the clinical subtype of periodic catatonia (Scharfetter and Nüsperli 1980; Slater and Cowie 1971). Periodic catatonia showed a surplus of familial aggregation of homogeneous psychoses and pronounced vertical transmission. In 10% of the families, three successive generations of family members had similar catatonic psychoses and had received hospital treatment. This supported suggestions of an autosomal dominant inheritance pattern in periodic catatonia (Leonhard 1999; Trostorff 1981).

Pairwise comparisons of index cases and their parents revealed patterns of anticipation—that is, the age at onset was significantly earlier among index cases than among the corresponding parents. Anticipation was present irrespective of the parental derivation of the disease and occurred even in pedigrees with three successive generations affected (Stöber et al. 1995). In several neurodegenerative diseases, the molecular basis of genetic anticipation is associated with unstable DNA expansions, but in schizophrenia the meaning of anticipation remains elusive (Vincent et al. 2000). Periodic catatonia was a promising candidate to screen for those expansions, but several genetic loci with tri- and oligonucleotide repeats or other repetitive elements affecting gene expression were not found causative in case-control association studies or linkage approaches (Bengel et al. 1998; Lesch et al. 1994; Stöber et al. 2000b). Evidence for the occurrence of a parent-of-origin effect was supported only by the finding that paternal transmission, compared with maternal transmission, was associated with a younger age at onset in the index cases. Results of the genomewide linkage analyses provided no support for a paternally imprinted locus acting on periodic catatonia. Furthermore, analysis of sex concordance by stratifying the affected siblings by sibship size and by the sex of the index cases revealed no evidence for sex-linked transmission (Franzek et al. 1995).

Toward the Molecular Basis of Periodic Catatonia

Genomewide Linkage Analyses

The next step in unraveling the genetic basis of periodic catatonia was a whole genome scan in 12 multiplex pedigrees segregating for periodic

catatonia (Stöber et al. 2000d). To replicate the initial findings of a major susceptibility locus on chromosome 15q15, a second genome scan in a new set of families was performed recently and successfully replicated the linkage to chromosome 15q (Stöber et al. 2002b). Subjects were considered affected if Leonhard's strict criteria for periodic catatonia were fulfilled (Leonhard 1999). Prior to subjects' inclusion in the respective genome scan, power calculations were performed to evaluate the potential informativeness of ascertained families (Stöber et al. 2001). Under an autosomal dominant affecteds-only model (analyses performed with affected individuals only) and a disease allele frequency of 0.001, a maximum expected LOD score of 5.7 was obtained in the family panel of the initial genome scan. The power in the presence of genetic homogeneity was 98.5% to detect LOD scores of 2.0 or greater and 94.5% for LOD scores of 3.0 or greater (five marker alleles, uniformly distributed; θ=0.05). Under the same analytical model, the second set of pedigrees achieved a maximum e-LOD of 2.3. The power to detect linkage in these four families was 57.9% to detect LOD scores of 2.0 or greater. Both linkage studies were performed with similar sets of microsatellite markers and mean marker distances. In the first study, DNA specimens were available for 135 individuals (61 males), including 57 affected subjects, and the second study included four multiplex pedigrees with 48 individuals (25 males), 21 of whom were affected. X chromosomal markers were not tested because periodic catatonia obviously does not have characteristics of X-linked inheritance (Franzek et al. 1995).

The statistical analyses were based on nonparametric, model-free methods that allow accurate analysis in a small number of extended pedigrees with arbitrary mixture of family structures, and parametric methods with an autosomal dominant affecteds-only model for two-point and multipoint linkage analysis. Nonparametric, model-free linkage analysis was performed with the GENEHUNTER-PLUS package, which allows *P* value estimation based on likelihood ratio tests in a one-parameter allele-sharing model. The most significant allele sharing between individuals affected with periodic catatonia in the pedigrees was on chromosome 15q15 at position 35.3 centimorgan (cM; Généthon human linkage map), and based on previous criteria for linkage (Lander and Kruglyak 1995), the nonparametric Z_{lr} score of 4.05 with *P* value 2.6×10^{-5} and a maximum LOD* score of 3.57 reached significant evidence for linkage. Furthermore, we found susceptibility for a second chromosomal locus for periodic catatonia on chromosome 22q13, which met criteria for suggestive evidence for linkage with $P<0.002$ (Table 15–3). Additionally, chromosomes 6, 11, 13, and 20 showed minor peaks, but these loci fell short of conventional standards for linkage. Inspection of the linkage results by family revealed that

different pedigrees were contributing to the findings at chromosome 15q and 22q, indicating genetic heterogeneity in periodic catatonia. At loci with Z_{lr} scores >2.5, two-point parametric LOD score analyses (Z_{max}) were performed under an autosomal dominant model with affecteds-only analysis. Two-point analyses produced a maximum LOD score of Z_{max}=2.75 at marker D15S1012 under the assumption of linkage homogeneity. When linkage heterogeneity was assumed, Z_{max}= 2.75 was obtained, with an estimated 100% of families linked. In the second candidate region, the maximum homogeneity LOD score was Z_{max}=1.04 at D22S1169, and the heterogeneity LOD score was 1.57, with an estimated 38% of families linked. Further analysis of the two largest pedigrees with seven affected individuals each gave 4-point LOD scores (VITESSE) of 2.59 (θ=0.00) at chromosome 22q and 2.89 (θ=0.029) at chromosome 15q candidate regions. All affected individuals of these pedigrees share a common marker haplotype at chromosomes 15q15 and 22q13, respectively. Several unaffected subjects carry the same haplotype and, thus, the putative susceptibility allele. Some of them are still at risk to develop the disease, but most of them must be considered as nonpenetrant carriers. This would be in agreement with the assumption of a major gene locus with reduced penetrance as was proposed by previous family studies.

Table 15–3. Multipoint nonparametric linkage analysis in the periodic catatonia sample

Chromosome	Coordinate (cM)	GENEHUNTER-PLUS		
		Z_{lr} score	LOD* score	*P*
Genome scan I (GS I)				
6	184.6	2.17	1.02	0.015
11	131.0	2.22	1.07	0.013
13	65.2	2.43	1.28	0.0075
15	**35.3**	**4.05**	**3.57**	**0.000026**
16	33.0	1.96	0.83	0.025
20	16.6	2.07	0.93	0.02
22	58.2	2.92	1.85	0.0018
Genome scan II (GS II)				
1	237.2	2.30	1.33	0.031
15	7.0	2.66	1.54	0.004
15	**32.3**	**2.34**	**1.19**	**0.005**

Note. Loci with *P* values < 0.025 in GS I and < 0.05 in GS II; GENEHUNTER-PLUS.

Applying the same diagnostic procedure and the same statistical analysis, we found significant allele sharing between affected individuals in the new data set at chromosome 15, with Z_{lr} scores of 2.66 (P=0.004) and 2.34 (P=0.005; Table 15–3) between marker D15S1234 and D15S1042, respectively. This was accounted for primarily by a single four-generation family that by itself generated a Z_{lr} score of 2.83 (P=0.004) (Stöber et al. 2002b). These results replicated the mapping of a periodic catatonia major gene locus to chromosome 15q and satisfied the criteria for confirmed linkage with a nominal P value of <0.01. Multipoint parametric analyses were performed under the assumption of an autosomal dominant model with affecteds-only analysis, and the maximum HLOD (heterogeneity LOD score) reached 1.26 at the chromosome 15 region, with a proportion of 44% of families linked. A locus on chromosome 1q obtained positive scores at position 237.2 cM (P=0.031) but did not meet the criteria for suggestive evidence for linkage. None of the other chromosomal loci reached P<0.05. The susceptibility region on chromosome 1q42 had attracted some attention in independent studies on schizophrenic psychoses (Ekelund et al. 2001; Millar et al. 2000). If there is significant heterogeneity in periodic catatonia, this could explain the failure to replicate the chromosome $22q_{tel}$ locus in the smaller second data set. In earlier studies, putative candidate loci, such as the synapsin III locus on chromosome 22q13 and the KCNN3 locus on chromosome 1q21, were excluded in periodic catatonia by means of linkage analysis in 12 multiplex pedigrees (Stöber et al. 2000b, 2000c).

Critical recombination events placed the disease gene locus around position 32.2 cM, now spanning a distance of ~11 cM and thereby improving substantially the earlier localization of the putative disease gene (Stöber et al. 2000d). On chromosome 15, the candidate segment overlapped with a locus for a putative biological endophenotype of schizophrenia, composite inhibitory neurophysiological deficit of the P50 auditory evoked response (Freedman et al. 1997). The neurophysiological deficit phenotype seemed to be linked to a more centromeric region; however, the putative locus spans ~45 cM, with the most positive Z-scores between 20.24 cM from *p*-ter to 25.30 cM. Analysis of this region with multiple flanking markers produced equivocal results, but recently support for the chromosome 15q14 locus came from chromosome 15 linkage scans in multiplex pedigrees and in an affected sib-pairs approach (Freedman and Leonard 2001; Gejman et al. 2001; Tsuang et al. 2001).

Meanwhile, further studies on critical meiotic breakpoints in linked pedigrees have precisely determined the critical region to a 7.3 Mbp region (A. Ekici, A. Reis, G. Stöber, unpublished data). Because the chromosome 15q sequence is now completed, further steps of the positional cloning

project will involve investigations of a dense set of SNPs (single nucleotide polymorphisms) and microsatellite markers in the delineated chromosomal region in linkage-disequilibrium studies in series of parent-offspring trios, systematic annotation of candidate genes expressed in brain, and large-scale mutation screening in family-based and case-control association studies.

KIAA0027/MLC1 at Chromosome $22q_{tel}$ and Periodic Catatonia

Recently, Meyer et al. (2001) reported that *KIAA0027* is involved in the pathogenesis of catatonic schizophrenia, via a putative dominantly acting missense mutation cosegregating in a large pedigree. This mutation had contributed most of the evidence for linkage to chromosome $22q_{tel}$ in periodic catatonia. *KIAA0027* was considered a positional candidate and was therefore screened for genetic variants. The 1040C>A variant (L309M) was not detected in unrelated controls, which led to the preliminary assumption that this variant is the disease-causing base change. *KIAA0027* was also delineated as the causative gene of a rare autosomal recessive spongiform leukodystrophy, megalencephalic leukoencephalopathy (MLC), with identification of several homozygous loss-of-function mutations, and was therefore renamed *MLC1* (Leegwater et al. 2001). A systematic mutation screening in 140 index cases with periodic catatonia and 5 cases with MLC detected a high degree of sequence diversity of *MLC1*, with evidence for further allelic heterogeneity of *MLC1* mutations in MLC, but unfortunately the study failed to validate an association of schizophrenia to genetic variants of *MLC1* (Rubie et al. 2003). Among periodic catatonia index cases, the mutation scan revealed 15 different single nucleotide polymorphisms, among them three coding variants: two of them were observed in controls at a significant frequency, and the L309M variant, which was previously supposed to be the causative factor for chromosome $22q_{tel}$–linked periodic catatonia, was found to be nonsegregating in a further multiplex pedigree. Furthermore, inconsistent amplification of exon 11 alleles (bearing the 1040C>A variant) was observed with use of the published analytical procedure and was resolved only when exonic primers directly adjacent to the L309M variant were employed. The allele-specific amplification seemed mainly due to tandem repeat elements, a high percentage of GC content of the intronic region, and a frequent insertion/deletion polymorphism, which obviously resulted in persistent secondary folding structures. In addition, MLC1 is a 377–amino acid protein with preferential expression in the brain but with considerable patterns in other tissues, particularly peripheral white blood cells. Although MLC1 shares low

homology with human voltage-gated potassium channels, it lacks the highly conserved pore region of this gene class. Alternatively, there exists low amino acid sequence similarity with different symporter gene families, indicating that MLC1 is a membrane protein with transport function for a specific, yet unknown substrate (Leegwater et al. 2001).

Thus, mutations in *MLC1* are causative for MLC but can be excluded as a susceptibility factor in schizophrenia. Preliminary reports of other groups also failed to support an etiologic relevance of this gene in schizophrenia (Devany et al. 2002), and more important, these studies ruled out that spongiform leukodystrophies and subtypes of schizophrenia are allelic disorders.

Gene-Environment Interactions Contributing to the Etiology of Catatonia

On pursuing environmental factors associated with the development of disease, perinatal and birth complications, as well as family constellations, seem to be attractive determinants. Beckmann and Franzek (1992) found familial schizophrenias—in particular, periodic catatonia—to be distinctly associated with lower birthrates during the winter and spring months following midgestational exposure to acute bronchitic diseases than the birthrates in the population at large. Clinical and birth history variables were investigated in 68 index cases from the initial family study, with the mothers available for interview (Stöber et al. 2002a). Here, parental transmission was evident in 44% of the periodic catatonia cases, compared with 3% of the systematic catatonia cases. In systematic catatonia, 34% of the index case individuals were exposed to prenatal infections, compared with 8% in periodic catatonia. On logistic regression analysis, exposure to gestational maternal infections significantly predicted diagnosis of systematic catatonia ($P<0.01$), and parental psychosis predicted diagnosis of periodic catatonia in the index cases ($P<0.001$). None of the other variables, such as gender, age at onset, obstetric complications, or maternal age reached significant log odds ratios. The risk of being exposed in systematic catatonia reached $P<0.001$ (odds ratio= 23.33; 95% confidence interval= 11.7–273.4), given a prevalence of gestational infections in the general population of 4%.

Regarding sibling constellations in periodic catatonia, Leonhard (1986, 1999) supposed that the probability of the illness becoming manifest increased as the number of siblings decreased. In the case of affected parents, the number of older sisters of male patients was significantly reduced compared with the number of younger sisters. This effect seemed to be most prominent if the mother was affected. In this configuration fre-

quency analysis, it was found that male index case individuals with periodic catatonia were significantly more often the youngest in the sibship with older sisters and brothers (Stöber et al. 2000a). Sibship size was, however, not correlated with the percentage of affected siblings within the families. Affected mothers had significantly more unaffected male offspring than expected, indicating that maternal affection may be related to the risk in male offspring (Stöber et al. 1998b). Fifty percent of informative families (affected mother with one male and one female offspring) had a firstborn sister, and these older sisters might have replaced the affected mother by assuming the role of guardian and protector (Leonhard 1999). Thus, psychosocial factors may work in favor of a reduced manifestation of the disease in the male offspring of affected mothers. Leonhard suggested that index case individuals with systematic catatonia were predominantly the only child, or they had distinct sibling constellations. However, Stöber et al. (2000a) found no distinct sibling configuration associated with systematic catatonia in males; females were significantly more often than expected the youngest of the siblings with older sisters and brothers or the oldest with younger sisters and brothers. Because these findings involve opposite directions, cautious interpretation is required.

Conclusion

Precise phenotypic delineation of the endogenous psychoses by the Wernicke-Kleist-Leonhard school offers a unique opportunity for genetic analysis. On the basis of twin and family studies, catatonia appears to be a complex disease involving genetic and environmental determinants. Systematic catatonias are mainly sporadic in appearance, with low heritability. Periodic catatonia aggregates with high concordance among monozygotic twins, with a high incidence of secondary cases within families and homogeneity of psychoses, and with evidence for a major gene effect demonstrated by a morbidity risk of ~27% among first-degree relatives.

On the molecular level, periodic catatonia is complex but displays true linkage to a major susceptibility locus on chromosome 15q15 and preliminary evidence for genetic heterogeneity. Parametric linkage and haplotype analyses of multiplex pedigrees support a single-gene model in this phenotype and an autosomal dominant mode of inheritance with reduced penetrance. Family constellations and other psychological factors may modify the penetrance of the disorder. If reduced penetrance is considered, the incidence of prenatal and perinatal complications, as well as psychosocial interactions, needs further scrutiny in unaffected relatives carrying the disease haplotype, to detect protective factors against psychotic breakdown. In contrast, exposure to maternal infections is con-

fined to the diagnostic category of systematic catatonia, adding further evidence for disparate pathophysiological mechanisms in different catatonia phenotypes.

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CHAPTER 16

ANIMAL MODELS

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Catatonia is a severe neurobehavioral syndrome that crosses diagnostic lines, appearing in mood and anxiety disorders and medical conditions, as well as schizophrenia. Despite the prevalence of catatonia and its obvious correlates in nature, the study of catatonia has not benefited from a concerted approach to behavioral modeling. With the growing understanding of the neurobiology and risk factors leading to catatonia, the field of catatonia research is poised for detailed neurobiological, anatomic, and genetic analysis. To do that will require well-characterized and valid animal models. In this chapter, I review the criteria for evaluation of models and discuss several animal models of potential use in the study of catatonia.

Classes of Behavioral Models

Four types of models are commonly used in psychopathology and psychopharmacology research. *Screening tests* are used most often for discovery of new drugs. Such tests are based on the actions of known drugs that serve as a reference point against which to compare the performance of new candidates. The utility of screening tests is in their ability to identify new drugs with clinical efficacy. There is no requirement that the behavior induced in a screening test resemble the clinical entity. For example, antidepressants can be screened using the forced swim test, wherein a rodent is made to swim in a chamber from which there is no escape. The duration of time until the animal stops swimming is reduced by effective antidepressants of several classes (Porsolt et al. 1977). This highly artificial screen bears little resemblance to the clinical entity of depression, but it is highly reliable at identifying new antidepressant compounds.

Biobehavioral assays model a physiologic action. That is, the animal is used as a means to assess the underlying physiology of a system. For example, increased locomotor activity in response to stimulants can be used to assess the physiologic state of the dopaminergic system. Such assays are used to study the mechanisms responsible for changes in brain function, most typically those resulting from chronic drug administration, brain lesions, or other similar experimental manipulations (Willner 1991).

Behavioral simulations attempt to encompass all aspects of a human disease, including causes and effects. A widely cited simulation of depression is learned helplessness (Seligman 1972). In this model, animals are subjected to uncontrollable stress, resulting in a behavioral profile strikingly similar to depression. Attempts to create such models for psychiatric disorders are difficult at best because of the mainly subjective nature of current diagnostic entities, and rudimentary knowledge of pathophysiology.

Last, *partial simulations* model a subset of signs or symptoms of a disorder rather than trying to model the entire disease entity. Such signs may not have diagnostic specificity, such as increased anxiety or increased startle reaction, but they have the advantage of being objectively and reliably measured and perhaps neurobiologically and genetically less complex.

Catatonia fits most conveniently into this last category. Catatonia encompasses a number of recognizable signs and symptoms that are readily modeled in animals. Behaviors such as immobility or autonomic instability and the effects of drugs for either treatment or induction of symptoms can all clearly be observed and quantified in animals.

Validation of Models

Face validity is the degree to which a model phenomenologically simulates the disorder being modeled. For a model to have face validity, it should appear similar to the disorder and have no major dissimilarities. Although it may seem as though this should be the most important criterion, face validity often does not suffice for an animal model to be useful. Difficulties with face validity are present at many levels. Most psychiatric symptoms are subjective in nature and therefore are not objectively quantifiable. Likewise, assessment of behavioral similarity is often based on subjective interpretation of animal behavior (particular behaviors of mice represent fear, aggression, etc.). Thus, the most intuitively important validity measure is neither necessary nor sufficient for establishing the validity of an animal model. Face validity often has important heuristic value early in the modeling process, because it can represent a *starting point* for establishing or disproving a model empirically (Willner 1991).

Construct validity is defined as the ability of a test to measure what is intended to be measured. An important aspect of construct validity is that it refers to the etiology of a behavior. Thus a model with good construct validity shares the same biology as the disorder it is intending to model. A model with good construct validity may have an entirely different behavior being measured but with the identical underlying neurobiology (Hinde 1976). Construct validity is widely considered to be the gold standard of validation of a model; however, it is only rarely achieved and then only after many years of intensive research. Clearly, a model's overall utility cannot be judged by its construct validity alone, but the degree to which a model has a high level of construct validity will enable more and better prediction of outcome of future experiments.

Predictive validity is the usefulness of a model for predicting the behavior of the human phenomenon. An animal model has predictive validity to the extent that it allows predictions about the human phenomenon based on the performance. A model with strong predictive validity will allow the assessment of new medications for the disorder, whereas a "screen" will only identify a drug of a similar class (Willner 1991).

Animal Models of Catatonia

Generally, animal paradigms for catatonia break down into three main classes: spontaneous, manipulation-induced, and drug-induced immobility. Unfortunately, these models have developed in diverse fields such as behavioral pharmacology and poultry science. As a result, the field has been hampered by the lack of both a common terminology to describe the observed phenomena and a common experimental organism on which to base all experiments. For example, manipulation-induced immobility is known variously as spontaneous catalepsy, tonic immobility, animal hypnosis, and pinch-induced catalepsy. The primary experimental models for these behaviors have been rabbits, chickens, guinea pigs, and mice. Immobility in wild animals suddenly confronted with a strong stimulus—for example, loud noise, deer in the headlights, or sudden appearance of a predator—is identified in the literature as freezing behavior, unconditioned freezing, tonic immobility, immobility reflex, spontaneous catalepsy, pseudocatalepsy, animal hypnosis, still reaction, paroxysmal inhibition, and feigned death. To make matters worse, manipulation-induced immobility and spontaneous immobility are often discussed together with little distinction, under the (unproven) assumption that the experimenter immobilizing the animal is a recapitulation of the natural threat phenomenon that induces freezing in the wild.

Despite the diversity of ways to induce immobility and the diversity of names, the behaviors are remarkably similar. In all cases, immobility is characterized by preserved muscle tone sufficient to sustain awkward postures, with simultaneous contraction of both flexor and extensor muscle groups. To emphasize the commonality of these behaviors and to facilitate interdisciplinary work in this field, Klemm (2001), in a recent review of this topic, suggested the term *behavioral arrest* to encompass all of the induced immobility phenomena. For clarity, in this chapter, I follow this behavioral arrest terminology.

Spontaneous Behavioral Arrest

Spontaneous behavioral arrest (SBA) refers to the behavior described by de Oliveira et al. (1997) as an "inborn behavioral inhibition characterized by profound physical inactivity and relative lack of responsiveness to the environment, triggered by an intense sensation of fear generated during prey-predator confrontation" (p. 3489). This defensive reaction is widespread in the animal world and functions as a nonspecific reaction to external threats and noxious stimuli. Such freezing serves a protective function, as it can make an animal both less visible and less attractive to predators. SBA is accompanied by a profound analgesia and reduced heart and respiratory rates; animals often appear to be playing dead. Humans display SBA most notably when frightened. Thus, freezing behavior represents a common evolutionary adaptation that likely confers a selective advantage for survival. Interestingly, freezing behavior in humans is also observed during normal thinking, when an individual is deep in concentration or when he or she is experiencing strong emotions such as severe grief or anxiety. The striking similarity of freezing behavior to the motor symptoms of catatonia leads to the testable hypothesis that both are controlled by the same neural mechanisms.

Experimentally, this behavior is closely approximated by the phenomenon of "spontaneous catalepsy" extensively studied by Kolpakov et al. (1996). Their paradigm is based on the observation that after tapping on the side of a rat's home cage, approximately 10% of outbred rats will rear, grab the ceiling of the cage with their forepaws, and freeze in place with an upward directed gaze. This posturing can remain from several seconds to several hours. Rats may let go of the bar but will continue to stay in a raised position. Hind legs if moved will stay lifted off the ground. Individual rats vary in the degree to which they demonstrate this response. This behavior is reminiscent of "nervous" pointer dogs, which are known to immediately assume a pointing posture on the approach of humans (Reese 1979; Reese et al. 1982). Other methods of inducing SBA in the laboratory

include exposing animals to visual or odor cues related to their natural predators (McGregor et al. 2002) or to a single mild foot shock (Contarino et al. 2002).

The data regarding the pharmacology of SBA in rats are limited. However, it is of interest that overall immobility time is *decreased* by the typical antipsychotic chlorpromazine. The serotonin 5-HT_{1A} receptor antagonists (8-OH-DPAT and flesinoxan) decrease immobility time, whereas serotonin 5-HT_2 antagonists (ritanserin and ketanserin) do not. Importantly, pretreatment with the benzodiazepine midazolam is effective at reducing immobility in response to predator odor cues (McGregor et al. 2002).

As in human catatonia, individual differences in SBA appear to be under genetic control. Kolpakov et al. (1999) succeeded in breeding a line of rats that display high levels of SBA. By 20 generations of breeding, 100% of these "genetically cataleptic" (GC) rats display some form of abnormal posturing when stressed. Compared with Wistar rats, GC rats show hypertension at rest and when stressed, increased immobility time in Porsolt swim test, and increased shock-induced aggression. Other correlated responses in this selected line include reversed hemispheric asymmetry, increased seizure threshold, and reductions in dopamine production in the striatum and nucleus accumbens. Interestingly, GC rats are more sensitive to neuroleptic-induced behavioral arrest, pointing to a possible genetic link between these two behaviors. Genetic analysis of GC rats indicates that predisposition to catalepsy is transmitted as an autosomal dominant trait with incomplete penetrance. The genetic loci controlling this behavior have yet to be identified.

As a model for catatonia, SBA has some limitations. In particular, the phenotype as described is highly variable and is characterized by either catatonic posturing, clinging to the cage lid, or the ability to maintain a posed posture. In addition, this behavior does not breed true within families. Within the GC-selected lines, the expression of spontaneous immobility is highly variable. Thus, measurement of spontaneous catalepsy, while intriguing, has difficulties with objective reliability. Establishing predictive and construct validity is hampered by the limited anatomic and pharmacologic data available with SBA paradigms.

Manipulation-Induced Behavioral Arrest

Manipulation-induced behavioral arrest (MiBA) is experimentally induced in a large number of species by holding an animal immobile on either its back or side for 10–15 seconds. Initial struggling is followed by a period characterized by a motionless posture maintained in the absence of further restraint. This period of immobility can remain for seconds to min-

utes. There are many similarities with catatonia, including muscular rigidity, decreased vocalizations, decreased autonomic function, altered electroencephalographic (EEG) profile, Parkinson-like tremors, and decreased response to external stimuli including increased threshold to pain (Gallup and Maser 1977). During an episode of tonic immobility, eyes are either closed or open, and the animal may appear dead. A variation of this behavior, *pinch-induced catalepsy*, is induced by holding a rat or mouse by the scruff of the neck before testing for immobility (Fundaro 1998). As noted, MiBA is indistinguishable phenomenologically from SBA, as previously described. The distinction is that *physical manipulation* is required to induce this behavior. It is hypothesized that MiBA is analogous to both the immobility demonstrated by young animals when lifted by the scruff of the neck by their mother and the model of SBA previously described.

MiBA is regulated by a variety of neuropharmacologic agents. Cholinergic agonists, typical antipsychotics, epinephrine, morphine, and tryptophan all increase MiBA duration, whereas tricyclic antidepressant and D-amphetamine decrease overall MiBA in chickens (Gallup and Maser 1977). Similarly, cholingeric agonists and typical antipsychotics increase, and tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) decrease, pinch-induced catalepsy in mice (Fundaro 1998). Contrary to prediction, in the chicken model of tonic immobility, benzodiazepines enhanced tonic immobility, whereas in guinea pigs, muscimol, a γ-aminobutyric acid (GABA) agonist, decreased immobilization time (Monassi et al. 1999).

Development of tonic immobility is controlled at least in part by the medullary portion of the hindbrain (Klemm 1969; Menescal-de-Oliveira and Hoffmann 1993; Monassi et al. 1999). Surgical transection caudal to the eighth cranial nerve in frogs leaves the response intact, as do transections caudal to the basal ganglia and to the thalamus (Klemm 1969). In addition, tonic immobility is enhanced after lesions of the septum, hippocampus, and cortex (Hatton et al. 1975; Woodruff et al. 1975). EEG slowing in both cortex and hippocampus accompanies cholinergic enhancement of tonic immobility. Cholinergic stimulation of the amygdala in the guinea pig results in reduction in tonic immobility time (Ramos et al. 1999), whereas cholinergic stimulation of the parabrachial nucleus enhances tonic immobility in guinea pigs (Menescal-de-Oliveira and Hoffmann 1993; Monassi et al. 1997). Unfortunately, there are no systematic studies of the role of either limbic or basal ganglia structures in a single model system. This fact severely hampers attempts to develop a comprehensive, experimentally testable model of the circuitry underlying tonic immobility.

In three species, MiBA duration has been found to be genetically determined. Japanese quails can be selectively bred for high or low duration

of MiBA following restraint or high-fear situations (Jones et al. 1994). Likewise, there are marked differences in MiBA among breeds of chickens (Gallup et al. 1976). Perhaps most important for future neurogenetic research, inbred mouse strains also differ in MiBA duration (Kulikov et al. 1993). These differences are correlated with higher levels of the serotonin synthetic enzyme tryptophan hydroxylase and lower serotonin receptor binding as measured by reduction in [^{3}H]ketanserin binding, consistent with the hypothesis that higher levels of serotonin with compensation of lower receptor binding contribute to the overall increased sensitivity to pinch-induced catalepsy (Kulikov et al. 1995). To date, the genes underlying these strain differences have not been determined.

Given the many apparent similarities between MiBA and catatonia, it is tempting to propose this as a potential model. The protocols for induction of the behavioral response are clear, simple, and easily reproducible. Measurement of the behavior is likewise unambiguous, and there is little test–retest variability. The marked phenotypic similarities between the described behavior and human catatonia are striking. Similar to SBA, MiBA is characterized by rapid onset of immobility without loss of consciousness, increased muscle tone, and EEG abnormalities. However, MiBA differs from clinical catatonia in that induction of the behavior requires physical restraint.

With regard to predictive validity, benzodiazepines, the most effective medications for catatonia, do not reverse tonic immobility in the chicken, the most widely studied species. In contrast, the guinea pig does show the predicted association with benzodiazepines. Thus, at least on the basis of medication criteria, the guinea pig model does have some degree of predictive validity. Unfortunately, little pharmacologic investigation has been performed in either rats or mice, the two species most likely to be useful for future genetic analysis.

Drug-Induced Behavioral Arrest

Drug-induced behavioral arrest (DiBA) (catalepsy) is defined as immobility in which there are varying degrees of enhanced muscular rigidity. It is characterized by the ability to maintain a posed awkward posture, most commonly evaluated by placing the animal in a rearing posture. There are many pharmacologic agents that are known to induce DiBA in rodents, including opiates, SSRIs, and calcium-channel blockers (Klemm 1989). Most relevant to the study of catatonia is typical-antipsychotic DiBA. Because antipsychotics can induce catatonia, and there is a hypothesized relationship between neuroleptic malignant syndrome (NMS) and catatonia (Fricchione 1985), antipsychotic DiBA may be an ideal animal model

for one or more subtypes of catatonia. Immobility induced by typical antipsychotics is indistinguishable from either of the two paradigms previously discussed.

Antipsychotic-induced catalepsy can be disrupted by anticholinergic medication (predictive of their utility in treating antipsychotic-induced parkinsonism), NMDA (*N*-methyl-D-aspartate) receptor antagonists (amantadine, MK801), and 5-HT_{1A} receptor agonists (e.g., 8-OH-DPAT). GABA antagonists including bicuculline and picrotoxin do not affect haloperidol-induced catalepsy; however, the GABA-B receptor agonist baclofen at low doses (1 mg/kg) markedly reduces the ability of haloperidol to induce catalepsy, whereas at higher doses (10 mg/kg), it has the reverse effect (Klemm 1989). Benzodiazepines, however, potentiate haloperidol's effects. Although not technically pharmacologic, chronic electroconvulsive stimulation (ECS) reduces haloperidol's ability to induce catalepsy, an effect possibly mediated through downregulation of striatal muscarinic receptors (Stanley and Lerer 1985).

Antipsychotic-induced catalepsy is mediated primarily through the extrapyramidal system via blockade of striatal dopamine$_2$ (D_2) receptors. Microinjection of haloperidol into the caudate putamen and globus pallidus, but not into the amygdala or cortex, induces catalepsy. Likewise, lesioning of the caudate putamen and globus pallidus results in an increase in spontaneous catalepsy, which is reversed by apomorphine and other dopamine agonists. Lesions of the amygdala and cortex have no effect (Nakano et al. 2000).

Individual differences in antipsychotic DiBA are genetically determined. Outbred mice can be selectively bred for sensitivity or insensitivity to neuroleptic-induced catalepsy to produce neuroleptic response (NR) and neuroleptic nonresponse (NNR) lines (R. Hitzemann et al. 1991). Correlated responses to the selection of the NR and NNR lines include increased D_2 somatodendritic receptor density in the NNR line and increased cholingeric cell number in the NR line (B. Hitzemann et al. 1994; R. Hitzemann et al. 1993; Kanes et al. 1993; Qian et al. 1992). Similarly, there are marked differences in sensitivity to haloperidol-induced catalepsy among 15 inbred mouse strains. The BALB/cJ strain is the most sensitive (ED_{50}=0.3 mg/kg), whereas the LP/J strain is the least sensitive (ED_{50}=9.5 mg/kg) (Kanes et al. 1993; Kanes et al. 1996). Genetic mapping for antipsychotic DiBA using a BXD recombinant inbred strain panel detected significant linkage on chromosomes 4, 15, and 9. The locus identified on chromosome 9 is important in that it appears to be either near or part of the D_2 receptor gene (*Drd2*) (Kanes et al. 1996).

As stated previously, antipsychotic DiBA is a potentially useful model for the study of both catatonia and NMS. There are several important ad-

vantages of this model. The behavior is easily induced and quantified. In mice and rats there is a high level of reliability of the measure (Kanes et al. 1993). With regard to validity, antipsychotic DiBA has both good face and good construct validity with the narrowly defined syndrome of drug-induced catatonia. Antipsychotic DiBA is less convincing as a model of NMS. In contrast to NMS, DiBA is not accompanied by hyperpyrexia, and it spontaneously remits within seconds to minutes. With regard to predictive validity, again the results are mixed. ECS is effective at inhibiting antipsychotic DiBA; however, medications that are effective in this model, including NMDA antagonists and anticholinergic agents, are ineffective in the treatment of catatonia or NMS.

Conclusion

Despite the extensive experimental experience with animal immobility, no one model is ideal for the basic study of catatonia. This should not be surprising, as none were specifically designed with catatonia in mind. As new insights into the clinical entity arise, it will become increasingly important to either develop new or further validate existing behavioral models.

To do this, several fundamental goals will need to be achieved. First, researchers in the field will need to focus on a single species in which to conduct future behavioral and genetic work. Because of the many genetic tools available, the technology to readily engineer new mutations, and the high degree of homology with the human genome, the laboratory mouse is an ideal model system in which to pursue such an effort. Next, it will likely be important to arrive at a series of standardized behavioral paradigms to study intensively. As the three paradigms discussed in this chapter all address apparently different but related aspects of catatonia, it may be necessary to use all of them to fully model all aspects of human catatonia. As the nature of the relationship between the different paradigms becomes clear, it will likely be possible to reduce the number of behavioral tests performed. An obvious advantage of such standardization is the ability to compare behavioral and pharmacologic data between laboratories. In addition, such an effort will benefit from ongoing large-scale phenotyping efforts in laboratory mice. Last, an effort must be made to define new behavioral protocols that can be tested in both humans and mice. Thus, the development of future animal models will proceed in parallel with the process of identifying accurate measures of the syndrome of catatonia itself. Only when convincing models are developed will the field of catatonia research be able to make use of the new technologies that are now so readily available.

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CHAPTER 17

BRAIN EVOLUTION AND THE MEANING OF CATATONIA

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I have frequently seen, on consultation in the telemetry unit, an unfortunate young man with a history of left temporal complex partial seizure disorder and unsuccessful epilepsy surgery. He often develops a postictal catatonic withdrawal state, which we lyse with lorazepam (Fricchione et al. 1983). Over the years I have asked him what his catatonic states are like. His answers are representative of what others have told me after their catatonic stupors.

He says that in his catatonia he feels all alone in the universe, dissociated from the human race, and unsure of whether he even exists. This separation state extends into his depression. "Everyone else is part of the flower, and I'm still part of the root." He often expresses a fervor of chaotic religious thought that is frayed and delusional and incapable of providing him with any solace. Instead of attaching him, his overt religiosity at these times is separative and disturbing. When asked if he feels suicidal, he frequently replies, "Why should I? I'm already dead." Indeed, the kind of depression that leads to suicide distorts reality to the point that the suicidal individual no longer sees any attachment solution as viable and safe. If suicide is the ultimate separation solution to intense melancholic pain, catatonic stupor is the penultimate one.

Are my patient's reflections to be considered rationalizations? confabulations? ravings? Or are they metaphors with authenticity in relation to

the source and target of this chapter—that is, the evolution of the brain and the meaning of catatonia? Perhaps his words are metaphors brimming over with meaning in light of what the reader has learned thus far about the history, epidemiology, clinical assessment, nosology, typology, diagnostics, treatment, and pathophysiology of catatonia. Our search for the meaning of catatonia will require us to focus on the evolution of life and the brain. In fact, we begin with the question "What is the brain for?" To answer this we must start with a few words on the development of cellular and vertebrate life.

The Evolution of Life

All life involves decision making along a spectrum of complexity. A primordial intelligence can be said to pervade the biosphere; organismic behavior is optimized in light of incoming data. The decision any organism must make is to mobilize or immobilize in the service of approach or avoidance. The action of any living organism is therefore that of a sensorimotor analyzer-effector (Cairns-Smith 1996). At its most basic level, life seeks to approach and attach to a source of energy and to avoid becoming a source of energy for some other organism.

This saga began with the proto-cell, the earliest life form. It persists today in bacteria, which in the process of chemotaxis move toward a gradient of energy metabolites. These prokaryotic cells therefore have a mechanism for chemoattraction as well as chemorepulsion. Even our own immune cells can be thought of as unicellular life forms engaged in chemoattraction and chemorepulsion. Darwinian evolution acknowledges the flow toward complexification in evolutionary time. Natural selection pressure working on genetic variabilities in individuals and probably between groups will purely by chance lead to increasingly complex individuals and species. But perhaps there is a selection bias that orients complexification. This selection bias reveals itself only when we look at the contingent life challenges faced by individuals and species in a particular way.

Most biological crises of evolutionary import can be described as "isolation challenges." Indeed, these are the kind of stressors that instigate the punctuation of the equilibrium among species in a particular environment that leads to evolutionary change (Eldredge and Gould 1972). Those individuals and clades best equipped to face the isolation or separation challenge with an attachment solution have the emergent probability of enjoying a survival advantage. Another way to conceptualize this is in terms of what can be called a "separation–attachment dialectical process" (Fricchione 2001). In most instances of evolutionary complexification, a sep-

aration challenge to the supra-ordinate system, be it an organism or a group, has led to an attachment solution among subordinates.

Let us now focus on vertebrate evolution in terms of the separation–attachment dialectical process. Porges (1998) proposed a "polyvagal theory of emotions," in which he examined the evolution of the vertebrate autonomic nervous system into three emotion subsystems. A naturally selected autonomic nervous system would need to be flexible in its response to challenge and allow for subtle modulation of an effector nervous system designed to mobilize the organism (sympathetic nervous system [SNS]) or to immobilize it (parasympathetic vagal nervous system) in the context of achieving separation or attachment. Porges provided evidence that the earliest vertebrates had a rudimentary unmyelinated vagal system, which eventually became the "vegetative" dorsal vagal complex (DVC), capable of causing immobilization in response to separation challenge. Later organisms evolved a SNS capable of mobilization as a strategy. Only in mammals, however, is there an advanced myelinated vagal system, the ventral vagal complex (VVC) or "smart" vagus. The VVC bestows an ability to fine-tune regulation of the separation–attachment strategies of immobilization and mobilization by subtly inhibiting the vagus and disinhibiting the sympathetic flow and vice versa. Thus, the VVC provides myelinated motor pathways to visceromotor organs including heart and lungs and to somatomotor areas including larynx, pharynx, and esophagus, allowing for speedy yet subtle regulation of social engagement (attachment-oriented) and disengagement (separation-oriented) behaviors.

The mammalian innovation, which allowed for modulating cardiac output and metabolic flow in a graded fashion, also permitted an extraordinary ability for self-calming that is not separative and immobilizing but is rather attaching and more social in nature. This involves a higher-level, social mobilization behavior well beyond that of seeking food or sexual objects. Although the mammalian improvement in metabolic resource management began as a better primitive attachment design solution to a separation challenge, such as food scarcity, the structures that evolved took on new importance when they were further selected and exapted to improve social attachment solutions to more and more complex separation challenges. A prime example of such a challenge would be the need for extended care of altricial young, who require maternal nurturance and care and a vocalization mechanism for calling when separated.

The polyvagal theory implies a hierarchical "if-then" default strategy to environmental challenges. Based on the Jackson (1958) concept of dissolution, which he used to explain neurological diseases, this phylogenetically based response strategy would predict that the most recently devel-

oped innovations would be tried first, and the most primitive would be tried as a last resort. In line with this, the VVC will help provide the initial response to separation challenge. Measured, metabolically efficient signaling and communication along with inhibition of SNS-mediated increased cardiac output and mobilization will be tried first. If this is ineffective or the challenge is overwhelming, there is withdrawal of VVC control, disinhibiting a SNS mobilization response. And if this approach fails, withdrawal of the SNS will disinhibit the more ancient DVC strategy, and the metabolically more conservative response of immobilization will be adopted. Although this strategy may be adaptive for primitive vertebrates, it may be lethal for mammals with apnea related to bronchial constriction and bradycardia secondary to sinoatrial parasympathetic effects.

One can model catatonia according to Jacksonian dissolution and Porges's polyvagal theory. When an individual social attachment solution strategy employing the smart vagus appears to fail (as it may in affective disorder and schizophrenic patients), then a disinhibited sympathetic mobilization strategy may be triggered (perhaps a catatonic excitement phase), to be followed, if it fails, by a vegetative vagal immobilization response (a traditional catatonic withdrawal).

It should be noted that these response strategies may blend together at transitions between the boundaries of the three emotion subsystems. The neurophysiological basis for a catatonic withdrawal state may therefore involve the activation of the DVC strategy, with residual SNS tachycardia also present. And certainly, catatonic dissolution can occur with neuromedical insults to the structures responsible for the advanced strategies. This was Jackson's point in the first place. This view gathers ethological strength from the observation that reptiles use immobilization more frequently than mammals, and the most primitive mammals, like the opossum, use it more in terms of the death feign than more advanced mammals.

The if-then default hierarchies involved in deciding to mobilize or immobilize, approach or avoid, attach or separate are the part of the complex life system that eventually becomes responsible for emergent properties (Holland 1998). There are innumerable levels of increasingly complex, supra-ordinate systems that distinguish the simple sensorimotor analyzer-effector life form from the human brain; however, all of this complexity may have evolved for one overarching aim—to improve an organism's negotiation of the avoidance–approach, separation–attachment process.

The human brain is the most complexified biological organ known. Although it evolved as a result of the separation–attachment dialectical process, it developed to such an extent that consciousness of separation and attachment emerged. Along the way, other emergent properties, such as lan-

guage, belief, and spirituality, arose as examples of attachment solutions to separation challenges. Perhaps this argument is best reviewed in light of the evolution of the brain from reptile to mammal-like reptile (therapsid) to mammal.

The Evolution of the Brain

The brain, from the functional neuroanatomic point of view, consists of loops that include basal ganglia, thalamic, and cortical interconnections (Figure 17–1) (Alexander et al. 1986, 1990). In the area of brain evolution, we can hypothesize that there was an evolution of basal ganglia thalamocortical loops. Periallocortical loops were followed by an overlayering of proisocortical loops, culminating in isocortical loops as afferentation from the thalamus moved into expanding frontal cortical zones with return connections to the thalamus and basal ganglia.

The most primitive loop is the protolimbic "loop," of which the reptile has a rudimentary version. This periallocortical loop would have basal ganglia–thalamo–amygdala–piriform and basal ganglia–thalamo–hippocampal components (Figure 17–2). Although this loop allows the reptile to perform primitive attachment functions in the context of food attainment and reproduction, it does not allow the reptile to be behaviorally oriented toward social attachment except by way of routinized behaviors and displays. The reptile has a social strategy that is predominantly one of separation. Indeed, the reptile mother, if given the chance, will often cannibalize its young as a source of food attachment. In contrast, the mammal has evolved a new level of attachment, that of the "mammalian behavioral triad" as described by MacLean (1990). This includes maternal nurturance and caring, the separation cry, and mammalian play. This behavioral triad can be understood as a reflection of loop evolution. We see movement from a primitive basal ganglia thalamocortical loop involving a protolimbic "cortical" region to a more advanced loop consisting of connections to new cortical regions—namely, the anterior cingulate (ACA) cortex and the medial orbital frontal (MOF) cortex—as part of mutational, medial dorsal, general pallium growth (Butler 1994). When MacLean (1990) did experiments on the thalamo-cingulate connection, it became evident that this connection had a special importance in mediating mammalian attachment. When the cingulate, along with a part of the supplementary motor area, is ablated, a mammalian infant, whether a hamster or a squirrel monkey, will demonstrate defective attachment behavior. It will no longer have a separation cry for its mother. Similarly, when this area is ablated in the mammalian mother, it will no longer behave in a caring and nurtur-

MOTOR
OCULOMOTOR
DORSOLATERAL PREFRONTAL
LATERAL ORBITOFRONTAL
ANTERIOR CINGULATE
MEDIAL ORBITOFRONTAL
CORTEX
STRIATUM
PALLIDUM
S. NIGRA
THALAMUS
SMA
APA, MC, SC
FEF
DLC, PPC
DLC
PPC, APA
LOF
STG, ITG, ACA
ACA
HC, EC, STG, ITG
PUT
CAUD (b)
dl-CAUD (h)
vm-CAUD (h)
VS
vl-GPi
cl-SNr
cdm-GPi
vl-SNr
ldm-GPi
rl-SNr
mdm-GPi
rm-SNr
rl-GPi, VP
rd-SNr
VLo, VLm
l-VAmc, MDpl
VApc, MDpc
m-VAmc, MDmc
pm-MD

Figure 17–1. Proposed basal ganglia thalamocortical circuits.

Parallel organization of the five basal ganglia thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra, and thalamus.

ACA=anterior cingulate area; APA=arcuate premotor area; CAUD=caudate [(b)=body; (h)=head]; DLC=dorsolateral prefrontal cortex; EC=entorhinal cortex; FEF=frontal eye fields; GPi=internal segment of globus pallidus; HC=hippocampal cortex; ITG=inferior temporal gyrus; LOF=lateral orbitofrontal cortex; MC=motor cortex; MD=medialis dorsalis; MDmc=medialis dorsalis pars magnocellularis; MDpc=medialis dorsalis pars parvocellularis; MDpl=medialis dorsalis pars paralamellaris; PPC=posterior parietal cortex; PUT=putamen; SC=somatosensory cortex; SMA=supplementary motor area; SNr= substantia nigra pars reticulata; STG=superior temporal gyrus; VAmc=ventralis anterior pars magnocellularis; VApc=ventralis anterior pars parvocellularis; VLm=ventralis lateralis pars medialis; VLo=ventralis lateralis pars oralis; VP=ventral pallidum; VS=ventral striatum.

cdm=caudal dorsomedial; cl=caudolateral; dl=dorsolateral; l=lateral; ldm=lateral dorsomedial; m=medial; mdm=medial dorsomedial; pm=posteromedial; rd=rostrodorsal; rl=rostrolateral; rm=rostromedial; vl=ventrolateral; vm=ventromedial.

Source. Adapted from Alexander et al. 1986.

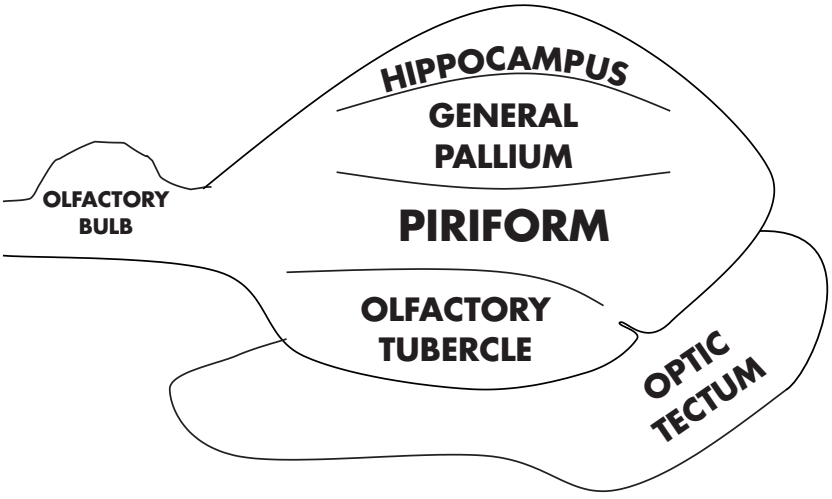


Figure 17–2. Green turtle brain: different pallial areas of a reptilian cerebrum are depicted.

The hippocampus and piriform areas are rudimentary areas of the like-named mammalian areas. The intermediately placed general pallium is destined to become the cingulate and entorhinal cortices and other medial regions in the mammal.

Source. Adapted from MacLean PD: *The Truine Brain in Evolution.* New York, Plenum, 1990. Used with permission.

ing way when the infant lets out a separation cry. The same effects can be elicited when morphine is applied to the anterior cingulate cortex. In humans, we have a more severe natural example of this in a neurological version of the catatonic syndrome called akinetic mutism. In this syndrome, which can be caused by bilateral anterior cingulate destruction, the person will no longer be able to verbalize and will be unable to move (MacLean 1990).

These evolutionary circuits are interconnected in at least three major ways (Groenewegen et al. 1990). There are "cortico"-cortical connections so that the limbic nuclei are connected to the ACA, which in turn is connected to the frontal cortices. There are cortical-striatal connections as well, so that these cortical zones are connected to the basal ganglia. Perhaps most important for our story, there are the mesostriatal and mesocorticolimbic medial forebrain bundle dopamine (DA) tracts running from the basal ganglia through to the nucleus accumbens, ACA, and prefrontal cortex (PFC). The thalamus is also connected to the dopaminergic system through γ-aminobutyric acid (GABA) and glutamate interneurons. The fact that brain circuits are both integrated and segregated accounts for the brain's neural complexity (Tononi et al. 1994).

Let me add a word here about the brain and its meaning in terms of separation and attachment. These basal ganglia thalamocortical loops are complexified versions of the nerve arcs that are situated between the sensory and motor systems in all living organisms with nervous systems, no matter how rudimentary. Somewhere along the line, a system was developed in which attachment and separation behaviors became valenced in terms of a "pleasurable" or "painful" marker. It may be that ancient chemicals such as opioids, present even in invertebrates, developed as a way of providing a pleasure- and painlike valence to the results of a behavior. The same could be said about the neurotransmitter DA.

Mesocorticolimbic and mesostriatal DA neurons have their terminal fields in various areas of the brain that are important for the evolutionary loop story. Thus, substantia nigra DA neurons have synapses in the caudate and putamen, and the ventral tegmental DA neurons have synapses in the nucleus accumbens in the limbic system and in the cortex, including the more ancient ACA archicortex and the newer prefrontal neocortex. When we talk about the evolution of advanced—that is, enhanced and refined—attachment strategies, we are also talking about more enhanced and refined uses of the dopaminergic system. For the mammal, not only is the attachment drive for food and sex now considered pleasurable, but also the attachment to offspring is pleasurable as well.

On an experiential basis, the memory of success (pleasure) and failure (pain) in terms of food and sex would be invaluable to the organism. Such a reward memory system would represent a vast complexification of the simple movement behavior of the unicellular organism. Indeed, there are connections between amygdala and hippocampus and between septum and hippocampus. These provide the organism with the opportunity to emotionally valence bits of experience in terms of food and sexual behavior. In mammals, there are tracts between the ACA and hippocampus to service the memory of social interaction. Depending on how complex a certain brain is, there will be a lesser to greater degree of "memory of the past" in regard to these experiences (MacLean 1990). This memory of the past will be based on long-term potentiation mechanisms in the hippocampus.

Neuroanatomists now have shown, using a quantitative technique called scalable architecture, that primate cerebrotypes have progressively changed and that neocortical volume fractions as compared with subcortical fractions have become successively larger in lemurs and lorises, New World monkeys, Old World monkeys, and hominoids (Clarke et al. 2001). This lends support to the idea that primate brain architecture has been driven by "directed selection pressure." I would submit that it is the survival advantage, imparted by co-opting mutation-based pallial fields for the purpose

Superior medullary lamina
Protolimbic
[Hippocampal–parahippocampal complex]
Piriform insular
Prefrontal
[DLPFC–LOFC]
Limbic
[Anterior cingulate–MOFC]
[Amygdala–septum]
Corticocortical
Corticolimbic
Corticostriatal
Dopamine
Thalamus
GABA
Neofronto-cerebellar (neodentate)
Fronto-cerebellar (dentate)
Thalamus/ olfactory bulb
Ventral tegmentum
Basal ganglia
Attachment (4)
Evolution
Attachment (3)
Evolution
Attachment (1, 2)

Figure 17–3. Brain loop evolution and attachment.

(1) To food (self-preservation)↔amygdala.

(2) To sexual mate (species preservation)↔septum.

(3) (a) Mammalian behavioral triad (maternal nurturance, separation cry, play). (b) Avoidance of painful separation (visceral, somatic, emotional) and approach to pleasurable attachment. (c) Memory of the past links the evocative emotional memory of the limbic system with the retrievable declarative memory of hippocampus-association cortices.

(4) Memory of the future. In the now-situation, the PFC makes possible effortful or strategic retrieval of important memories of the past, optimizing appraisal of the "what" and "where" of attachment and providing for the ability to plan based on memory of the future.

DLPFC = dorsolateral prefrontal cortex; GABA = γ-aminobutyric acid; LOFC = lateral orbitofrontal cortex; MOFC = medial orbitofrontal cortex; PFC = prefrontal cortex.

of complexified and enhanced attachment solutions to contingent separation challenges, that provided the directed selection pressure and in effect biased cerebrotype evolution.

So, in the context of evolutionary loop design, one sees a progression from earlier, more primitive levels of attraction behavior upward to parent–child and social attachment. These behaviors are mediated by the basal ganglia– or thalamo–amygdala, hippocampal, and septal protolimbic loops, upward to the ACA/MOF and PFC loops (Figure 17–3).

Important Evolved Nodal Points on the Brain Loops

The ACA appears to be necessary in proceeding from initial analysis to movement states. Devinsky et al. (1995) stratified ACA premotor processing into three levels. In the first place, when a response selection to move or not to move is to be made, area 24′ is activated and engaged. Sensory stimuli devoid of emotional significance may be associated with diminished ACA activity. In the second place, specific movement repertoires that are not dependent on autonomic nervous input usually involve ACA skeletomotor areas in cingulate sulcal depths. In the third place, when autonomic energy is essential to the movement response, ACA visceromotor and skeletomotor areas will be coactivated.

The ACA, as previously outlined, hints at how affect and cognition can be synthesized in the brain. In addition to ACA connections to limbic structures (e.g., the amygdala and the hippocampus) and to the great visceral nerve—the vagus—the ACA has strong bidirectional connections to dorsal, medial, and inferior prefrontal cortices. Although affective states and intellectual data are separated, they may come together in the ACA. Here emotional memory and a cognitive cue may meld and elaborate an engrammatic experience. In terms of mood disorder, there is evidence of reduced glial cell density and neuronal size in the ACA cortex in subjects with major depression (Cotton et al. 2001). As Devinsky et al. (1995) put it, "The cingulate gyrus may be viewed as both an amplifier and filter, interconnecting the emotional and cognitive components of the mind" (p. 298).

In terms of memory, the cingulate serves as a crossroads for processing of amygdala-generated emotional memory, PFC-generated cues, and the hippocampal and medial temporal lobe memory system (MTLMS)–generated engrams. The ACA is dependent on information processing to fulfill its premotor function of selecting an appropriate response. It also is strongly involved, especially on the right, in selective attention. The ACA

attachment synthesis of emotion and cognition might then be used in premotor response selection and goal direction according to the pleasure and pain valences of past separation and attachment outcomes stored in memory.

Schore (1996, p. 75) hypothesized that the right MOF cortex is the major prefrontal-limbic component in providing "executive control function for the entire right cortex, the hemisphere that modulates affect, nonverbal communication, and unconscious processes." Schore cited evidence that the orbitofrontal cortex is the neural substrate of temperament as it develops in the initial year and a half of a child's life. It regulates the activation of the emotive circuitry, which comprises basal ganglia thalamocortical loops. He talked of "particular socioaffective imprinting experiences" of attunement during which the mother's thalamocorticolimbic output, especially that from the right orbitofrontal region, will provide a "template for the imprinting of the infant's developing corticolimbic regions." Indeed, there is now evidence that the attachment behavior of a mother toward her child will influence her infant's frontal lobe activity.

The right MOF cortex also helps modulate the autonomic nervous system, as the right hemisphere appears to be dominant in autonomic regulation and temperament development. One temperamental extreme may involve a sympathetic flavor—early practicing, excitatory, and exploratory—and the other extreme may be more parasympathetic—late practicing, inhibitory, and withdrawn. The ACA can be thought of as the rostral limbic system in league with the amygdala, periaqueductal gray, and ventral striatum, as well as with the MOF and anterior insular cortices. This network emotionally valences external and internal stimuli, in comparison with "memory of the past" stimulated experiences, so that the mammal can be motivated to avoid or approach depending on the external and internal environmental context.

The evolutionary purpose for this architecture was to select for organisms better equipped to negotiate repulsion–attraction on one level and avoidance–approach on another. An emotion–cognition attachment solution has obvious advantages for any organism faced with the need to select a response in the context of separation challenge. An emotional response devoid of cognition forfeits contextual details of *what* is to be avoided or approached and *where* the organism is in relation to the *what*. A cognitive response devoid of emotion forfeits the attentional energy that links with memory outcomes and therefore deprives the organism of the motivation to choose approach or avoidance. The mammal uses its synthesizing ACA and MOF abetted by its polyvagal system for fine-tuned response selection in an energy-efficient manner. This results in avoidance–approach mobilizations that serve to enhance and refine the very nature of attachment.

Now if the ACA/MOF basal ganglia thalamocortical loop evolved to mediate the brain motive and reward circuitry and its emotional valencing as it pertains to mammalian behavioral attachment, what can be said of the dorsal lateral PFC loop? The executive functions of the human brain are mediated in the PFC. Human beings are endowed with the ability to foresee certain consequences related to their actions and thus adjust their behavior accordingly. Ingvar (1985) has written about humans' "memory of the future" in relation to their memory of the past. The PFC supervises the temporal organization of cognition and behavior while maintaining the action programs or plans for future cognition and behavior. In the extensive connections of the dorsolateral PFC to the ACA/MOF cortex and the connection of them both to the MTLMS (hippocampus) and association cortices, the network from memory of the past to the "now-situation" to memory of the future is set. The memory of past attachment serves as an attractant in the formation of our memory of the future. We long for relationships that are associated with attachment security and solace and even for those that are simply familiar (consider the affect associated with human nostalgia). This would be natural for a conscious mammal. Of course, once mammals who have adopted an attachment strategy for survival become conscious of their memory of the past in relation to their memory of the future, "paradise is lost"; for those conscious mammals will always be beset by the knowledge that what they face is separation from those they love and are attached to.

We have not discussed the basal ganglia part of the circuitry except to say it is a center for motor functioning. In point of fact, the basal ganglia may be primarily responsible for electroencephalographic desynchronization in the executive forebrain (Brown and Marsden 1999). This may permit response selection and movement to ensue. From clinical neurology there comes evidence that basal ganglia dysfunction allows slow, idling cortical rhythms to predominate. Desynchronization of the surface electroencephalographic activity, which correlates with local circuit gamma frequency synchronization, is faulty. Thus, in parkinsonism patients with low basal ganglia dopaminergic flow, there is impaired desynchronization with loss of the normal Piper rhythm in muscle. When treatment with levodopa, a dopamine agonist, is given, EEG desynchronization and the Piper rhythm are restored. Akinesia, abulia, and bradyphrenia are disorders characterized by slowing of movement and of thought processes. These too are characterized by impaired desynchronization with concomitant reduction in local circuit neuron 30 to 50 Hz synchronization. I suspect that the neuropsychiatric syndrome of catatonic stupor also produces this faulty frontal desynchronization related to basal ganglia dysfunction.

But how does this fit in with the thalamo-cortical system? When we review the basic Alexander basal ganglia thalamocortical architecture, we

surmise that the critical output summation of the basal ganglia flows to the modulation of something Carlsson called the "thalamic filter" (Carlsson and Carlsson 1990). Thus, when levodopa increases DA activity in the striatum, a GABA neuron is inhibited, thereby disinhibiting the globus pallidus externa (GPe) GABA interneuron in the indirect pathway, which inhibits the subthalamic nucleus glutamate excitatory neuron thus reducing globus pallidus interna (GPi) GABA inhibition on the thalamus and increasing thalamo-cortical activity (Figure 17–4). The thalamic filter is widened, and the thalamic glutamate neuronal flow to the cortex is increased; desynchronization with subsequent gamma synchronizations in local cortico-cortical tracts takes place. Excessive dopaminergic flow leading to excessive inhibition of GPi GABA outflow to thalamus may lead to excessive gamma synchronization with resultant dyskinesias, choreas, and thought overactivity disorders such as catatonic excitement, mania, or schizophrenia. Inadequate dopaminergic flow leading to inadequate inhibition of GPi GABA outflow to thalamus may lead to inadequate gamma desynchronization with resultant akinesias and thought underactivity disorders such as catatonic stupor.

Of course we are dealing with loops. It is not as if the basal ganglia are "in charge." There are corticostriatal as well as corticothalamic tracts, perhaps most importantly for our purposes, from the ACA/MOF cortices and from the dorsolateral PFC. There are also important reciprocal and direct thalamo-amygdala pathways. Through glutamate fibers, these will set the gain in the striatum and subthalamic nucleus and in the thalamus, thereby making use of memory to focus our attention and indeed our consciousness on the aspects of life that are meaningful.

In summary, the ACA in its connection with the PFC is an extremely important nodal point in the mesocorticolimbic motive circuitry. In this regard, Damasio (1994) believes the ACA is the brain's "fountainhead region." He surmises that the ACA, probably in combination with the supplementary motor area, is the area where "emotion/feeling, attention, and working memory interact so intimately that they constitute the cause for the energy of both external action (movement) and internal action (thought animation, reasoning)." Given what we know of the importance of the ACA and the thalamocingulate pathway for the mammalian behavioral triad, it comes as no surprise that the ACA would indeed be the mammalian brain's fountainhead in terms of motivation, movement, and thought animation. All mammals, especially humans, will think and move in the face of the core evolutionary separation–attachment process as it pertains to maternal nurturance, the separation cry, and social interaction. The ACA will process sensory stimuli in special consideration of separation–attachment issues and will, in cooperation with the connected MOF, SMA, and

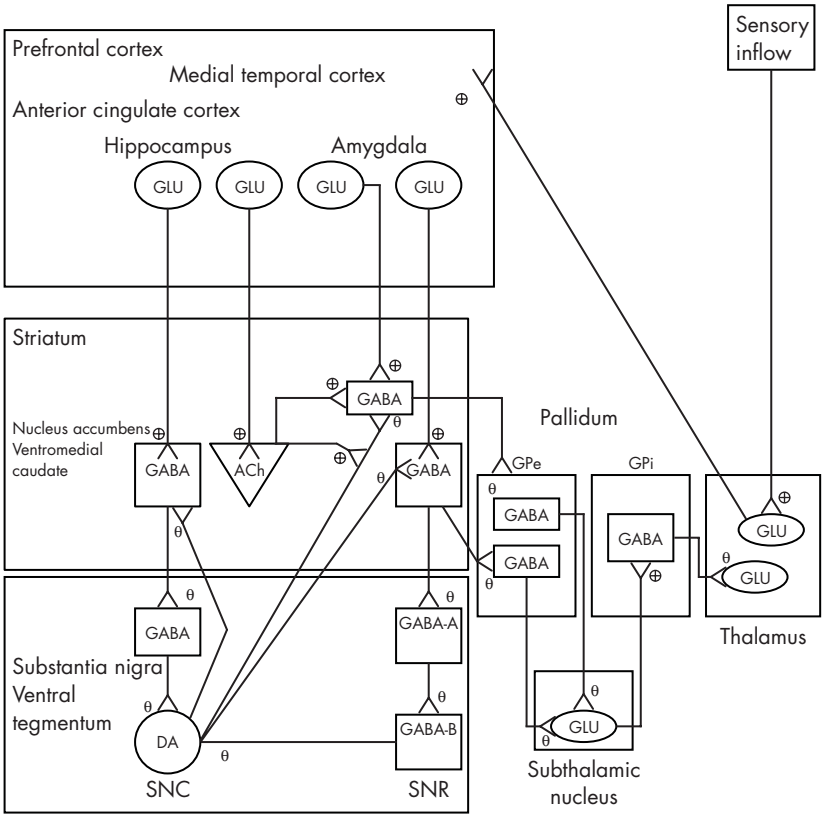


Figure 17–4. Corticolimbic-mesolimbic subcortical connections in the corticostriato-thalamo-cortical loop.

ACh = acetylcholine; DA = dopamine; GABA = γ-aminobutyric acid; GABA-A= GABA-A receptors; GABA-B=GABA-B receptors; GLU = glutamine; GPe = globus pallidus externa; GPi = globus pallidus interna; SNC = substantia nigra compacta; SNR = substantia nigra reticulata.

Source. Adapted from Carlsson M, Carlsson A: "Interactions Between Glutamatergic and Monoaminergic Systems Within the Basal Ganglia—Implications for Schizophrenia and Parkinson's Disease." *Trends in Neuroscience* 13:272–276, 1990. Copyright 1990, with permission from Elsevier Science; Csernansky JG, Murphy GM, Faustman WO: "Limbic/Mesolimbic Connections and the Pathogenesis of Schizophrenia." *Biological Psychiatry* 30:383–400, 1991. Copyright 1991, with permission from The Society of Biological Psychiatry; and Fricchione GL, Carbone L, Bennett WI: "Psychotic Disorder Caused by a General Medical Condition, With Delusions: Secondary 'Organic' Delusional Syndromes" (Delusional Disorders, Sedler M, Editor). *Psychiatric Clinics of North America* 18:363–378, 1995. Used with permission.

PFC, initiate movement responses based on MTLMS memories of the past that hold the promise of reexperiencing positive attachment if a similar strategy is adopted. Perhaps for the person in catatonic withdrawal, based on neuromedical or psychiatric conditions, there is little promise of reexperiencing positive attachment (Fricchione et al. 1995). "My only

choice was suicide or a survivor state deep in my inner shell," as my patient expressed it.

Catatonia and the Brain

Taylor (1990) concluded that the catatonic syndrome is primarily a frontal lobe disorder, whereas Rogers (1991) cited evidence that it is primarily a basal ganglia disorder. I have proposed that the catatonic syndrome is actually a disorder of basal ganglia thalamo (limbic)–cortical circuits (Fricchione et al. 1997). Any neuromedical or psychiatric disturbance significant enough to disrupt the GABA–DA balance in the mesostriatal-mesocorticolimbic medial forebrain bundle DA tracts with terminal fields in the ACA and the PFC anywhere along the circuitry will potentially set off a catatonic response from a more primitive protolimbic loop. Using functional magnetic resonance imaging and magnetoencephalography, Northoff (2000) presented findings indicating that in primary psychogenic catatonia there is reduced activity in the MOF during negative emotional stimulation, suggesting that perhaps psychogenic catatonia has its initiation there. Areas such as the right parietal cortex may also be involved through connections to the right MOF cortex. Insofar as cerebellar and brain stem disorders will also disturb this circuitry, they will also have the potential to cause catatonia, as will scores of other insults to basal ganglia thalamocortical loops, particularly if the ACA/MOF circuit is affected (Fricchione et al. 1997; Joseph 1999).

The restitutive hypothesis of DA receptor activity may offer a physiologic explanation for catatonia (Fricchione 1985; Friedhoff 1983). It assumes that the dopaminergic system is involved in protecting against the emergence of psychotic symptoms through downregulation of DA receptors in the face of biological or psychological events that would tend to destabilize the system (Friedhoff 1983). The dopaminergic system then may improve homeostasis by spontaneous downregulation of its own function. This downregulation is usually sufficient to ward off a psychotic state. Sometimes, however, the stressors are so severe that downregulation is not adequate to prevent psychosis. Neuroleptics will sometimes help in remission of symptoms by producing a further decrease in DA activity. However, in some the further decrease in DA activity by DA blockade may lead to neuroleptic-induced catatonia or neuroleptic malignant syndrome.

Different pathways to catatonia may be accounted for if we employ the restitutive hypothesis. The hyperdopaminergic mesolimbic system will adjust itself in such a way as to attempt restoration of homeostasis (i.e., downregulation of DA receptors). As Friedhoff (1983, 1995) pointed out,

an adjustment will likely affect other brain systems. The ones likely to be rapidly adjusted are the mesostriatal system with GABAergic feedback from the nucleus accumbens through the globus pallidus to the pars reticulata of the substantia nigra; and the hypothalamic dopaminergic system, which may have cell bodies in the substantia nigra. They too may then downregulate. If these areas become severely hypodopaminergic yet psychosis continues, psychogenic and then lethal catatonia may ensue. Use of cataleptogenic neuroleptics could hasten the catatonia in this situation through DA blockade (Kim and Hassler 1975).

There is an animal model of catatonia that supports this view. Stevens et al. (1974) instilled bicuculline, a GABA-A antagonist, into the ventral tegmentum area of cats. Slinking, hiding, evidence of fear, staring, sniffing, and a catatonic stance were noted. When bicuculline was given in the ventral tegmentum after systemic haloperidol, marked dystonic postures were produced. Picrotoxin, an antagonist at the chloride channel of the benzodiazepine–GABA-A recognition site, was administered in the ventral tegmentum areas as well. Smaller doses induced fear and staring, whereas larger doses produced prolonged severe dystonia, especially following haloperidol. In the rat, microinjection of the GABA-A agonist muscimol into the ventral tegmentum area produces a dose-dependent increase in motor activity. This effect is antagonized by ventral tegmentum area administration of bicuculline or by haloperidol administration (Kalivas et al. 1990). Animal models of catatonia have much to teach us about pathophysiology and reflect the evolutionary persistence of the catatonic strategy (see Chapter 16, "Animal Models," this volume).

Conclusion

The human brain represents the most advanced sensorimotor analyzer-effector forged under the evolutionary selection pressure of separation challenges requiring attachment solutions. Thus when pallial growth zones became available through mutation, the challenge of offspring in need of nurturance felt by mammal-like reptiles was met by the attachment solution of a basal ganglia–thalamic afferent linkup with newly formed archicortical terminal zones, setting the stage for mammal-like behavior. Separation–attachment response selection then became enhanced and refined with the coming on line of mammalian basal ganglia thalamocortical circuitry capped by the ACA and MOF cortices. "Memory of the past" information was made available through superior medullary laminar flow from the entorhinal hippocampal region to the ACA. Although past memory was a good mechanism, allowing for better attachment responses to separation challenges, think what social survival advantage

accrued from development of the ability to form a "memory of the future"! In facing social group separation threats, the great trick of planning and then executing an effortful future memory, based on past cues with separation–attachment content and context, would enhance and refine the individual's ability to formulate group attachment solutions. An evolutionary separation challenge felt at the level of a supra-ordinate social group would select for the subordinate individuals best outfitted in design space to formulate such group attachment solutions and to carry them out. Further mutational pallial growth became exapted for this purpose, forming the neocortical areas in the advanced PFC basal ganglia thalamocortical loops. The potential for human civilization based on consciousness, language, information sharing, and altruism emerged (see Fricchione 2001 for detailed discussion).

But in a Jacksonian dissolution sense, there remains the potential for less adaptive strategies. On the individual level, these include both primitive approach–attachment and primitive avoidance–separation behaviors. Catatonic withdrawal can be understood as an example of the latter.

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