Am. J. Hum. Genet. 41:839–866, 1987

A Controlled Study of Tourette Syndrome. VII. Summary: A Common Genetic Disorder Causing Disinhibition of the Limbic System

DAVID E. COMINGS

*Department of Medical Genetics, City of Hope National Medical Center, Duarte, CA

SUMMARY

Tourette syndrome (TS) is one of the most common genetic disorders affecting man. Approximately one in 100 individuals manifests one or more of the aspects of the *TS* gene. This series of papers has emphasized that although motor and vocal tics are the hallmark of TS, the complete range of behavioral problems is much broader. This spectrum of behavior can be explained on the basis of the *TS* gene causing an imbalance of the mesencephalic-mesolimbic dopamine pathways, resulting in disinhibition of the limbic system.

INTRODUCTION

Tourette syndrome (TS) is a genetic disorder, and studies in two different centers (Comings et al. 1984; Pauls and Leckman 1986) have shown that the frequency of the gene is .006. This means that 1 in 83 persons carries a *TS* gene. When family members with TS or motor or vocal tics (chronic motor tics [CMT]) are included, the penetrance is 70% in males and 30% in females (Comings et al. 1984). When obsessive-compulsive behaviors (OCB) are included, the penetrance may approach 100% in males and 71% in females (Pauls and Leckman 1986). On the basis of these figures, approximately one in 100 persons will at some time in his or her life express some symptoms of the TS-CMT-OCB spectrum. Thus, the TS spectrum is one of the most common genetic disorders affecting man. This series of papers has defined the breadth of this spectrum.

The present DSM III (1980) (and DSM III R [1987]) diagnostic criteria for TS

Received December 10, 1986; revision received April 9, 1987.

Address for correspondence and reprints: Dr. David E. Comings, Department of Medical Genetics, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010.

 0002-9297/87/4105-0007$02.00

are (1) onset before 21 years of age, (2) presence of more than one motor tic, (3) presence of at least one vocal tic, (4) suppressibility of symptoms for minutes to hours, (5) a waxing and waning course, and (6) presence of symptoms for at least 1 year. Coprolalia is not one of the diagnostic criteria, since it is the exception rather than the rule; in most series only 30% of TS patients have coprolalia. The ability of the patient to suppress the tics must be kept in mind. The complete suppression of all tics while in the doctor's office is very common. As a result, a careful history is often more informative than the physical examination. Since the intensity of the symptoms can wax and wane, there may be times when there are no tics. Thus, a longitudinal history, covering the patient's entire life, is important. Taking a careful family history is also critical. In some relatives the other manifestations of the TS spectrum are more prominent than the motor or vocal tics.

The Spectrum of Behavioral Disorders in TS

The results of the previous papers in this series on TS are summarized in figure 1. Attention-deficit disorder (ADD) with or without hyperactivity (ADD/H) is 10 times more common in children with TS than in the general population. OCB is five times, conduct disorder 17 times, requirement for special classes five times, stuttering five times, dyslexia six times, panic attacks 13 times, multiple phobias three times, depression 11 times, and mania and severe test anxiety approximately 20 times more common in TS patients than in controls. This indicates that although the presence of motor and vocal tics may be the most obvious aspect of TS, it is actually a broadly based behavioral spectrum disorder. Our previous genetic studies (Comings and Comings 1987*c*) and the recent ones of Pauls and Leckman (1986) have indicated that the *TS* gene may manifest as OCB only. Our extensive genetic pedigrees on 800 TS families indicate that the *TS* gene can also be expressed as ADD, ADD with hyperactivity (ADDH), conduct disorder, stuttering, dyslexia, panic attacks, agoraphobia, phobias, depression, and manic-depressive disorder either without tics or with very minor tics. This finding is based on the frequency of these disorders in obligate carriers of a *TS* gene (i.e., individuals with a child, as well as a parent or sibling, with TS) who themselves do not have tics. These observations lead to the concept that some cases of ADD, ADDH, conduct disorder, stuttering, dyslexia, panic attacks, phobias, depression, and manic-depressive disorder may be secondary to a *TS* gene. Such a tentative diagnosis (e.g., ADDH probably due to a *TS* gene) is suggested when an individual with one of the above disorders has a strong family history of TS but does not fit the criteria of TS or CMT. In many children in whom we have tentatively proposed such a diagnosis, the full spectrum of TS has subsequently appeared.

Correlation Coefficients

Table 1 summarizes the correlation coefficients between the different behavioral scores from the preceding papers in this series. Features of particular note are the following:

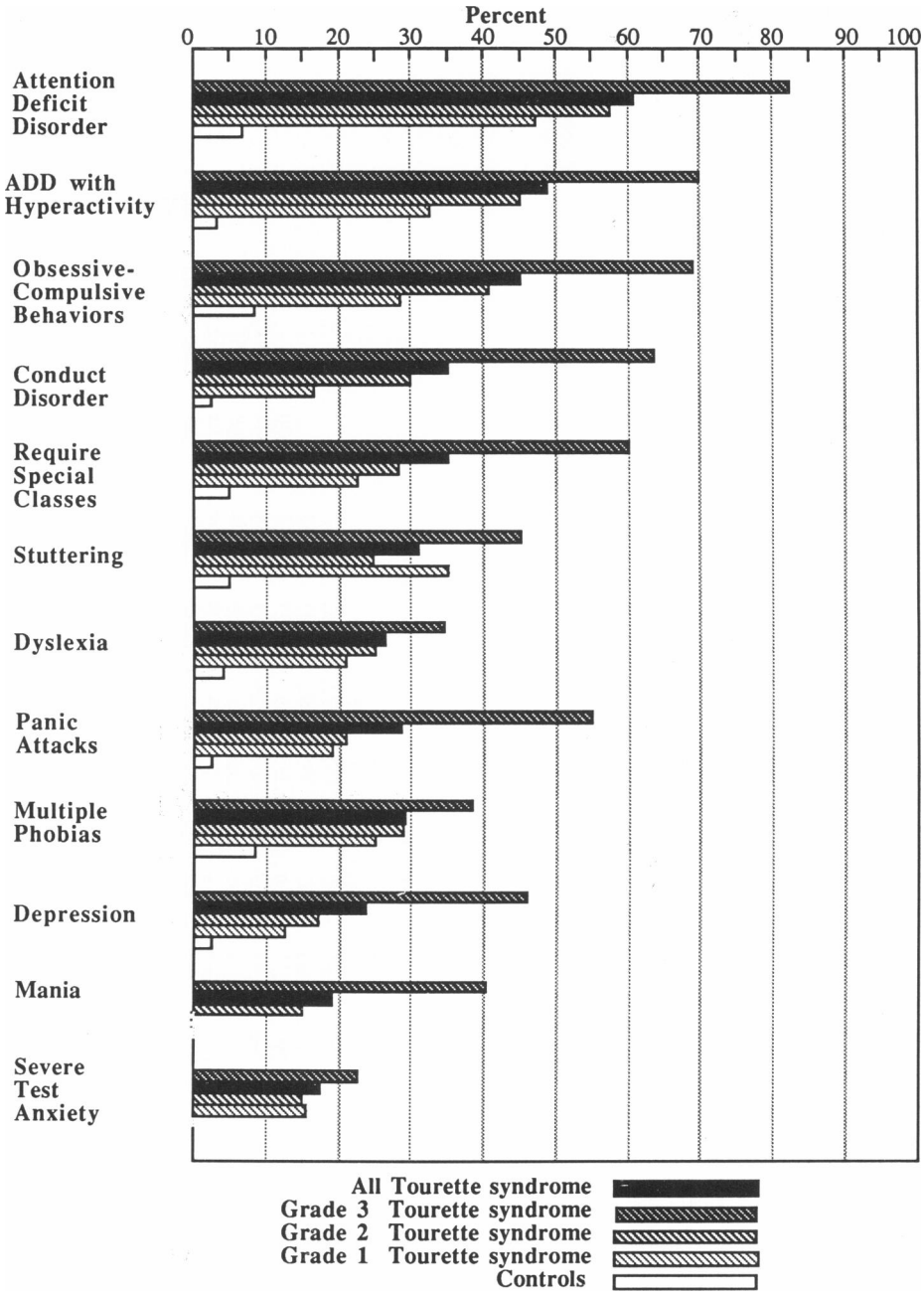

FIG. 1.—Summary of various behaviors in all TS patients and in the different grades of TS

TABLE 1

CORRELATION COEFFICIENTS

					Behavioral Score									
	ADD	ADDH	Age at Onset of TS	No. of Tics	Conduct Problems	Obsessions	Compulsions	Obsession-Compulsion	Depression	Beck	Mania	Panic	Phobia	Schizoid
ADD	...													
ADDH	.947	...												
Age at onset of TS	−.197	−.200	...											
No. of tics	.121	.172	.168	...										
Score:														
Conduct problems	.476	.490	−.131	.147	...									
Obsessions	.121	.133	−.051	.260	.246	...								
Compulsions	.393	.408	−.090	.442	.450	.367	...							
Obsession-compulsion	.344	.361	−.090	.430	.451	.732	.902	...						
Depression	.066	.086	.102	.267	.395	.392	.343	.433	...					
Beck	.099	.077	.030	.193	.396	.39	.337	.427	.630	...				
Mania	.246	.291	−.009	.347	.467	.428	.491	.558	.634	.498	...			
Panic	.034	.051	−.006	.154	.208	.45	.259	.398	.468	.461	.447	...		
Phobia	−.011	−.008	.179	.138	.163	.333	.209	.308	.404	.452	.272	.434	...	
Schizoid	.110	.133	−.090	.221	.387	.496	.434	.547	.388	.480	.521	.448	.305	...
Sleep-problem	.353	.407	−.118	.181	.294	.177	.299	.301	.206	.208	.263	.264	.207	.251

Age at onset.—There was a slight negative correlation between the age at onset of motor and vocal tics and the ADD, ADDH, conduct, and sleep-problem scores, indicating that the earlier the onset of tics the more severe these problems tend to be. By contrast, there was a slight positive correlation between the age at onset and phobias and number of tics.

ADD/H score.—The ADD and ADDH scores showed the greatest correlation with the conduct score, indicating that the more severe the ADD/H the more severe the conduct problems. The next highest correlation was with the compulsions and sleep-problem scores. By contrast, the lowest correlations were with the phobia, depression, and Beck scores.

Number of tics.—These correlations are important for the concept that the *TS* gene may manifest with severe behavioral problems despite the presence of few tics. This is verified by the minimal correlation between number of tics and the conduct score ($r = .147$). There is also little correlation between the number of tics and ADD, ADDH, panic attacks, and phobias. Intermediate correlations were seen for the depression ($r = .267$) and Beck ($r = .193$) scores. The highest correlations were with the compulsion ($r = .442$) and mania ($r = .347$) scores.

Conduct score.—The higher correlations ranged from .387 to .490 for the ADD, ADDH, compulsions, depression, Beck, mania, and schizoid scores. Although there was a poor correlation between ADD/H and depression scores, both of these conditions were common in conduct disorder. The combined presence of ADD/H, depression, and compulsions enhanced the likelihood of conduct problems.

Obsession and compulsion score.—The combined obsession-compulsion score showed a high correlation with many other aspects of TS, including ADD, ADDH, number of tics, conduct, depression, Beck, mania, panic attacks, and schizoid behaviors. This finding is consistent with OCB being a major form of expression of the *TS* gene (Pauls and Leckman 1986; Comings and Comings 1987*b*, 1987*c*).

Depression, Beck, and mania scores.—The high correlation between the depression and Beck scores indicates that when patients had a history of depression anytime in their life they also tended to be depressed at the time of completion of the questionnaire. The very high correlation between the depression score and the mania score ($r = .634$) is particularly important, since it indicates that the depression in TS is manic-depressive in nature. As discussed previously, this is consistent with the mood disorder of TS being an integral part of the expression of the gene rather than simply a reaction to having tics. Consistent with this is the fact that correlation between the depression score and number of tics was relatively low ($r = .267$).

Panic and phobia scores.—The correlation coefficient between the panic-attacks and phobia scores was .434. Both of these scores showed the highest correlation with the depression, Beck, and mania scores and the next highest correlation with the obsessive-compulsive score.

Schizoid score.—There was a high correlation between the schizoid score

and the obsessive-compulsive (r = .547), mania (r = .521), and Beck (r = .480) scores.

Sleep.—Not unexpectedly, the sleep-problem score showed the highest correlation with the ADDH score (r = .407). Its next highest correlation was with the obsessive-compulsive score (r = .301). The earlier the onset of TS the worse the sleep problems.

TS—A Disorder of Disinhibition

These studies indicate that TS is not simply a disorder of motor and vocal tics. The *TS* gene results in a pleiotrophic array of symptoms as described in the preceding papers in this series. Although many psychiatric disorders—such as alcoholism (Goodwin 1979; Schuckit 1986), schizophrenia (Rosenthal 1980; Kendler et al. 1982; Kety 1983; McGue et al. 1986), panic attacks (Crowe et al. 1983), depression, and manic-depressive disorder (Gershon et al. 1982; Weissman et al. 1984) have been shown to have a strong genetic basis, the relatives of those afflicted tend to show a narrow spectrum of disorders closely related to that shown by the propositus. By contrast, the *TS* gene presents a much wider spectrum. Many of the features of TS can be visualized as *disinhibited,* active, intrusive symptoms; these include motor tics, vocal tics, obsessive thoughts, compulsive behaviors, repetititive stereotyped movements, attentional disorders, motor hyperactivity, echolalia, palilalia, echopraxia, coprolalia, copropraxia, panic attacks, phobias, manic symptoms, auditory hallucinations, perserverations, short temper, easy frustration, easiness to anger, constant confrontation, exhibitionism, excessive touching, sexual touching, and conduct and sleep disorders. As will be discussed below, most of these symptoms can be explained as a disinhibition of functions controlled by the limbic system.

TS and Dopamine

There are a number of reasons to believe that some of the symptoms in TS are the result of increased activity or hypersensitivity of dopaminergic neurons. The most compelling reasons are that haloperidol, a postsynaptic dopamine-2 receptor antagonist (Crese et al. 1976), is the most effective drug in the treatment of the motor and vocal tics and that dopamine agonists can exacerbate the symptoms (Feinberg and Carroll 1979; Lowe et al. 1982). The fact that homovanilic acid (HVA), a metabolite of dopamine, is decreased in cerebral spinal fluid of TS patients (Cohen et al. 1978, 1979; Butler et al. 1979) speaks in favor of a hypersensitivity of dopamine receptors rather than hyperactivity of dopamine neurons. However, there are also cogent reasons to believe that many of the symptoms are due to a decreased activity of some dopamine neurons.

The Limbic System

In 1937 Papez (1937) proposed an anatomical basis for the emotions by correlating anatomic, clinical, and experimental data suggesting that the hypothalamus, thalamic nuclei, gyrus cinguli, hippocampus, and their interconnections constitute a harmonious mechanism that regulates emotions. This

concept has been elaborated by MacLean (1949, 1952, 1954) and others (Isaacson 1974; Livingston and Hornykiewicz 1978; Trimble 1984; Trimble and Zarifian 1984). Following are a number of observations from animal and human studies that provide evidence that the basic defect in TS may be a disinhibition of the limbic system.

ANIMAL STUDIES

The LeMoal, Ventral Tegmental Area (VTA), or A10 Syndrome

In a series of many papers spanning 18 years, LeMoal and his colleagues have described the neurobehavioral abnormalities resulting from lesions of the VTA and related areas of dopamine-rich neurons of the mesencephalon (LeMoal et al. 1969, 1975, 1976, 1977*a*, 1977*b*; Stinus et al. 1978; Galey et al. 1976, 1977, 1979; Simon and LeMoal 1984). In many ways this syndrome serves as an animal model of TS.

The destruction of the dopamine neurons in the VTA of rats results in diverse disturbances of behavior, including motor hyperactivity, hyperreactivity to sounds, increased sensitivity to frustration, impaired learning, perseveration, disorganization of orderly sequencing behavior, and behavioral disinhibition. The effects of such lesions were so widespread that Simon and LeMoal (1984) commented: "It is difficult to accept that the disruption of the dopaminergic neurons of the VTA alone would bring about such a variety of defects." The diversity of the syndrome could only be explained by an examination of the influence of the dopaminergic neurons on a wide variety of brain structures. These multiple interactions are illustrated in figure 2. The mesencephalic dopaminergic neurons project in three major ways—the A10 dopaminergic neurons of the VTA project to limbic (mesolimbic) and cortical (mesocortical) structures, and the A9 dopaminergic neurons of the substantia nigra project to the striatum (nigrostriatal) (Ungerstedt 1971*b*; Fallon and Moore 1978). These multiple interactions are further summarized in figure 3.

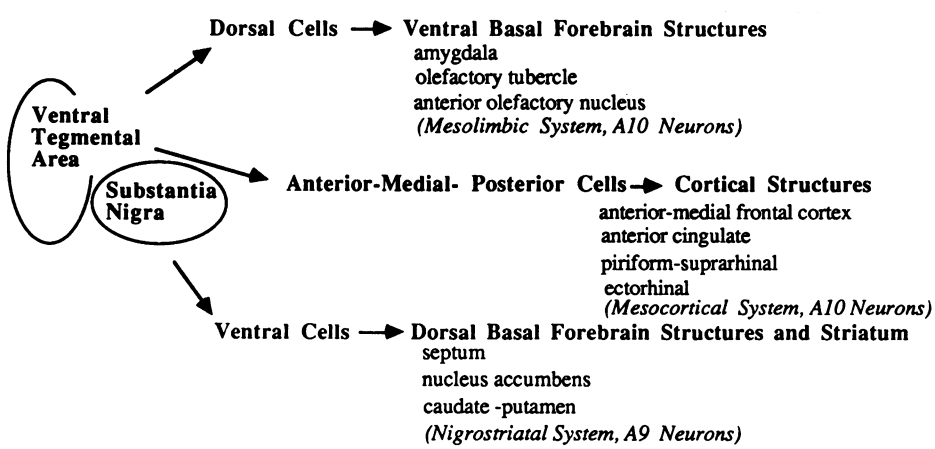

FIG. 2.—Dopamine neuron interconnections (Fallon and Moore 1978)

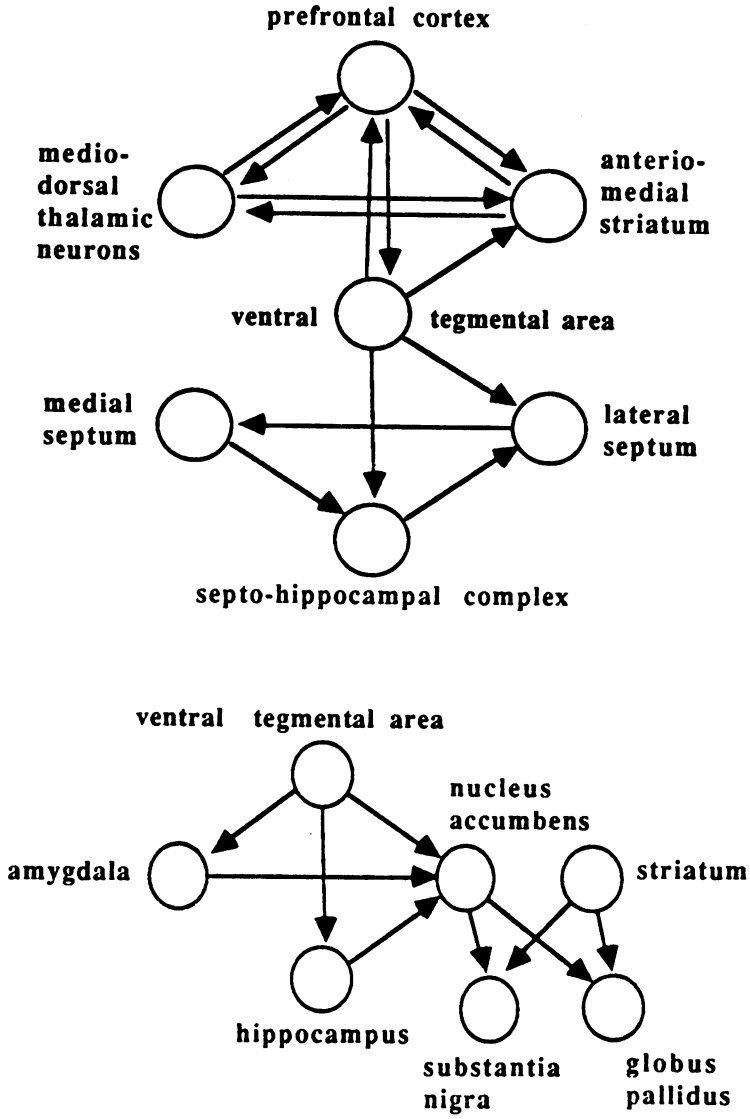

FIG. 3.—Interconnections between the prefrontal cortex, VTA, and other brain regions (redrawn from Simon and Le Moal 1984).

The A9 Syndrome

Selective destruction of the A9 or nigrostriatal pathways produces a syndrome that in some ways is the converse of the A10 syndrome. Complete bilateral degeneration of these pathways produces severe adipsia and aphagia, hypoactivity, difficulties in initiating activity, and loss of exploratory behavior and curiosity (Ungerstedt 1971*a*). When animals with such lesions were injected with apomorphine, a dopamine agonist, they showed increased motility,

sniffing, licking, and biting (Kelly et al. 1975). They soon developed a furious compulsive gnawing, which was far more violent than that seen in unlesioned animals. Some lesioned animals even chewed up their front paws, bit off their fingers, or ate into their own abdomens (Ungerstedt 1971*a*). This reversal of effect by a dopamine agonist supports the conclusion that the aphagic, adipsic, and hypoactive syndrome is due to the interruption of the nigrostriatal dopamine pathways.

Lesions of the Prefrontal Cortex and Motor Hyperactivity

The prefrontal cortex is innervated by dopaminergic pathways from the VTA and by noradrenergic pathways from the locus ceruleus (Ungerstedt, 1971*b;* Lindvall et al. 1978). Radiofrequency lesions to the VTA result in marked motor hyperactivity and high levels of unproductive activity (LeMoal et al. 1969, 1975, 1977*a;* Stinus et al. 1977; Tassin et al. 1978; Sessions et al. 1980). The degree of hyperactivity is related to the degree of decrease of dopamine in the prefrontal cortex ($r = -0.82$) (Tassin et al. 1978); for example, an 80% decrease in the dopamine of the frontal cortex resulted in an 800% increase in motor hyperactivity (Tassin et al. 1978). Like ADDH in children, the motor hyperactivity was decreased by chronic d-amphetamine treatment (Stinus et al. 1977; Sessions et al. 1980). Lesions of the medial frontal cortex induced by injection of a dopamine analogue, 6-hydroxydopamine (6-OHDA) also induce motor hyperactivity (Pycock et al. 1980*a,* 1980*b*). This finding suggests that the mesocortico-frontal dopamine neurons exert an inhibitory control on locomotor behavior (Glowinski 1981; Bernardi et al. 1982; Glowinski et al. 1984), a conclusion that is further verified by the observation that the cells of the anteromedial frontal cortex are inhibited by the microiontophoretic application of dopamine (Bunney and Aghajanian 1976). By contrast, the dopamine neurons projecting to the nucleus accumbens stimulate motor activity (Costall and Naylor 1975). The locomotor hyperactivity produced by d-amphetamine in normal rats is inhibited by injection of haloperidol into the nucleus accumbens but not by injection into the nucleus caudatus (Pijenburg et al. 1975). These observations indicate the important role of the mesocortical dopamine systems in motor hyperactivity.

Injection of 6-OHDA into neonatal rats produces a marked depletion of brain dopamine. Such animals show an ADDH-like syndrome characterized by development of motor hyperactivity and learning and attentional defects (Shaywitz et al. 1976*a,* 1976*b,* 1978; Eastgate et al. 1978; Erinoff et al. 1979; Thieme et al. 1980; Miller et al. 1981). At intermediate doses of 6-OHDA the motor hyperactivity subsides as the animals grow older, although the cognitive defects persist into adulthood, as is the case in human ADDH (Weis et al. 1971; Bellak 1979). At higher doses of 6-OHDA the hyperactivity persists throughout adulthood (Erinoff et al. 1979; Miller et al. 1981). In some studies (Shaywitz et al. 1976*a,* 1978) but not others (Eastgate et al. 1978; Thieme et al. 1980) stimulants have reduced the hyperactivity in lesioned animals. On the basis of the failure of amphetamines to significantly improve the hyperactivity and learning and attentional defects, Thieme et al. (1980) suggested that the selective lesion

of meso-frontal DA pathways is a better model of childhood ADD than is a more generalized destruction of DA pathways.

As in TS, there is also a significantly reduced turnover of HVA in the cerebrospinal fluid of ADDH children (Shaywitz et al. 1975).

Lesions of the Prefrontal Cortex and Cognitive Defects

The prefrontal cortex and anterior striatum are critical in learning new tasks. Simon et al. (1986) investigated the role in learning of the A10 dopamine neurons projecting to the prefrontal cortex. By means of repetitive trials a group of 15 rats were taught a task until they reached a defined level of achievement. This required an average of 147 trials. Six of the rats received an injection of a nontoxic material into the area of the A10 dopaminergic neurons in the ventral tegmental area; after injection only 70 trials were required for the rats to relearn the task. Nine of the rats were injected with 6-OHDA. These rats required 313 trials to relearn the task. Before the injection the average number of errors in the last 60 trials was 4.7 for all the rats. After the injections, the control rats averaged only 5.1 errors, whereas the injected rats averaged 19.6 errors. Examination of the brains of the rats after the lesions showed that the dopamine content of the frontal cortex had been decreased 69%, that of the nucleus accumbens 85%, and that of the anterior part of the striatum 73%.

Similar effects on learning have been reported in monkeys (Brozoski et al. 1979), following treatments that depleted dopamine in the prefrontal cortex by as much as 87%. The defects could be reversed with L-dopa or small doses of apomorphine, which stimulates postsynaptic dopamine receptors. It is intriguing that clonidine, a noradrenergic agonist that effectively treats both the tics and attentional defects in some TS patients, also improved the performance of the lesioned monkeys. Ablative lesions of the dorso-lateral prefrontal cortex in monkeys result in profound defects in recent memory, learning, and retention (Markowitsch and Pritzel 1977). When rats, cats, and monkeys are compared, the latter show the most severe defects and also have the greatest mass of fronto-limbic connections (Markowitsch and Pritzel 1977). Significant cognitive defects also occur following prefrontal lesions in man (see below).

Activation of the Mesocortical Dopaminergic Neurons by Stress

Stress markedly enhances the utilization of dopamine in the prefrontal cortex (Thierry et al. 1976; Lavielle et al. 1979; Bannon and Roth 1983). There is a moderate increase in the cingular cortex and nucleus accumbens but no increase in the other limbic structures, such as the olfactory tubercle, septum, amygdala, or the striatum. The increase in dopamine breakdown produced in the VTA is apparently due to release of dopamine from the dendrites. This activation is inhibited by benzodiazepines, which enhance gamma-aminobutyric acid (GABA) activity (Fadda et al. 1978; Lavielle et al. 1979). The genetic background affects the degree of stress-produced activation of prefrontal dopamine. When two strains of mice were subjected to stress, the strain that had a naturally high level of emotionality showed a significantly greater stress-produced activation of prefrontal dopamine (Hervé et al. 1979; Glowinski 1981)

than did the control strain. The former strain also had a less well-developed noradrenergic input from the locus coeruleus, an area that plays a role in the regulation of mesocortical-frontal dopamine neurons.

Animals treated with constant doses of amphetamines show a progressive enhancement or sensitization of stereotypic behaviors and locomotion (Klawans and Margolin 1975). Stress, in the form of tail pressure, can sensitize animals to these effects of amphetamines and vice versa, suggesting that stress and amphetamines are interchangeable in their ability to produce sensitization (Antelman et al. 1980). In humans acute psychotic episodes can be precipitated by stress in schizophrenics (Roberts 1977) and cause a relapse of amphetamine psychosis in abstinent individuals during remission. Stimulants may produce their psychotogenic actions by imitating the effects of stress (Post 1975).

These results suggest that the mesocortical dopaminergic pathways may play a critical role in the regulation of emotional stress (Thierry et al. 1976). Disinhibition of these pathways could account for the poor tolerance of stress exhibited by TS patients.

The Frontal Dopamine System and Response to Neuroleptics

Haloperiodol produces a greater increase in the dopamine turnover in the frontal cortex than it does in the striatum or tuberculum olfactorium (Laduron et al. 1977). After chronic treatment, tolerance to this effect develops in the striatum and tuberculum olfactorium, but the increased turnover persists in the frontal cortex. These results have suggested that the primary site of action of the antipsychotic effect of neuroleptics may be in the frontal cortex.

Other Aspects of Frontal Lobe Lesions

In object-discrimination tests monkeys with frontal lobe lesions show an increased tendency to prefer any novel object over a tried, familiar one (Nauta 1971). Mothers of TS and ADD children often complain that their children will demand a new toy, then tire of it immediately and want something new. In the so-called go–no go test (Dabrowska 1972; Drewe 1975), the animal must not only learn to respond to a particular signal but also withhold response to another signal that randomly alternates with the first. Animals with frontal lobe lesions score more errors of commission than do controls (Iversen and Mishkin 1970). Such errors of commission are also common in ADD children (McClure and Gordon 1984). In delayed-alteration tests, animals with frontal lobe lesions tend to perseverate in a particular choice despite the poor reward.

Lesions of the Septum and the Hyperresponse Syndrome with Perseveration

Suppression of food reward has the following two effects on rat behavior: (1) an initial behavioral activation consisting of increased attempts to obtain a food reward and (2) eventual extinction of this increased behavior. Dopaminergic lesions of the lateral septum of the limbic system result in an increase in the initial behavioral activation and in a striking persistence of this behavior, i.e., in perseveration or decreased extinction of the behavior (Simon and LeMoal 1984); this response has been termed the hyperresponse syndrome (Isaacson

1974; Gage et al. 1978). The septal-hippocampal pathways have also been implicated in the generation of anxiety (Gray 1982).

Septal Lesions and Polydipsia

When rats are intermittently deprived of food, they show an increased intake of water. This is termed schedule-induced polydipsia. Such polydipsia is markedly increased following electrolytic (Harvey and Hunt 1964; Donovick and Burright 1968) or 6-OHDA (Taghzouti et al. 1985*b*) lesions of the lateral septum. Such lesions also increase behavioral reactivity and have an energizing effect in situations involving frustrative nonreward. We have observed that many TS patients have polydipsia. Similar observations were made by Moldofsky et al. (1974).

Lesions of the Limbic System and Sleep Disturbance

Sleep disturbances have been noted following destruction of limbic-area structures such as the anterior raphe nuclei (Carli and Zanchette 1965; Jouvet 1969, 1972). Fibers from this area pass through the VTA (Ungerstedt 1971*b*). Radiofrequency lesions of the VTA result in significantly decreased frequency of wakefulness, in slow-wave sleep and desynchronized sleep, and in significantly increased duration of wakefulness and slow-wave sleep (LeMoal et al. 1975). Similar results have been noted in cats (Carli and Zanchetti 1965).

Vocalizations and the Limbic System

Although vocalizations have never been produced by stimulation of the hippocampus or amygdala in humans, in both cats and monkeys stimulation of these and other limbic and hypothalamic areas produces vocalizations (Devinsky 1983). The cingulate gyrus is of particular interest. It connects to both cortical and limbic structures known to be involved in vocalizations and receives dopamine projections from the VTA; and lesions of it are sometimes successful in relieving obsessive-compulsive symptoms (Devinsky 1983).

Lesions of the Nucleus Accumbens and Defective Spatial Discrimination

The nucleus accumbens has both extrapyramidal (striatal) and limbic characteristics. It has been termed the filter (Costa 1977) or interface between the limbic and motor systems (Mogenson et al. 1980). 6-OHDA lesions of the nucleus accumbens result in defects in spatial discrimination characterized by an inability of rats to choose the arm of the T-test opposite to the one that had previously been rewarded (Simon and LeMoal 1984; Taghzouti et al. 1985*a*, 1985*c*). When the food reward is withheld, again the lesioned animals perseverated in choosing the arm that last contained the food.

Motor and Vocal Tics and Stereotyped Behaviors

The major diagnostic criteria of TS are the presence of motor and vocal tics and of stereotyped behaviors. Correlates of these behaviors in animal models are excess gnawing, biting, licking, sniffing, and repetitive head and limb movements. These stereotyped behaviors can be induced by the administration of

amphetamines or apomorphine, both dopaminergic agonists. Lesions in various parts of the brain indicate that these stereotyped behaviors are due to the excessive stimulation of mesolimbic-mesocortical (A10) and nigrostriatal (A9) dopaminergic neurons (Kelly and Iversen 1976; Iversen and Koob 1977). As in the case of motor hyperactivity, 6-OHDA lesions in various structures—such as the VTA, caudate putamen, globus pallidus, substantia nigra, nucleus accumbens, tuberculum olfactorium, and central amygdaloid nucleus—can either enhance or abolish the stereotyped behaviors, depending on the extent of the lesion (Costall et al. 1977). Stereotyped behaviors and hyperactivity can also be caused by injection of dopamine into various mesolimbic areas (Costall and Naylor 1975). The induction of hyperactivity by means of direct application of dopamine suggests that the lesions of the VTA that result in hyperactivity and stereotyped movements do so by means of the compensatory increase in dopaminergic activity of other neurons (see below).

The Isolation Syndrome

Behavior in many animals, especially rodents, is altered by isolation. Although increased aggressive behavior is especially prominent, other behaviors include increased vocalizations, increased muscular tone, increased general reactivity, increased locomotor activity, hyperirritability, compulsive aggressive behavior, increased inner tension, decreased learning ability, defective memory consolidation, and deviated sexual activity (Valzelli 1973). The similarity of many of these changes to the behavior spectrum in TS is especially intriguing in view of the observation that in isolated rats there is a decrease in dopamine turnover in the mesocortical pathways and a compensatory increase in dopaminergic activity in the mesostriatal and mesolimbic pathways (Blanc et al. 1980; Glowinski et al. 1984).

Anger, Rage, Hypersexuality, and Limbic Lesions

The classical studies of Klüver and Bucy (1939) showed that bilateral temporal lobectomy in monkeys produced docility, hyperactivity, hypersexuality, and oral tendencies (putting objects in the mouth and licking, swallowing, sniffing, and salivation). This stimulated many investigations of the effect of temporal lobe lesions on behavior. Similar results are seen in humans, except that docility may be replaced by aggressiveness (Terzian and Ore 1955). The results have varied depending on the location of the lesions and the animal used (Wood 1958). Lesions of the lateral amygdaloid nucleus tend to produce hypersexuality whereas lesions of the basal medial or central amygdaloid nucleus often produce aggressive behavior and rage attacks at the slightest of stimuli. Lesions of one nuclear area appear to result in disinhibition of other nuclei.

HUMAN STUDIES

The Frontal Lobe Syndrome

The prefrontal cortex, with all its rich connections to the limbic system and other sensory inputs, acts as the "cortical modulator of the limbic system"

(Nauta 1971). Information on the function of the frontal lobe in man can be obtained from studies of behaviors in individuals with various brain lesions. When the frontal lobes are destroyed, a specific frontal lobe syndrome develops (Luria 1980), characterized by lack of spontaneous behavior and inability to carry out purposive, goal-directed actions. These individuals are unable to produce stable plans and become inactive and aspontaneous. They are unable to evaluate their attempts, are not critical of their behavior, cannot control their actions, and continue to perform automatic actions that had long ceased to be meaningful, without any attempt at correction. In patients with the severest forms of this syndrome, the critical attitude toward their own actions and the conscious evaluation of their behavior are impaired. Their thinking tends to be concrete. Attempts to follow actions of others may result in stereotyped movements, echopraxiac actions, and perseverations. One patient with a massive frontal lobe tumor, when asked to draw a circle, filled the page with circles. Attention is easily distracted by irrelevant stimuli, and there is difficulty organizing attention and keeping it focused on a definite plan. There may also be uncontrollable impulsive actions performed without either realization of the probable results or concern with the consequences. In short, there is a lack of drive coupled with impulsivity and inability to critically evaluate one's own behavior. Although patients with frontal lobe lesions have no problems with simple arithmetic problems such as addition and subtraction, important disturbances begin to appear when the task extends beyond the limits of simple habitual operations to requiring a series of successive, mutually dependent components that constitute a complex intellectual activity, such as carrying over the tens column or performing operations requiring several steps (Luria 1980). They will often attempt to simplify a task by carrying out only one fragment of it instead of the whole process. A disturbance of the blood supply to the anterior zones of the limbic regions leads to marked defects in memory. There are also inappropriate sexual behavior, changes in emotion and affect, an inability to screen out multiple visual stimuli (Torrey and Peterson 1974), and disinhibition leading to markedly abnormal behavior associated with outbursts of irritability and aggression (Mesulam 1986*b*).

Recent studies by Lhermitte and co-workers (Lhermitte 1986; Lhermitte et al. 1986; Mesulam 1986*b*) have emphasized a syndrome in patients with frontal lobe lesions, a syndrome that consists of imitation behavior in repeating the gestures of the examiner, utilization behavior in compulsive grasping and utilization of objects in the environment, and stereotypy, disinterestedness, and indifference with regard to social rules. Although there are many similarities between imitation behavior and echopraxia, Lhermitte et al. (1986) felt that there was more intellectual input in imitation behavior. However, the etiologies are also different. The imitation behavior results form neoplastic masses whereas the postulated lesion in TS is a selective defect in mesocortical dopamine pathways. It has been suggested that the parietal lobe tends to create links of direct impulsive dependence between the subject and stimuli from the outside world and that this is inhibited and modulated by the frontal lobe. As

such, impulsiveness would be an expected result of a defect in frontal lobe dopamine pathways.

Lesions from Encephalitis Lethargica

In relationship to the etiology of TS, Devinsky (1983) has pointed out that OCB and tics are especially common among postencephalitic Parkinson disease patients who have oculogyric crises. The vocalizations are similar to those seen in TS, consisting of grunts, barks, squawks, and cursing. Emotional thoughts often precipitate the oculogyric crises; and during such attacks these individuals may be overwhelmed with "forbidden thoughts" and anxiety. The lesions in postencephalitic Parkinson disease are diffuse and involve not only the pars reticulata of the substantia nigra but the VTA, periaqueductal grey, and midbrain tegmentum. These TS-like symptoms are not present in idiopathic Parkinson disease, in which the neuronal degeneration is limited to the pars compacta of the substantia nigra (Schwab et al. 1951). Tumors involving the VTA and nearby structures result in behavioral changes consisting of mood swings, irritability, lack of motivation, attentional difficulties, fluctuating hyper- and hypoactivity, and auditory hallucinations (Trimble and Cummings 1981). These findings are consistent with the notion that VTA is a primary site of pathology in TS.

Dopamine, Serotonin, and Norepinephrine Metabolism in TS

HVA, a principal metabolite of dopamine in the cerebrospinal fluid, is often used as an index of dopaminergic activity in the brain. The baseline and accumulated levels of cerebrospinal fluid HVA in TS patients is below the level in controls (Cohen et al. 1978, 1979; Butler et al. 1979). These findings are consistent with either a primary loss of dopaminergic cells resulting in hypersensitive postsynaptic receptors or a primary hypersensitivity causing feedback inhibition of the dopaminergic cell (Devinsky 1983). I would add a third possibility—namely, a primary loss of dopaminergic cells in the mesocortical pathway leading to a hypersensitivity of mesostriatal and mesolimbic dopamine neurons. Abnormalities of serotonin metabolism, consisting of decreased cerebrospinal fluid levels of 5-hydroindolacetic acid (Cohen et al. 1978, 1979; Butler et al. 1979), and abnormalities of norepinephrine metabolism, consisting of increased cerebrospinal fluid 3-methoxy-4 hydroxyphenylglycol, have been reported. The major involvement of dopamine neurons in the VTA has been described above. In addition, the VTA has descending fibers to the midbrain tegmentum, to the serotonergic raphae nuclei and central grey, and to the noradrenergic locus ceruleus and receives ascending fibers from the raphi nuclei and locus ceruleus (Beckstead et al. 1979). Thus, a lesion of the VTA could affect all three types of neurotransmitters.

Amphetamine Psychosis

Chronic excess use of amphetamines results in amphetamine psychosis, which is indistinguishable from paranoid schizophrenia. (Connell 1958; Angrist

and Gershon 1970; Costa and Garattini 1970; Griffith et al. 1972). Amphetamine releases dopamine and norepinephrine from their storage sites and prevents their inactivation by reuptake (Costa and Garattini 1970). Chronic administration of d-amphetamines in guinea pigs results in increased sensitivity to d-amphetamine and in apomorphine-induced stereotyped behavior (Klawans and Margolin 1975).

Schizophrenia and the Limbic Dopamine System

Numerous researchers have suggested that schizophrenia can be explained as a defect in the dopamine neurons, especially those of the limbic system (Matthysee 1973; Stevens 1973; Hökfelt et al. 1974; Owen et al. 1978). I believe such a statement is equally or even more true for TS.

Cocaine Psychosis

As discussed above, the *TS* gene results in a wide spectrum of psychiatric disorders. In an essay on cocaine psychosis, Post (1975) pointed out that depending on the dosage and chronicity of administration, cocaine can produce euphoria, dysphoria, schizophreniform psychosis, hyperactivity, insomnia, hypersexuality, aggressiveness, inattention, hallucinations, and stereotyped behaviors. This drug affects dopamine metabolism and the activity of other neurotransmitters, including norepinephrine and serotonin. Post's contention was that the same neurotransmitter substances may be involved in multiple psychiatric syndromes, in contrast with the one illness/one transmitter models. In TS, in addition to dopamine both norepinephrine and serotonin have been implicated (Cohen et al. 1978, 1979; Butler et al. 1979). TS may be presenting us with the same lesson—namely, that a wide spectrum of disorders can arise from a common defect. Incidentally, cocaine can markedly exacerbate the symptoms of TS patients (Mesulam 1986*a*).

GABA and Baclofen in TS

GABA is the major inhibitory neurotransmitter of the central nervous system. The VTA receives major GABA synaptic inputs from the nucleus accumbens (Wolf et al. 1978; Yim and Mogenson 1980). Both dopaminergic and nondopaminergic neurons are inhibited by these interactions. Injection of picrotoxin, a GABA-receptor antagonist, into the VTA results in increased locomotor activity, owing to the disinhibition of dopaminergic neurons (Yim and Mogenson 1980). The primary neurons affected appear to be those from the VTA to the nucleus accumbens, since prior administration of spiroperidol, a dopamine-receptor antagonist, attenuates the effect. If dopaminergic hyperactivity in the VTA is playing a role in TS, then GABAergic drugs should be of benefit. I have observed that some TS patients show a moderate improvement in symptoms when treated with baclofen, a GABA-B-receptor agonist (Bowery et al. 1980; Hill and Bowery 1980).

Carbamazepine for the Behavioral Disorders in TS

If severe behavioral problems in TS do not respond to the control of motor and vocal tics with haloperidol, pimozide, or clonidine, or to the control of ADDH with methylphenidate, or to a trial of a tricyclic antidepressant such as imipramine, we have found that carbamazepine (Tegretal) is often effective, even in subjects with a normal EEG. Carbamazepine has well-documented action on limbic-system structures (Post and Uhde 1984). In its inhibition of amygdala-kindled focal seizures, carbamazepine ranks first in relative potency among the commonly used anticonvulsants (Albright and Burnham 1980). It has also been found to be quite effective in the treatment of manic-depressive disorder (Post and Uhde 1984).

PET Scanning

In TS patients PET scanning with ^{18}F-fluorodeoxyglucose has shown possible hypermetabolism of portions of the frontal and temporal lobes (Chase et al. 1984). When dopamine D_2 receptors were analyzed with ^{11}C 3-N methylspiperone, there was no evidence of either dopaminergic hypersensitivity of the caudate or serotonergic-receptor abnormalities (Singer et al. 1985). This finding does not rule out either the hypofunctioning of mesostriatal dopamine pathways or dopamine receptor hypersensitivity in noncaudate regions, possibilities that have been proposed in the present paper. These relatively small brain-stem areas are beyond the sensitivity of the PET scanner.

An Imbalance of Mesencephalic Dopamine Systems in TS

In TS, the response of the motor and vocal tics to haloperidol suggests that the problem is one of dopaminergic hyperactivity or hypersensitivity. However, the attentional and cognitive problems, which respond to dopaminergic agonists, and the TS symptoms consistent with the frontal lobe syndrome suggest that, in other areas, there is dopaminergic hypoactivity. Specific lesions of various dopamine and norepinephrine neurons in the mesencephalon can produce hypersensitivity of other dopamine neurons (Pycock et al. 1980*a*, 1980*b*; Glowinski et al. 1984). As an example, destruction of dopamine terminals within the medial prefrontal cortex of the rat produces enhanced dopamine turnover and utilization in the striatal and limbic subcortical pathways and decreased 5-hydroxytryptamine, GABA, glutamate decarboxylase, and choline acetyltransferase in the basal ganglia (Pycock et al. 1980*a*, 1980*b*). These lesions also produce motor hyperactivity and potentiate the stereotypic effects of amphetamines (Singer et al. 1985). These data indicate that the frontal cortex dopamine systems can regulate various subcortical neurotransmitter mechanisms.

This imbalance can also be documented physiologically. Animals that have been held in isolation for several weeks develop the "isolation syndrome," which has many behavioral features in common with TS (see above). In these animals dopamine utilization is reduced in the prefrontal cortex and, con-

versely, is increased in the nucleus accumbens and striatum (Blane et al. 1980; Glowinski et al. 1984). These findings demonstrate that the various branches of the mesolimbic, mesostriatal, and mesocortical dopamine systems can be regulated independently and that hypoactivity of the mesocortical dopamine neurons may result in hypersensitivity of the subcortical mesostriatal and mesolimbic pathways.

The data reviewed in this article are consistent with the notion that the primary abnormality in TS is a genetic defect in either (1) the mesocortical or prefrontal dopamine pathways, resulting in a disinhibition of prefrontal lobe functions and a compensatory increase in mesostriatal and mesolimbic dopamine pathways or (2) both mesocortical and mesolimbic dopamine pathways, causing disinhibition of prefrontal, striatal, and limbic systems and resulting in dopamine hypoactivity in some areas and compensatory dopamine hypersensitivity in others. Table 2 summarizes the symptoms of TS that appear to have analogies to behavioral changes in both animal and human systems.

Focusing on the specific area of the brain and type of neurons that may be involved in TS helps to clarify thinking about the possible basic genetic mechanism causing this disorder. If the primary defect is an abnormality in mesocortical or mesencephalic dopaminergic neurons but not in basal ganglion dopamine neurons, then a global genetic defect such as abnormality in dopamine metabolic enzymes or receptors seems unlikely. One possible candidate would be an abnormality in a neuromodulating neuropeptide capable of selectively affecting a subset of the dopamine neurons. The most likely candidates are those that are known to modulate dopaminergic neurons. These include cholecystokinin-8-sulfate (Fuxe et al. 1980; Hökfelt et al. 1980; Skirboll et al. 1981), substance P (Stinus et al. 1978; Bannon et al. 1983; Kelley et al. 1985), neurotensin (Nemeroff et al. 1980; Kalivas et al. 1983), B-endorphin (Stinus et al. 1980; Sandyk 1985), dynorphin (Haber et al. 1986), and gastrin-releasing hormone (bombesin) (Schultz et al. 1984). Space does not allow a detailed examination of these, except to note that dynorphin has been reported to be virtually absent in the globus pallidus of one TS patient, whose clinical picture suggests that he could be a homozygote (Haber et al. 1986). As has been proposed for β-endorphin in schizophrenia (de Wied 1979), the selectiveness of the defect may be due to abnormalities in the degradation enzymes rather than in the neuropeptide itself. Elsewhere we have reported a balanced translocation cosegregating with TS in a large family, a finding suggesting that the gene in this family might be at 18q22.1 (Comings et al. 1986*a*, 1986*b;* Donnai 1987). Of considerable interest is the fact that the gastrin-releasing-hormone (bombesin) gene is in this area (Lebacq-Verheyden et al. 1987; Naylor et al. 1987). Injection of bombesin into the ventricles of rats causes motor hyperactivity, stereotyped behaviors, and hypersexuality (Pert et al. 1980; Merali et al. 1983; Schultz et al. 1984).

Therapeutic Implications of Dopamine Hypo- and Hyperactivity

Several investigators have commented on the possibility that in schizophrenia the positive symptoms (auditory and visual hallucinations, paranoia) may

TABLE 2

CORRELATION BETWEEN TS AND EXPERIMENTAL ABNORMALITIES OF MESENCEPHALIC DOPAMINERGIC NEURONS

TS	Experimental
A. LeMoal Syndrome (Lesions of VTA Dopaminergic Neurons)	
Motor hyperactivity	Motor hyperactivity
ADD	Attentional defects
Learning disorders	Cognitive defects
Perseveration (lack of extinction)	Perseveration
Ease of frustration, short temper	Hyperresponse syndrome
Rigidity (have to have things one's own way)	Impairment of behavioral flexibility
Poor response to stress	Poor response to stress
Sleep disturbance	Sleep disturbance
B. Defects in Mesocortical-Prefrontal Dopaminergic Neurons and the Frontal Lobe Syndrome	
Motor hyperactivity	Motor hyperactivity
Cognitive defects	Cognitive defects
Impulsivity	Impulsivity
Echopraxia	Echopraxia
Perserveration	Perseveration
Difficulties with math	Difficulties with math
Inability to take responsibility for one's own actions	Inability to take responsibility for one's own actions
Inappropriate sexual behavior	Inappropriate sexual behavior
Inability to screen out multiple visual stimuli	Inability to screen out multiple visual stimuli
Poor retention	Poor memory
C. Stimulation of Mesencephalic Dopaminergic Neurons with Amphetamine and Apomorphine	
Sniffing	Sniffing
Licking, biting	Licking, biting
Repetitive head and limb movements	Repetitive head and limb movements
Self-stimulation	Self-stimulation
Paranoia	Paranoia
Auditory hallucinations	Auditory hallucinations
Poor response to stress	Poor response to stress
D. Defects in Mesolimbic Dopaminergic Neurons	
Exhibitionism	Abnormal sexual behavior
Sexual touching (coprolalia?)	Abnormal sexual behavior
Rage reactions	Rage reactions

be due to dopaminergic hyperactivity whereas the negative symptoms may be due to dopaminergic hypoactivity (Chouinard and Jones 1978; Haracz, 1982; Glowinski et al. 1984). Even though L-dopa excerbates the symptoms of schizophrenia, chronic administration of L-dopa with neuroleptics has been of therapeutic value for negative symptoms (Chouinard and Jones 1978; Haracz 1982). Treatment of TS presents a similar paradox. Most TS cases begin with ADD/H and then develop motor and vocal tics several years later (Comings and Comings 1984, 1987*a*). The fact that some children with ADD/H develop tics after

treatment with stimulant medication has been taken as a proscription against the use of such medications in ADDH children with a family history of TS (Lowe et al. 1982). Our alternative view is that this is the expected natural history of the approximately one-third of ADD/H cases that are due to a *TS* gene. In two separate series (Comings and Comings 1984, 1987*a*) the duration of time between the onset of ADD/H and the onset of tics has been longer in ADD/H children who received methylphenidate than in those who did not. This finding and the above considerations raise the possibility that if the primary defect in TS is hypofunctioning of the mesocortical dopaminergic pathways with subsequent compensatory development of hypersensitivity of subcortical dopamine pathways leading to motor and vocal tics, then treatment with dopamine agonists in the ADD/H stage might prevent or delay onset of tics. L-Dopa has been reported to be effective in the treatment of some TS patients (Friedhoff 1982; Kondo and Noura 1982). These are obviously complex issues (Price et al. 1986). In our practice approximately one-third of TS patients require treatment with both haloperidol (or pimozide) and methylphenidate for optimal control of their symptoms. *If* the present hypothesis is correct, the judicious treatment, with dopamine agonists, of ADD/H secondary to a *TS* gene *might* prevent both the secondary hypersensitization of subcortical dopamine pathways and the development of the full spectrum of TS symptoms. If such were the case, then the development of a specific genetic test for the early detection of symptomatic children carrying the TS mutation would be particularly important.

Serotonin and TS

The emphasis in the present review has been on dopamine. Since serotonin is an inhibitory neurotransmitter, virtually all of the above discussion could equally apply to a central serotonin deficiency in TS, one causing a disinhibition of the limbic system and a compensatory hypersensitivity of some dopaminergic neurons. This will be discussed in more detail elsewhere.

Why Are the Disinhibition Disorders So Common?

The limbic system has been characterized as controlling the four F's—fight, flight, feeding, and sexual activity (Pribram 1971). It has not escaped my attention that the reason many of the disorders described in the present series of papers are so common is that they are (1) genetic, (2) dominant, and (3) result in disinhibition, especially of sexual activity.

REFERENCES

Albright, P. S., and W. M. Burnham. 1980. Development of a new pharmacological seizure model: effects of anticonvulsants on cortical- and amygdala-kindled seizures in the rat. Epilepsia **2**:681–689.

Angrist, B. M., and S. Gershon. 1970. The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. Biol. Psychiatry **2**:95–107.

Antelman, S. M., A. J. Eichler, C. A. Black, and D. Kocan. 1980. Interchangeability of stress and amphetamine in sensitization. Science **207**:329–331.

Bannon, M. J., P. J. Elliott, J. E. Alpert, M. Goedert, S. D. Iversen, and L. L. Iversen. 1983. Role of endogenous substance P in stress-induced activation of mesocortical dopamine neurons. Nature **306**:791–792.

Bannon, M. J., and H. Roth. 1983. Pharmacology of mesocortical dopamine neurons. Pharmacol. Rev. **35**:53–68.

Beckstead, R. M., V. B. Domesick, and W. J. H. Nauta. 1979. Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Res. **175**:191–217.

Bellak, L. 1979. Psychiatric aspects of minimal brain dysfunction in adults. Grune & Stratton, New York.

Bernardi, G., E. Cherubini, M. G. Marciani, N. Mercuri, and P. Stanzione. 1982. Responses of intracellularly recorded cortical neurons to the iontophoretic application of dopamine. Brain Res. **245**:267–274.

Blanc, G., D. Hervé, H. Simon, A. Lisoprawski, J. Glowinski, and J. P. Tassin. 1980. Response to stress of mesocortico-frontal dopaminergic neurons in rats after long-term isolation. Nature **284**:265–267.

Bowery, N. G., D. R. Hill, A. L. Hudson, A. Duble, D. N. Middlemiss, J. Shaw, and M. Turnbull. 1980. (-) Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. Nature **283**:92–94.

Brozoski, T. J., R. M. Brown, M. E. Rosvol, and P. S. Godman. 1979. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science **205**:929–931.

Bunney, B. S., and G. K. Aghajanian. 1976. Dopamine and norepinephrine innervated cells in the rat prefrontal cortex: pharmacological differentiation using microiontophoretic techniques. Life Sci. **19**:1783–1792.

Butler, I. J., S. H. Doslow, W. E. Siefert, R. M. Caprolai, and H. S. Singer. 1979. Biogenic amine metabolism in Tourette syndrome. Ann. Neurol. **6**:37–39.

Carli, G., and Z. Zanchetti. 1965. A study of pontine lesions suppressing deep sleep in the cat. Arch. Ital. Biol. **103**:751–788.

Chase, T. N., N. L. Foster, P. Fedio, R. Brooks, L. Mansi, R. Kessler, and G. D. Chiro. 1984. Gilles de la Tourette syndrome: studies with the fluoride-18-labeled fluorodeoxyglucose positron emission tomographic method. Ann. Neurol. (Suppl.) **15**:S175.

Chouinard, G., and B. D. Jones. 1978. Schizophrenia as a dopamine-deficiency disease. Lancet **2**:99–100.

Cohen, D. J., B. A. Shaywitz, B. Caparulo, J. G. Young, and M. B. Bower, Jr. 1978. Chronic multiple tics of Gilles de la Tourette's disease: CSF acid monamine metabolites after probenecid administration. Arch. Gen. Psychiatry **35**:245–250.

Cohen, D. J., B. A. Shaywitz, J. G. Young, B. Caparulo, and M. B. Bowers, Jr. 1979. Central biogenic amine metabolism in children with the syndrome of chronic multiple tics of Gilles de la Tourette. J. Am. Acad. Child Psychiatry **18**:320–341.

Comings, D. E., and B. G. Comings. 1984. Tourette's syndrome and attention deficit disorder with hyperactivity: are they genetically related? J. Am. Acad. Child Psychiatry **23**:138–146.

———. 1987*a*. A controlled study of Tourette syndrome. I. Attention-deficit disorder, learning disorders, and school problems. Am. J. Hum. Genet. **41**:701–741.

———. 1987*b*. A controlled study of Tourette syndrome. IV. Obsessions, compulsions, and schizoid behaviors. Am. J. Hum. Genet. **41**:782–803.

———. 1987*c*. Hereditary agoraphobia with panic attacks and hereditary obsessive-compulsive behavior in relatives of patients with Tourette syndrome. Br. J. Psychiatry **148** (in press).

Comings, D. E., B. G. Comings, E. J. Devor, and C. R. Cloninger. 1984. Detection of major gene for Gilles de la Tourette syndrome. Am. J. Hum. Genet. **36**:586–600.

Comings, D. E., B. G. Comings, G. Dietz, D. Muhleman, T. A. Okada, F. Sarinana, R.

Simmer, R. Sparkes, M. Crist, and D. Stock. 1986*a*. Linkage studies in Tourette syndrome. Am. J. Hum. Genet. **39**:A151.

Comings, D. E., B. G. Comings, G. Dietz, D. Muhleman, T. A. Okada, F. Sarinana, R. Simmer, and D. Stock. 1986*b*. Evidence the Tourette syndrome gene is at 18q22.1. Paper presented at the International Congress of Human Genetics, Berlin, September 22–26.

Connell, P. H. 1958. Amphetamine psychosis. Chapman & Hall, London.

Costa, E. 1977. Morphine, amphetamine and non-cataleptogenic neuroleptics. Pp. 557–563 *in* E. Costa and G. L. Gessa, eds. 1977. Nonstriatal dopaminergic neurons. Raven, New York.

Costa, E., and S. Garattini, eds. 1970. Amphetamines and related compounds, Raven, New York.

Coastall, B., C. D. Mardsen, R. J. Naylor, and C. J. Pycock. 1977. Stereotyped behavior patterns and hyperactivity induced by amphetamine and apomorphine after discrete 6-hydroxydopamine lesions of extrapyramidal and mesolimbic nuclei. Brain Res. **123**:89–111.

Costall, B., and R. J. Naylor. 1975. The behavioral effects of dopamine applied intracerebrally to areas of the mesolimbic system. Eur. J. Pharmacol. **32**:87–92.

Crese, I., D. R. Burt, and S. H. Snyder. 1976. Dopamine receptor binding predicts clinical and pharmacological potencies of anti-schizophrenic drugs. Science **192**:481–483.

Crowe, R. R., R. Noyes, D. L. Pauls, and D. Slymen. 1983. A family study of panic disorder. Arch. Gen. Psychiatry **40**:1065–1069.

Dabrowska, J. 1972. On the mechanism of go–no go symmetrically reinforced tasks in dogs. Acta Neurobiol. Exp. (Warsz.) **32**:345–359.

Devinsky, O. 1983. Neuroanatomy of Gilles de la Tourette's syndrome. Arch. Neurol. **40**:508–514.

de Wied, D. 1979. Schizophrenia as an inborn error in the degradation of B-endorphin—a hypothesis. Trends Neurosci. **2**:79–82.

Diagnostic and statistical manual of mental disorders. 3d ed. (DSM-III). 1980. American Psychiatric Association, Washington, D.C.

Diagnostic and statistical manual of mental disorders. 3d ed, revised. (DSM III R). 1987. American Psychiatric Association, Washington, D.C.

Donnai, D. 1987. Gene localization in Tourette syndrome. Lancet **1**:351–354.

Donovick, P. J., and R. G. Burright. 1968. Water consumption of rats with septal lesions following two days of water deprivation. Physiol. Behav. **3**:285–288.

Drewe, E. A. 1975. Go–no go learning after frontal lobe lesions in humans. Cortex **11**:8–16.

Eastgate, S. M., J. J. Wright, and J. S. Werry. 1978. Behavioral effects of methylphenidate in 6-hydroxydopamine-treated neonatal rats. Psychopharmacology **58**:157–158.

Erinoff, L., R. G. MacPhail, A. Heller, and L. S. Seiden. 1979. Age-dependent effects of 6-hydroxydopamine on locomotor activity in the rat. Brain Res. **164**:195–205.

Fadda, F., A. Argiolas, M. E. Melis, A. M. Tissari, P. L. Onali, and G. L. Gessa. 1978. Stress-induced increase in 3,4-dihydroxyphenacetic acid (DOPAC) levels in the cerebral cortex and in n. accumbens: reversal by diazepam. Life Sci. **23**:2219–2224.

Fallon, J. H., and R. Y. Moore. Catecholamine innervation of the basal forebrain. IV. Topography of the DA projection to the basal forebrain and neostriatum. J. Comp. Neurol. **180**:545–580.

Feinberg, M., and B. J. Carroll. 1979. Effects of dopamine agonists and antagonists in Tourette's disease. Arch. Gen. Psychiatry **36**:979–985.

Friedhoff, A. J. 1982. Receptor maturation in pathogenesis and treatment of Tourette syndrome. Pp. 133–140 *in* A. J. Friedhoff and T. N. Chase, eds. Gilles de la Tourette syndrome. Raven, New York.

Fuxe, K., K. Andersson, V. Locatelli, L.F. Agnati, T. Hökfelt, L. Skirboll, and V. Mutt. 1980. Cholecystokinin peptides produce marked reduction of dopamine turn-

over in discrete areas in the rat brain following intraventricular injection. Eur. J. Pharmacol. **67**:329–331.

Gage, F. H., D. C. Olton, and G. L. Murphy. 1978. Septal hyperactivity: a multivariate analysis of neuroanatomical correlates. Physiol. Psychol. **6**:314–318.

Galey, D., R. Jafford, and M. LeMoal. 1976. Spontaneous alternation disturbance after lesions of the ventral mesencephalic tegmentum in the rat. Neurosci. Lett. **3**:65–69.

———. 1979. Alteration behavior, spatial discrimination, and reversal after electrocoagulation of the ventral mesencephalic tegmentum in the rat. Behav. Neurol. Biol. **26**:81–88.

Galey, D., H. Simon, and M. LeMoal. 1977. Behavioral effects of lesions in the A10 dopaminergic area of the rat. Brain Res. **124**:83–97.

Gershon, E. S., J. Hamovit, J. J. Guroff, E. Dibble, J. F. Leckman, W. Sceery, S. D. Targum, J. I. Nurnberger, L. R. Goldin, and W. E. Bunney. 1982. A family study of schizoaffective, bipolar I, bipolar II, unipolar and normal control probands. Arch. Gen. Psychiatry **39**:1157–1165.

Glowinski, J. 1981. Present knowledge on the properties of the mesocortical-frontal dopaminergic neurons. Pp. 15–28 *in* S. Matthysee. Psychiatry and the biology of the human brain: a symposium dedicated to Seymour S. Kety. Elsevier North-Holland, New York.

Glowinski, J., J. P. Tassin, and A. M. Thierry. 1984. The mesocortical-prefrontal dopaminergic neurons. Trends Neurosci. **7**:415–418.

Goodwin, D. W. 1979. Alcoholism and heredity. Arch. Gen. Psychiatry **36**:57–61.

Gray, A. J. 1982. The neuropsychology of anxiety: an enquiry into the function of the septo-hippocampal system. Oxford University Press, Oxford.

Griffith, J. D., J. Cavanaugh, J. Held, and J. A. Oates. 1972. Dextro-amphetamine. Arch. Gen. Psychiatry **26**:97–101.

Haber, S. N., N. W. Kowall, J. P. Vonsattel, E. D. Bird, and E. P. Richardson. 1986. Gilles de la Tourette's syndrome: a postmortem neuropathological and immunohistochemical study. J. Neurol. Sci. **75**:225–241.

Haracz, J. L. 1982. The dopamine hypothesis: an overview of studies with schizophrenic patients. Schizophr. Bull. **8**:438–468.

Harvey, J. A., and H. F. Hunt. 1964. Effect of septal lesion on thirst in the rat as indicated by water consumption and operant responding for water reward. J. Comp. Physiol. Psychol. **59**:49–56.

Hervé, D., H. Simon, G. Blanc, A. Lisoprawski, M. LeMoal, J. Glowinski, and J. P. Tassin. 1979. Increased utilization of dopamine in the nucleus accumbens but not in the central cortex after dorsal raphe lesions in the rat. Neurosci. Lett. **15**:127–133.

Hill, D. R., and N. G. Bowery. 1980. ^{3}H-baclofen and ^{3}H-GABA bind to bicuculline-insensitive $GABA_B$ sites in rat brain. Nature **290**:149–152.

Hökfelt, T., A. Ljungdahl, K. Fuxe, and O. Johansson. 1974. Dopamine nerve terminals in the rat limbic cortex: aspects of the dopamine hypothesis of schizophrenia. Science **184**:177–179.

Hökfelt, T., L. Skirboll, J. F. Rehfeld, M. Goldstein, K. Markey, and O. Dann. 1980. A subpopulation of mesencephalic dopamine neurons projecting to the limbic areas contains a cholecystokinin-like peptide: evidence from immunochemistry combined with retrograde tracing. Neuroscience **5**:2093–2124.

Isaacson, R. L. 1974. The limbic system. Plenum, New York.

Iversen, S. D., and G. F. Koob. 1977. Behavioral implication of dopaminergic neurons in the mesencephalic system. Adv. Biochem. Psychopharmacol. **16**:209–214.

Iversen, S. D., and M. Mishkin. 1970. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp. Brain Res. **11**:376–386.

Jouvet, M. 1969. Biogenic amines and the states of sleep. Science **163**:31–41.

———. 1972. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle. Ergeb. Physiol. **64**:165–307.

Kalivas, P. W., S. K. Burgess, C. B. Nemeroff, and A. J. Prange, Jr. 1983. Behavioral

and neurochemical effects of neurotensin microinjection into the ventral tegmental area of the rat. Neuroscience **8**:495–505.

Kelley, A. E., M. Cador, and L. Stinus. 1985. Behavioral analysis of the effect of substance P injected into the ventral mesencephalon on investigatory and spontaneous motor behavior in the rat. Psychopharmacology **85**:37–46.

Kelly, P. H., and S. D. Iversen. 1976. Selective 6-OHDA induced destruction of mesolimbic dopamine neurons: abolition of psychostimulant-induced locomotor activity in rats. Eur. J. Pharmacol. **40**:45–56.

Kelly, P. H., P. Seviour, and S. D. Iversen. 1975. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. **94**:507–522.

Kendler, K. S., A. M. Gruenberg, and J. S. Strauss. 1982. An independent analysis of the Copenhagen sample of the Danish adoption study of schizophrenia. IV. The relationship between major depressive disorder and schizophrenia. Arch. Gen. Psychiatry **39**:639–642.

Kety, S. S. 1983. Mental illness in the biological and adoptive relatives of schizophrenic adoptees: findings relevant to genetic and environmental factors in etiology. Am. J. Psychiatry **140**:720–727.

Klawans, H. L., and D. I. Margolin. 1975. Amphetamine-induced dopaminergic hypersensitivity in guinea pigs. Arch. Gen. Psychiatry **32**:725–732.

Klüver, H., and P. C. Bucy. 1939. Preliminary analysis of functions of the temporal lobes in monkeys. Arch. Neurol. Psychiatry **42**:979–1000.

Kondo, K., and Y. Nomura. 1982. Tourette syndrome in Japan: etiologic considerations based on associated factors and familial clustering. Pp. 271–276 *in* A. J. Friedhoff and T. N. Chase, eds. Gilles de la Tourette syndrome. Raven, New York.

Laduron, P., K. DeBie, and J. Leysen. 1977. Specific effect of haloperidol on dopamine turnover in the frontal cortex. Nauyn-Schmiedebergs Arch. Pharmacol. **296**:183–185.

Lavielle, S., J. P. Tassin, A. M. Thierry, G. Blanc, D. Herve, C. Barthelemy, and J. Glowinski. 1979. Blockade by benzodiazepines of the selective high increase in DA turnover induced by stress in mesocortical dopaminergic neurons of the rat. Brain Res. **168**:585–594.

Lebacq-Verheyden, A.-M., V. Bertness, I. Kirsch, G. F. Hollis, O. W. McBride, and J. Battey. 1987. Human gastrin-releasing peptide gene maps to chromosome band 18q21. Somatic Cell Mol. Genet. **13**:81–86.

LeMoal, M., B. Cardo, and L. Stinus. 1969. Influence of ventral mesencephalic lesions on various spontaneous and conditioned behaviors in the rat. Physiol. Behav. **4**:567–572.

LeMoal, M., D. Galey, and B. Cardo. 1975. Behavioral effects of local injections of 6-hydroxydopamine in the medial ventral tegmentum in the rat: possible role of the mesolimbic dopaminergic system. Brain Res. **88**:190–194.

LeMoal, M., L. Stinus, and D. Galey. 1976. Radiofrequency lesion of the ventral mesencephalic tegmentum: neurological and behavioral considerations. Exp. Neurol. **50**:521–535.

LeMoal, M., L. Stinus, H. Simon, J. P. Tassin, A. M. Thierry, G. Blanc, J. Glowinski, and B. Cardo. 1977*a*. Behavioral effects of a lesion in the ventral mesencephalic tegmentum: evidence for involvement of A10 dopaminergic neurons. Pp. 237–245 *in* E. Costa and G. L. Gessa, eds. Nonstriated dopaminergic neurons. Vol. **16** of Advances in Biochemical Psychopharmacology. Raven, New York.

LeMoal, M. L., R. Jaffard, and D. Galey. 1977*b*. Effects of the ventral mesencephalic tegmentum lesion on the spontaneous alteration behavior and on spatial discrimination and reversal learning in T-maze. Brain Res. **127**:383.

Lhermitte, F. 1986. Human autonomy and the frontal lobe. Part II. Patient behavior in complex and social situations: the "environmental dependency syndrome." Ann. Neurol. **19**:335–343.

Lhermitte, F., B. Pillon, and M. Serdaru. 1986. Human autonomy and the frontal lobe.

Part I. Imitation and utilization behavior: a neuropsychological study of 75 patients. Ann. Neurol. **19**:326–334.

Lindvall, O., A. Bjorklund, and I. Divac. 1978. Organization of catecholamine neurons projecting to the frontal cortex in the rat. Brain Res. **142**:1–24.

Livingston, K. E., and O. Hornykiewicz. 1978. Limbic mechanisms: the continuing evolution of the limbic system concept. Plenum, New York.

Lowe, T. L., D. J. Cohen, J. Detlor, M. W. Kremenitzer, and B. A. Shaywitz. 1982. Stimulant medications precipitate Tourette's syndrome. JAMA **247**:1729–1731.

Luria, A. R. 1980. Higher cortical functions in man. 2d ed. Basic Books, New York.

McClure, F. D., and M. Gordon. 1984. Performances of disturbed hyperactive and nonhyperactive children on an objective measure of hyperactivity. Abnorm. Child Psychol. **12**:561–571.

McGue, M., I. I. Gottesman, and D. C. Rao. 1986. The analysis of schizophrenic family data. Behav. Genet. **16**:75–87.

MacLean, P. D. 1949. Psychosomatic disease and the "visceral brain." Psychosom. Med. **11**:338–353.

———. 1952. Some psychiatric implications of physiological studies on the frontotemporal portion of the limbic system (visceral brain). Electroencephalogr. Clin. Neurophysiol. **4**:407–418.

———. 1954. The limbic system and its hippocampal formation. J. Neurosurg. **11**:29–43.

Markowitsch, H. J., and M. Pritzel. 1977. Comparative analysis of prefrontal learning functions in rats, cats, and monkeys. Psychol. Bull. **84**:817–837.

Matthysee, S. 1973. Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? Fed. Proc. **32**:200–205.

Merali, Z., S. Johnston, and S. Zalcman. 1983. Bombesin-induced behavioral changes: antagonism by neuroleptics. Peptides **4**:693–697.

Mesulam, M.-M. 1986*a*. Cocaine and Tourette's syndrome. New Engl. J. Med. **315**:398.

Mesulam, M.-M. 1986*b*. Frontal cortex and behavior. Ann. Neurol. **19**:320–325.

Miller, F. E., T. G. Heffner, C. Kotabe, and L. S. Seiden. 1981. Magnitude and duration of hyperactivity following neonatal 6-hydroxydopamine in relationship to the extent of brain dopamine depletion. Brain Res. **229**:123–132.

Mogenson, G. J., D. J. Jones, and C. Y. Yim. 1980. From motivation to action: functional interface between the limbic system and the motor system. Prog. Neurobiol. **14**:69–97.

Moldofsky, H., C. Tullis, and R. Lamon. 1974. Multiple tic syndrome (Gilles de la Tourette's syndrome). J. Nerv. Ment. Dis. **15**:282–292.

Nauta, W. J. H. 1971. The problem of the frontal lobe: a reinterpretation. J. Psychiatr. Res. **8**:167–187.

Naylor, S. L., A. Y. Sakaguchi, E. Spindel, and W. W. Chin. 1987. Human gastrin-releasing peptide gene is located on chromosome 18. Somatic Cell Mol. Genet. **13**:87–91.

Nemeroff, C. B., D. Luttinger, and A. J. Prangle, Jr. 1980. Neurotensin: central nervous system effects of a neuropeptide. Trends Neurosci. **3**:212–215.

Owen, F., T. J. Crow, M. Poulter, A. J. Cross, A. Longden, and C. J. Riley. 1978. Increased dopamine-receptor sensitivity in schizophrenia. Lancet **2**:223–225.

Papez, J. W. 1937. A proposed mechanism of emotion. Arch. Neurol. Psychiatry **38**:725–743.

Pauls, D. L., and J. F. Leckman. 1986. The inheritance of Gilles de la Tourette syndrome and associated behaviors: evidence for autosomal dominant transmission. New Engl. J. Med. **315**:993–997.

Pert, A., T. W. Moody, C. B. Pert, L. A. Dewald, and J. Rivier. 1980. Bombesin: receptor distribution in brain and effects on nociception and locomotor activity. Brain Res. **193**:209–220.

Pijenburg, A. J. J., W. M. M. Hönig, and J. M. Van Rossum. 1975. Inhibition of

D-amphetamine-induced locomotor activity by injection of haloperidol into the nucleus accumbens of the rat. Psychopharmacologia **41**:87–95.

Post, R. M. 1975. Cocaine psychoses: a continuum model. Am. J. Psychiatry **132**:225–231.

Post, R. M., and T. W. Uhde. 1984. Carbamazepine in the treatment of mood and anxiety disorders: implications for limbic system mechanisms. Pp. 134–147 *in* M. R. Trimble and E. Zarifian, eds. Psychopharmacology of the limbic system. Oxford University Press, Oxford.

Pribram, K. H. 1971. Languages of the brain—experimental paradoxes and principles in neuropsychology. Prentice-Hall, Englewood Cliffs, NJ.

Price, R. A., J. F. Leckman, D. L. Pauls, D. J. Cohen, and K. K. Kidd. 1986. Gilles de la Tourette's syndrome: tics and central nervous system stimulants in twins and nontwins. Neurology **36**:232–237.

Pycock, C. J., C. J. Carter, and R. W. Kerwin. 1980*a*. Effect of 6-hydroxydopamine lesions of the medial prefrontal cortex on neurotransmitter systems in subcortical sites in the rat. J. Neurochem. **34**:91–99.

Pycock, C. J., R. W. Kerwin, and C. J. Carter. 1980*b*. Effect of lesion on cortical dopamine terminals on subcortical dopamine receptors in rats. Nature **286**:74–77.

Roberts, E. 1977. Gamma aminobutyric acid system and schizophrenia. Pp. 347–357 *in* E. Usdin, D. A. Hamburg, and J. D. Barchas, eds. Neuroregulators and psychiatric disorders. Oxford University Press, London.

Rosenthal, D. 1980. Genetic aspects of schizophrenia. Pp. 3–33 *in* Handbook of biological psychiatry: part III. Marcel Dekker, New York.

Sandyk, R. 1985. The opiate system in Gilles de la Tourette's syndrome. Neurology **35**:449–450.

Schuckit, M. A. 1986. Genetic and clinical implications of alcoholism and affective disorder. Am. J. Psychiatry **143**:140–147.

Schultz, D. W., P. W. Kalivas, C. B. Nemeroff, and A. J. Prange, Jr. 1984. Bombesin-induced locomotor hyperactivity in evaluation of the involvement of the mesolimbic dopamine system. Brain Res. **304**:377–382.

Schwab, R. S., H. D. Fabing, and J. S. Prichard. 1951. Psychiatric symptoms and syndromes in Parkinson's disease. Am. J. Psychiatry **107**:901–907.

Sessions, G. R., J. L. Meyerhoff, G. J. Kant, and G. F. Koob. 1980. Effects of lesions of the ventral medial tegmentum on locomotor activity, biogenic amines and response to amphetamine in rats. Pharmacol. Biochem. Behav. **12**:603–608.

Shaywitz, B. A., D. J. Cohen, and M. B. Bowers, Jr. 1975. CSF amine metabolites in children with minimal brain dysfunction (MBD)—evidence for alteration of brain dopamine. Pediatr. Res. **9**:385A.

Shaywitz, B. A., J. H. Klopper, and J. W. Gordon. 1978. Methylphenidate in 6-hydroxydopamine-treated developing rat pups. Arch. Neurol. **35**:463–469.

Shaywitz, B. A., J. H. Klopper, R. D. Yager, and J. W. Gordon. 1976*a*. Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine. Nature **261**:153–155.

Shaywitz, B. A., R. D. Yager, and J. H. Klopper. 1976*b*. Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. Science **191**:305–307.

Simon, H., and M. LeMoal. 1984. Mesencephalic dopaminergic neurons: functional role. Pp. 293–307 *in* Catecholamines: neuropharmacology and central nervous system—theoretical aspects. Alan R. Liss, New York.

Simon, H., B. Scatton, and M. LeMoal. 1986. Dopaminergic A10 neurons are involved in cognitive function. Nature **286**:150–151.

Singer, H. S., D. F. Wong, M. Tiemeyer, P. Whitehouse, and H. N. Wagner. 1985. Pathophysiology of Tourette syndrome: a positron emission tomographic and postmortem analysis. Ann. Neurol. **18**:416.

Skirboll, L. R., A. A. Grace, D. W. Hommer, J. Rehfeld, M. Goldstein, T. Hökfelt, and B. S. Bunney. 1981. Peptide-monoamine coexistence: studies of the actions of cholecystokinin-like peptides on the electrical activity of midbrain dopamine neurons. Neuroscience **6**:2111–2124.

Stevens, J. R. 1973. An anatomy of schizophrenia. Arch. Gen. Psychiatry **29**:177–189.

Stinus, L., A. E. Kelley, and S. D. Iversen. 1978. Increased spontaneous activity following substance P infusion into A10 dopaminergic area. Nature **276**:616–618.

Stinus, L., O. Gaffori, H. Simon, and M. LeMoal. 1977. Small doses of apomorphine and chronic administration of D-amphetamine reduce locomotor hyperactivity produced by radiofrequency lesion of dopaminergic A10 neurons area. Biol. Psychiatry **12**:719–732.

Stinus, L., G. F. Koob, N. Ling, F. E. Bloom, and M. LeMoal. 1980. Locomotor activation induced by infusion of endorphins into the ventral tegmental area: evidence for opiate interactions. Proc. Natl. Acad. Sci. USA **77**:2323–2327.

Stinus, L., L. Simon, and M. LeMoal. 1978. Disappearance of hoarding and disorganization of eating behavior after ventral mesencephalic tegmentum lesion in rats. J. Comp. Physiol. Psychol. **92**:289–296.

Taghzouti, K., A. Louilot, T. P. Herman, M. LeMoal, and H. Simon. 1985*a*. Alteration behavior, spatial discrimination, and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat. Behav. Neurol. Biol. **44**:354–363.

Taghzouti, K., H. Simon, R. Dantzer, and M. LeMoal. 1985*b*. The effect of 6-OHDA lesions of the lateral septum on schedule-induced polydipsia. Behav. Brain Res. **15**:1–8.

Taghzouti, K., H. Simon, A. Louilet, J. P. Herman, and M. LeMoal. 1985*c*. Behavioral study after local injection of 6-hydroxydopamine into the nucleus accumbens in the rat. Brain Res. **344**:9–20.

Tassin, J. P., L. Stinus, H. Simon, G. Blanc, A. M. Thiery, M. LeMoal, B. Cardo, and J. Glowinski. 1978. Relationship between the locomotor hyperactivity induced by A10 lesions and destruction of the frontocortical dopaminergic innervation in the rat. Brain Res. **141**:267–281.

Terzian, H., and G. G. Ore. 1955. Syndrome of Klüver and Bucy reproduced in man by bilateral removal of the temporal lobes. Neurology **5**:373–380.

Thieme, R. E., H. Dijkstra, and J. C. Stoff. 1980. An evaluation of the young-lesioned rat as an animal model for minimal brain dysfunction (MBD). Psychopharmacology **67**:165–169.

Thierry, A. M., J. P. Tassin, G. Blanc, and J. Glowinski. 1976. Selective activation of the mesocortical dopaminergic system by stress. Nature **263**:242–244.

Torrey, E. F., and M. R. Peterson. 1974. Schizophrenia and the limbic system. Lancet **2**:942–946.

Trimble, M. R. 1984. Limbic system disorders in man. Pp. 110–124 *in* M. R. Trimble and E. Zarifian, eds. Psychopharmacology of the limbic system. Oxford University Press, Oxford.

Trimble, M. R., and J. L. Cummings. 1981. Neuropsychiatric disturbances following brain stem lesions. Br. J. Psychiatry **138**:56–59.

Trimble, M. R., and E. Zarifian, eds. 1984. Psychopharmacology of the limbic system. Oxford University Press, Oxford.

Ungerstedt, U. 1971*a*. Aphagia and adipsia after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. Acta Physiol. Scand. [Suppl.] **367**:95–121.

———. 1971*b*. Stereotaxic mapping of the monamine pathway in the rat brain. Acta Physiol. Scand. **367**:1–48.

Valzelli, L. 1973. The "isolation syndrome" in mice. Psychopharmacologia **31**:305–320.

Weis, G., M. Klaus, J. Werry, V. Douglas, and E. Nemeth. 1971. Studies on the hyperactive child. VIII. Five-year follow-up. Arch. Gen. Psychiatry **24**:409–414.

Weissman, M. M., E. S. Gershon, K. K. Kidd, B. A. Prussoff, J. F. Leckman, E. Dibble, J. Hamovit, D. Thompson, D. L. Pauls, and J. J. Guroff. 1984. Psychiatric disorders in the relatives of probands with affective disorders. Arch. Gen. Psychiatry **41**:13–21.

Wolf, P., H.-R. Olpe, D. Avrith, and H. L. Haas. 1978. GABAergic inhibition of neurons in the ventral tegmental area. Experientia **34**:73–74.

Wood, C. D. 1958. Behavioral changes following discrete lesions of temporal lobe structures. Neurology **8**:215–220.

Yim, C. Y., and G. J. Mogenson. 1980. Electrophysiological studies of neurons in the VTA of Tsai. Brain Res. **181**:301–313.