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The Psychobiology of Mania

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regularly respond or, as described below, may develop a manic episode during treatment.' The differential development of hypomania in bipolar compared to unipolar individuals treated with L-Dopa is also described below in the discussion of the "switch" into mania. Bipolar patients have also been reported to have a modest antidepressant response to l-tryptophan administration, while unipolar patients were unchanged,' suggesting that one factor in the conflictual reports of the antidepressant efficacy of this drug may represent patient population selection factors.

Clinical, Behavioral, and Cognitive Features of Mania

The clinical phenomena of the manic state have been described in detail in Kraepelin's monograph and in other texts. The typical acute manic state is generally clinically differentiable from other psychiatric syndromes on the basis of a marked increase in motor and verbal hyperactivity, interpersonal provocativeness and manipulation, distractibility, a clear sensorium, and, most often, elation and grandiosity. A state of labile affect, with a breakthrough of depressive or dysphoric affect with irritability and anger, is frequently observed. Sleeplessness, impaired judgment, and an increase in aggressive and sexual impulses are also common. In some instances, delusional thinking, hallucinations, and confusion may develop, particularly as the course of the manic state peaks or becomes prolonged, with minimal interruption for sleep or nutritional input.

Despite the apparent distinctiveness of the typical manic state, it has been suggested that frequent misdiagnosis, especially of individuals exhibiting labile affect or psychotic phenomena associated with mania, may account for the reported decreased incidence of manic-depressive illness in the United States in the last several decades.' A diminished interest in patient classification, and the efficacy of phenothiazine drugs in the treatment of most acute psychoses including both mania and schizophrenia, contributed to this problem. In contrast, the advent of lithium treatment has recently been accompanied by an apparent increase in the reported incidence of mania, and reawakened interest in the phenomenology of manic behavior.

Behavioral Changes During Mania. The symptoms occurring during manic episodes in one hundred patients were cataloged by Winokur, Clayton, and Reich. While euphoria was present in almost all patients, the affective state was generally highly labile, with over two-thirds of the patients exhibiting depression. Reactive irritability and hostility were prominent, and the greatest degree of motor hyperactivity was associated with the most severe' thought disorder and the presence of delusions.

It has recently been demonstrated that some manic symptoms are common to all patients, but that others are characteristic of only some manic individuals on the basis of data from a rating scale permitting continuous quantitative behavioral monitoring of manic patients. The behavioral

symptoms that correlated most clearly with severity of mania (as rated independently by psychiatrists), and that were found on a factor analysis of the scale to represent a single, dominant "core-mania factor" in all patients, included such symptoms as increased motor activity, increased speech, distractibility, poor judgment, diminished impulse control, anger, irritability, argumentativeness, and interpersonal demandingness.' Mania-scale items reflecting euphoria and grandiosity were less uniformly found elevated in all manic patients, and were found to be inversely correlated with items reflecting paranoid and destructive behavior, which were elevated in only some individuals. On the basis that similar ratings on the core-mania items were found in both the 70 percent of patients with high elation-grandiosity ratings but low paranoid-destructive ratings, and in the 30 percent of patients with low elation-grandiosity but high paranoid-destructive ratings, it was suggested that these differences might provide a quantitative definition of two subgroups of manic patients for evaluation in pharmacologic and other clinical studies.

Psychotic Phenomena During Mania. Delusions occur in approximately one-half of all patients with mania, while hallucinations occur in one-third of manic episodes. Ideas of reference, persecutory, and other paranoid thinking, passivity delusions, symbolism, and confusion may also occur during mania.'' The presence of a thought disorder on Bannister's grid test for schizophrenic thought disorder did not differentiate manic from

schizophrenic individuals. Significant numbers of typically manic patients (15 to 30 percent) also exhibit Schneider's first-rank symptoms of schizophrenia. These recent observations, emphasizing the difficulties in diagnostic evaluations based on Bleulerian and other symptom-related schema, have raised questions concerning the validity of earlier genetically oriented studies that suggested a clear separation between affective disorders and schizophrenia.

The occurrence of borderland conditions between mania and schizophrenic excitement was recognized by Meyer, Bleuler and Brill and has sometimes been designated as "schizoid-manic" states. Separate "delusional" and "delirious" types of mania were differentiated by Kraepelin from "acute" mania. Some of these patients exhibited clinical pictures as diverse as recurrent excited paranoid states and severely disorganized, generally undifferentiated psychotic states with some manic features. They were grouped together primarily on the basis of their tendency to remit and to not lead to chronic personality disorganization as in schizophrenia. Similar, more modern data on remission rates have been interpreted both to indicate a more favorable prognosis for schizophrenia (when these episodes have been included in the statistics of acute schizophrenic episodes) and an equally favorable prognosis for such "schizoaffective" patients or other manic patients with psychotic phenomena, compared to manic patients without delusions or hallucinations.

Differentiating manic-psychotic individuals from schizophrenic individuals may be difficult and in some instances impossible in the midst of an acute episode. Longitudinal analysis or reconstruction of the symptomatologic picture in the earliest stages of the psychotic episode may reveal typical manic behavior that was superseded by a less well differentiated psychosis. In addition, it has been suggested that factors other than symptoms may be of help, in that manic episodes are more likely to occur in individuals with a history of periodic recurrences who have symptom-free intervals associated with successful interpersonal relationships. During the acute episode, and particularly at its onset, purposeful hyperactivity and interpersonal involvement in provocative, manipulative ways are far more characteristic of typical manic behavior than the more panicky, disorganized activity associated with the primarily autistic preoccupations of the schizophrenic individual. Fluctuating or fleeting delusional and hallucinatory phenomena are also more characteristic of mania than is a fixed, detailed delusional structure.

Nonetheless, criteria based on symptoms alone may be insufficient to reliably discriminate in all cases between patients with affective disorders, schizoaffective states, and schizophrenia. One discriminant function analysis of clinical phenomena in a large number of patients with affective psychoses and schizophrenia concluded that the distribution of patients was not different from a normal distribution, a finding in agreement with other data

from a variety of sources, including some genetic studies, and suggesting a continuum of clinical states from schizophrenia through schizoaffective disorders to the affective disorders. It is not clear yet whether psychotic phenomena during mania represent a secondary form of response to an especially severe or prolonged manic state or whether they only occur in certain individuals separately predisposed to a disorganization or disintegration of the personality.

Depressive Affect During Mania. Although depression and mania have often been considered "opposite" affective states, the existence of bursts of depressive affect and thought content during manic episodes has occasionally been described, f More recently, quantitative evidence of the coexistence of a depressive affect during manic episodes has been provided, verifying that most manic patients do exhibit some depressive affect during manic episodes and that depression is not negatively correlated with total mania ratings or even with rated elation in manic patients over an eight-hour assessment period. This suggests that most manic patients manifest to some degree a combined manic-depressive picture, although fewer manic individuals (20 to 35 percent) have the more marked "mixed" or labile state described in some patients by Kraepelin.

In addition to frank depressive thought content and depressive affect, a more diffuse dysphoria together with irritability and expressed hostility has

been observed in some manic patients exhibiting mood lability. Manic episodes are immediately preceded by depressive periods in over 50 percent of patients, and one study also documented the occurrence of depressive episodes within one month subsequent to a manic period in over half of the patients studied.

Cognition During Mania

Reduced attention span, distractibility, impaired memory, and flight of ideas with clang associations, rhyming, and punning have all been described as clinical phenomena during mania. However, there have been only a few quantitative investigations of cognitive characteristics of the manic state. In a study of time sense, hypomanic individuals grossly overestimated a three-second time interval. Reaction time to auditory and light stimuli was found to be reduced and to be inversely correlated with severity of mania in several studies. Impaired self-judgment of symptomatologic behavior was observed in hypomanic and manic individuals compared to the results in the same individuals when non-manic.

Verbal learning was found to be impaired in individuals studied while manic compared both to non-manic periods in the same patients and to normal controls. Increased errors of commission and a substitution of intrusive responses for those presented were characteristics differentiating

impaired learning during mania from the learning impairment seen in depressed and psychotomimetic drug-treated patients. In particular, it appeared that the co-occurrence of a deficit in word associations, representing a shift to less common and more idiosyncratic associative responses, which were also less stable, was an important con-tributary factor to the learning impairment. The number of idiosyncratic associations (defined according to the expected frequency of responses found in age- and sex-matched normals) was over 50 percent greater than the number in schizophrenic patients and several-fold greater when compared to patients with spontaneous, and drug-induced, psychotic symptoms.

This thinking disorder in manic patients was fully reversible in that verbal associations reverted to normal patterns after manic behavior ceased. Of particular note was the occurrence of some identical idiosyncratic associations in subsequent manic periods, suggesting that some cognitive aspects of the individual are differentially available to him during this altered behavioral state. While it has recently been demonstrated in studies with drugs that learning which occurs in a particular state (e.g., information acquired during alcohol administration) is less retrievable in a nondrug state, and vice versa, evidence concerning the possibility that clinical-psychiatric states may represent the emergence of cognitive or behavioral patterns distinct from those usually available to the individual has not previously been presented.

Hypomania versus Mania. Hypomania has generally been considered as simply a milder form of mania, involving, in particular, less impairment of judgment and self-control and an absence of psychotic symptoms. While hypomanic symptoms are seen in patients who exhibit full-blown manic episodes, particularly toward the end of a treated episode, hypomanic behavior also occurs in other individuals who never develop mania, e.g., the cyclothymic or "bipolar II" patient group. Such individuals, who do not require specific treatment for spontaneously developing periods of increased activity or euphoria, or who develop such symptoms during treatment with antidepressant drugs, have been found to manifest some differences from both typical bipolar ("bipolar I") patients and also from unipolar-depressed patients. While their visual cortical evoked response patterns and their high incidence of antidepressant responses to lithium suggested that these patients most resembled the bipolar group, their responses to other drugs, some biologic measures, including monoamine oxidase and 17-hydroxy-corticosteroid determinations, and some clinical features, suggested either a closer resemblance to the unipolar group or the possibility that they represented a discrete subgroup of patients separate from other depressed individuals. A particularly high incidence of suicide was found in this group in one study.

A prolonged, sometimes chronic or even fixed "characterologic" hypomanic state may be seen in some individuals who maintain a state of

increased activity with diminished sleep, extraversion, often youthful appearance (frequently enhanced by acting and even dressing somewhat like a little boy or girl), and cheerful optimism. While sometimes adaptive and successful as a life style, difficulties arise from over-involvement and distractibility, labile affect, and replacement of ready conversation and wit by flamboyant argumentativeness; these personality characteristics often lead to marital and occupational instability. Many of these individuals may never experience a full-blown manic-psychotic episode.

Biologic Phenomena Associated With the Steady-State of Mania

Mania is associated with profound alterations in many bodily functions that complicate the assessment of the specificity and significance of other biologic changes observed during the manic state. In addition, the tolerance of the manic individual for the restrictions of a controlled study is limited, and greater than normal variance in experimental results related to impaired cooperation, if not outright sabotage, may occur. Some of the changes occurring as concomitants of mania that may contribute to some of the biologic (and possibly psychologic) alterations observed include: (a) markedly increased physical activity; (b) decreased sleep; (c) altered dietary intake, ranging from hyper-bulimia to the more common reduced intake resulting from distractibility and excess activity; (d) similar extremes of fluid intake and urinary output, ranging from marked increases to states of

dehydration; and (e) associated alterations in gastrointestinal function.

Mania and Catecholamines. Evidence from pioneering studies in animals and in man, of drugs capable of altering behavior and mood, suggested that mania might be related to excess activity of central adrenergic neurons. Early investigations of urinary catecholamines had generally indicated elevated norepinephrine and epinephrine excretion in hypomanic and manic patients, especially when manic and depressed phases were compared in cycling patients. However, interpretation of these results is confounded by the preponderant contribution to urinary catecholamines and catecholamine metabolites from the peripheral autonomic nervous system and the adrenal gland rather than the brain, especially since marked alterations in physical activity regularly accompany manic behavior, and physical activity can elevate urinary and even cerebrospinal fluid amines and their metabolites. The relevance of these observations can by no means be dismissed, since catecholamine excretion in disproportionate excess to pedometer-measurement motor activity has been observed in some studies of mania, and one catecholamine metabolite, 3-methoxy, 4-hydroxyphenylglycol (MHPG) has been suggested to yield an estimate of central nervous system catecholamine activity.

More recently, increased urinary dopamine excretion has also been reported in manic patients. While dopamine excretion in urine has been

suggested to be little affected by muscular work, no confirmatory evidence of increased brain dopamine release was obtained from studies of the principal metabolite of dopamine, homovanillic acid (HVA) in the cerebrospinal fluid, since HVA levels have not generally been found to be any higher in manic patients compared to depressed patients or controls. However, one more recent study observed higher cerebrospinal fluid HVA levels during mania, although these levels were not as high as those found to be associated with increased physical and mental activity.

Three-methoxy, 4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine in the brain, was found not to be regularly elevated in the cerebrospinal fluid of manic patients, although a few patients had high levels. It was also demonstrated that physical activity could produce elevations in MHPG, both in cerebrospinal fluid and in urine, further indicating the difficulties in evaluating catecholamine changes in this disorder.

Mania and Indoleamines. Much of the pharmacologic evidence used to implicate catecholamines in affective disorders, such as that based on the effects of MAO inhibitors, tricyclic drugs, and reserpine, has been used to implicate the indoleamines as decreased in depression and possibly, at least in the case of tryptamine, as increased in mania. However, the application of this indirect pharmacological reasoning to mania does not hold well, probably because of the non-specificity of action of the drugs studied.

In direct studies of cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA), this major metabolite of serotonin was found to be decreased during mania in two studies, but slightly increased or not different from control values in other studies. These discrepant results may be related to differences in psychomotor activity in the different patient groups, since CSF 5-HIAA is increased after exercise and after increased physical and mental activity ("simulated mania"). However, in two studies manic patients (as well as depressed patients) were found to respond to the administration of probenecid with a smaller increase in 5-HIAA than in controls.

Also against the theory that an excess of an indoleamine like serotonin might be contributory to manic symptoms is the evidence that methysergide, an indoleamine receptor blocker, was found to be ineffective in treating mania in a controlled, double-blind study by Coppen et al. and in another study by Fieve et al., although several earlier studies had suggested a possible rapid therapeutic effect with this agent. In fact, 1-tryptophan, the amino acid precursor of serotonin, has been shown to have some antimanic action in a small number of patients. The possible contribution of 1-tryptophan's sedative effects to this proposed antimanic action has not yet been evaluated. Thus, the current evidence would be more congruent with a decrease in serotonin or serotonin metabolism during mania than an increase in this or other indoleamines, although the evidence certainly is not conclusive.

Carbohydrate Metabolism in Mania. Glucose tolerance (as measured by the rate of glucose utilization following an intravenously administered glucose load) is higher in patients studied while manic compared to values obtained during remission induced by two weeks of lithium carbonate treatment. The hypoglycemic response to injected insulin is also increased during mania compared to remission values. Since the patients who did not improve with lithium had negligible changes in glucose utilization and insulin sensitivity, these changes were thought to be produced by the change in behavior rather than to represent a pharmacologic effect of lithium. However, several studies in animals and man have indicated that lithium has some anti-insulin effects.

The increased glucose tolerance observed in manic patients is an opposite finding from the decreased glucose tolerance observed in some but not all studies of depressed patients. Again, in contrast to manic patients, insulin sensitivity was decreased in psychotically depressed patients.

Electrolyte and Water Metabolism in Mania. Patients when manic have generally been found to manifest increased urinary volume and increased sodium excretion during mania; elevations in total body water and calculated extracellular fluid space have also been described; however, all studies are not in full agreement.t In investigations using isotope dilution techniques to measure sodium distribution among the different body

compartments, Coppen et al. found that calculated residual sodium was markedly increased in manic patients, and moderately increased in depressed patients, compared to control values from the literature. Residual sodium is thought to represent intracellular plus some bone sodium. Neither extracellular sodium nor the twenty-four-hour exchangeable sodium was significantly changed in their patients. Recovery from mania was associated with a return toward normal residual sodium values. A more recent study did not replicate these findings.

In studies of sodium transport, no difference was found in the rate of transfer of Na and K from plasma to cerebrospinal fluid in manic compared to depressed and normal patients. However, sodium reabsorption from salivary ducts was reduced in both the manic and depressed patients studied by Glen. Several studies have indicated that manic patients appear to excrete a smaller proportion of administered lithium during the initial phase of treatment. Similar lithium retention has been shown experimentally to result from sodium depletion produced by low dietary intake or increased urinary sodium loss. However, it is unlikely that the increased urinary sodium loss observed during mania represents the full explanation for lithium retention during mania. Contrary to the rapid rise in serum lithium levels and increased side effects that follow sodium restriction or diuretic-drug-induced sodium loss, manic patients generally have a remarkable tolerance for lithium and demonstrate lower lithium levels per dose administered and fewer side

effects compared to other patients.

Adrenal Corticosteroids in Mania. Plasma cortisol levels are normal or slightly elevated in manic patients, although diminished diurnal variation in plasma steroid levels has been observed, a change reflecting primarily a diminished reduction in plasma levels in the latter part of the day. Cortisol production rates in hypo-manic patients are normal. While one patient with regular forty-eight-hour cycles between mania and depression had markedly diminished urinary 17-hydroxycorticosteroids during mania, other cycling patients have not exhibited similar patterns, and it appears that individual patients may have either reduced, unchanged, or increased plasma cortisol levels and urinary 17-hydroxycorticosteroid levels during mania. These results suggest that hypomania or mania per se do not result in any regular alteration in corticosteroids, although steroid changes may occur in manic just as in other psychiatric patients in relation to changes in circadian activity or to individually significant stresses resulting from interpersonal conflicts or personality disintegration.

Another adrenal corticosteroid, aldosterone, has been studied in manic patients because of its role in sodium and water metabolism. Although one manic-depressive patient with forty-eight-hour cycles was found to exhibit reduced aldosterone excretion during manic compared to depressed days, two other studies have demonstrated increased urinary aldosterone

excretion and increased aldosterone production rates in manic patients. While these aldosterone changes have been shown to correlate with sodium balance and extracellular fluid shifts, it is also likely that activity, diet, and weight differences in the manic patients may contribute to these results.

Other Biologic Changes During Mania. Tyrosine administration leads to higher and more sustained elevations in plasma tyrosine levels ("impaired tyrosine tolerance") in manic patients compared to normals. Increased urinary adenosine 3, 5' cyclic monophosphate (cyclic AMP) excretion has been reported during mania in some studies but not others. Cyclic AMP excretion is reduced in association with a therapeutic response to lithium. However, cerebrospinal fluid levels of cyclic AMP were not found to be elevated during mania. Serum levels of the muscle enzyme, creatinine phosphokinase, are elevated in some manic individuals, as has also been reported in individuals with schizophrenia, other psychotic states, and certain central nervous system and muscle disorders.

Sleep in Mania. Although sleeplessness is a cardinal feature of mania, manic patients report sleeping well and feeling rested after only a short sleep period. EEG sleep studies have documented a marked reduction in total sleep time and in rapid eye movement sleep time during mania; slow wave sleep is less disturbed. The "switch period" into mania is associated with an abrupt decline in REM sleep in both spontaneous and L-Dopa-induced hypomanic

and manic episodes. In general, drugs that increase functional brain catecholamines (e.g., L-Dopa) or reduce brain indoleamines (e.g., para-chlorophenylalanine) decrease rapid eye movement sleep, while drugs with reverse effects on catecholamines (e.g., alpha-methyl-para-tyrosine) or indoleamines (5-hydroxytryptophan) enhance rapid eye movement sleep.

Behavioral and Biological Changes During the "Switch Process" in Manic-Depressive Cycles

The process of the switch into and out of mania has recently been studied in some detail. These transitional periods are of special theoretical interest because of their potential for revealing contributory behavioral and biochemical events prior to the development of nonspecific changes secondary to altered activity, diet, sleep deprivation, and other aspects of the steady-state of mania.

Spontaneous Switches into Mania

A review of the behavioral phenomena observed in ten spontaneous switches from depression into mania and seven switches from mania into depression revealed several characteristic features of each of these transition times. Most switches into mania were preceded by a depressive period of moderate intensity characterized by withdrawn, self-seclusive behavior with reduced speech and motor activity accompanied by drowsiness. Immediately

prior to the development of manic symptoms, all of the patients manifested a brief “normal” period with the sudden appearance of increased environmental and interpersonal interests and appropriate speech and activity.

The buildup of the manic phase following the normal period ranged from a few hours to a few days in duration. Three frequently observed phases were characteristic. Phase one was the first day of the onset of mania and was typified by a sudden marked increase in talking and physical activity. The second phase was characterized by incessant speech and shouting, constant movement, poor judgment, sexual preoccupations, the demanding of staff attention, anger, aggressiveness, and, at times, elation, and laughing. Phase three was characterized by grandiose and sometimes paranoid psychotic ideation, flight of ideas including rhyming and punning, and inability to accept limits.

A number of psychologically significant events occurred prior to the switches into mania. Discussion of discharge plans from the hospital appeared to be the environmental event that occurred most commonly prior to mania in this study. It is a clinical impression that home visits from the hospital, along with impending discharge, are frequently occasions of considerable psychological stress to bipolar patients. However, obtaining passes and discharge-planning status may also simply signifying increasing

activity prior to the onset of a manic episode, rather than representing an active precipitant of mania.

In another study, the question of precipitating events prior to manic episodes was assessed by evaluating the number of pre-mania stresses that were severe, unusual in the patient's life, and judged "likely to precipitate mania." In one hundred manic episodes, thirty stressful events could be documented; however, eighteen of these events represented discontinuation of phenothiazine or lithium medication (six patients) or treatment with antidepressant drugs or ECT (twelve patients), conditions known to be associated with triggering the onset of mania. Thus, known significant psychological stresses were thought to be present in only 12 percent of the patients developing mania. This low incidence of psychological precipitants has been reported in other studies, although serious methodological problems limit the meaningfulness of such statistics.

The amount of total sleep and rapid eye movement sleep were both decreased immediately prior to and during the switch into mania. Urinary norepinephrine excretion was significantly elevated on the day prior to and during the manic episodes, while smaller and non-statistically significant changes were observed in the excretion of epinephrine, dopamine, 3-methoxy, 4-hydroxyphenylglycol (MHPG) and 5-hydroxyindoleacetic acid. Urinary cyclic AMP excretion exhibited a brief peak on the day of the switch

into mania and decreased subsequently. Changes in urinary levels of cyclic AMP may well reflect the associated alterations in catecholamines or other hormones accompanying the behavioral changes, or may be directly involved in the switch process itself.

The switch from mania to depression is characterized by a number of different features. Unlike the switch into mania, this transition period rarely occurred abruptly. Rather, the patients manifested the following gradual behavioral shifts, often extending over a period of weeks: mania, hypomania, a short, unstable transitional period with labile mood and activity, followed by the onset of depression, with prominent psychomotor retardation. A diagrammatic representation of typical switch sequences is presented in Figure 23-1.

Drug-Related. Switches into Mania

The occurrence of some hypomanic and manic attacks in apparent relationship to the administration of psychoactive drugs that alter biogenic amines may be of some importance in understanding the "switch process."

Switches During Tricyclic Antidepressant Administration. In one study, three bipolar patients given tricyclic antidepressants developed typical manic episodes that were characterized by sequential changes in mood and behavior very similar to those observed in spontaneous switches, including

the presence of a brief “normal” period. In two of these three cases, the switches occurred after four days of tricyclic drug treatment, i.e., much earlier than the antidepressant effects of these drugs usually occur. No manic episodes developed in the non-bipolar patients, although some of these patients exhibited increased activity and mild hypomanic symptoms after several weeks of treatment.

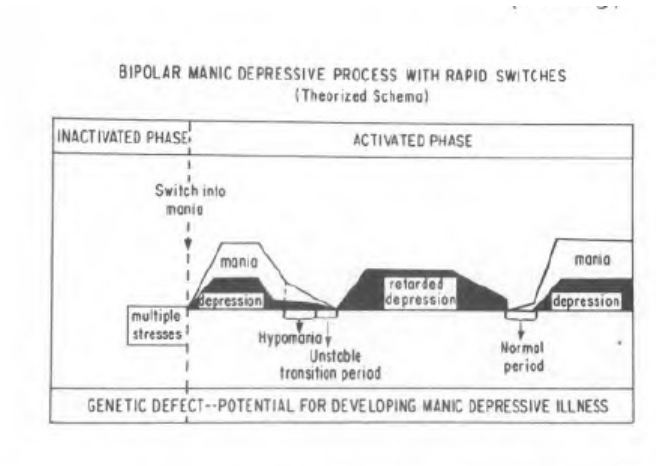

Figure 23-1.
Bipolar manic depressive process with rapid switches (theorized schema).

In papers from the literature dealing with the possible association between tricyclic medication and the onset of mania, data were available concerning previous psychiatric disorders in sixty-seven of one hundred and sixty patients who were reported as developing mania or hypomania during tricyclic drug treatment. Of the fifteen patients who developed full-blown

mania in this group, 66 percent had a past history of mania, 27 percent a past history of depression, 7 percent a past history of schizophrenia, and none of the patients lacked a history of mental illness.

Thus, bipolar patients appear to have the highest predilection for mania during tricyclic drug administration. An additional five patients with past histories of mania received equal or greater doses of tricyclic drugs in this study and did not develop mania. Thus, it appears likely that other variables in addition to the medication may play a role in the onset of these manic episodes.

The mechanism by which the tricyclic drugs might act as a pharmacological trigger for mania is not yet clear. The antidepressant activity of these drugs has been most frequently assigned to a central potentiation of adrenergic neuro-activity resulting from inhibition of biogenic uptake. Recently, potentiation of norepinephrine effects as well as inhibition of biogenic amine uptake have been reported in patients receiving these drugs. It is possible that patients with manic histories are unusually sensitive to these effects of tricyclic drug treatment.

Switches During L-Dopa Administration. In the course of a study designed to evaluate the possible antidepressant effects of L-Dopa (L-3,4-dihydroxyphenylalanine) , the amino acid precursor of the catecholamines

dopamine and norepinephrine, eight of nine bipolar patients developed hypomanic episodes during the time of L-Dopa treatment. Only one of thirteen unipolar-depressed patients developed a similar episode, despite similar dosage and similar duration of L-Dopa administration in both groups. Antidepressant effects of L-Dopa were minimal in the patients as a whole, with only 25 percent of the patients exhibiting some improvement. However, it was noteworthy that all of the patients who improved had features of psychomotor retardation as part of their depressive symptomatology, and that among these patients who improved several relapsed following placebo substitution.

The hypomanic episodes during L-Dopa treatment were generally similar to the patients' prior episodes in that they began abruptly and were characterized by increased speech, hyperactivity, increased social interaction, intrusiveness, sleeplessness, grandiosity, and some minimal euphoria. They were different from the spontaneous switches into mania and the switches associated with tricyclic drugs in their brevity (they usually were only two or three days in duration) and in their mildness. Only two of the patients developed full-blown manic episodes requiring specific treatment beyond the discontinuation of L-Dopa. Only one of the patients who became hypomanic was considered to have become clearly less depressed while receiving L-Dopa.

In the patients developing hypomania and mania during both L-Dopa and tricyclic antidepressant drug treatment, total sleep and rapid eye movement sleep were reduced, as in the patients developing mania spontaneously. Urinary dopamine excretion was markedly increased, as expected, during L-Dopa administration. In a small subsample of patients studied during L-Dopa administration, some smaller elevations of urinary norepinephrine metabolites were also observed.

The induction of hypomania by the catecholamine precursor L-Dopa supports the postulated importance of catecholamines in the manic phase of affective disorders. However, these results do not provide conclusive evidence indicating a disorder in catecholamine metabolism in manic-depressive patients, since large doses of L-Dopa have stimulant properties in animals and may well have similar effects in man. These results do indicate a greater susceptibility to the excitant effects of L-Dopa in the manic-depressive patients who develop hypomanic episodes. Further study is needed to determine whether this susceptibility represents a specific abnormality in catecholamine metabolism, for example, a reduced metabolic capacity for an amine excess produced by an L-Dopa load. Alternatively, it may be that the patient prone to a manic or hypomanic episode is more sensitive to the stimulant effects of L-Dopa and other agents such as tricyclic antidepressants, monoamine oxidase inhibitors, electroshock treatment, or psychological stresses on some other genetic or developmental basis. In any case, the

regular occurrence of typical hypomanic symptoms in bipolar patients treated with L-Dopa, and the development of acute manic episodes in other bipolar patients in close association with tricyclic drug administration, serves to implicate a change in brain amines, specifically an increase in catecholamines, in the switch process. The fact that L-Dopa can produce hypomania in susceptible individuals without reversing depression suggests that mania and depression are not simply opposite poles of the same continuum.

Monoamine Oxidase (MAO) Inhibitors. These drugs are of particular interest because, like L-Dopa and imipramine (and possibly the amphetamines), they act as behavioral activating agents via effects on the neurotransmitter amines. In normal individuals, as well as in medical patients without psychiatric histories, their administration can produce mood lability and behavioral alterations, including the precipitation of manic episodes and the production of exacerbations in psychotic symptomatology in some schizophrenic patients. They also appear to potentiate the psychotomimetic effects of some amino acids, including L-methionine and possibly L-Dopa. The possibility of endogenously reduced MAO activity acting as a predisposing factor in the behavioral switch mechanism is a particularly intriguing question.

Amphetamines. These agents can provoke behavioral, mood, and

motor activity changes in animals and man and appear to act via effects on catecholamines. Normal individuals as well as psychiatric patients generally develop transient hyperactivity and sometimes euphoria and with smaller doses hypomania and manic episodes have been precipitated in some individuals receiving amphetamines or other direct-acting sympathomimetic agents. Larger doses given over a longer duration often lead to behavioral depression and psychosis with paranoid symptoms predominating. The postdrug period is typified by a "crash" period of severe, depressive-like symptoms.

Adrenal Corticosteroids. The administration of exogenous steroids in the treatment of various medical disorders, as well as the increased endogenous production of steroids in Cushing's syndrome, is associated with mood lability and other psychiatric symptoms. Euphoria and full-blown manic episodes are apparently more common during exogenous steroid treatment, while depressive symptoms occur more often in Cushing's syndrome. The possible role that the adrenal corticosteroids may play in the triggering of psychopathology on the basis of their effects on electrolytes and biogenic amines at the neuronal membrane has been the subject of several reviews.

Direct Brain Stimulation. Increased communication and mild euphoria have been reported to follow electrode stimulation of the median forebrain

bundle, as well as direct physical stimulation during surgery involving hypothalamic areas. Stimulation of the amygdala in one instance yielded increased activity, rushing thoughts, and pressure of speech, and, in other instances, anger and a delayed-rage reaction.

Drugs in the Treatment of Mania

Lithium carbonate, the phenothiazines, and the butyrophenones are the drugs most used in the treatment of mania. Electroconvulsive therapy, although effective in some patients, has been mostly replaced by drug treatment. Most manic patients (more than 80 percent) respond to drugs, although large doses of the antipsychotic drugs and treatment with lithium carbonate for over a week may be required for full therapeutic benefit. Several recent reviews of the efficacy of lithium and other drugs in the treatment of mania are available, and this section will focus only on the ways in which the effects of these drugs may contribute to the understanding of the pathogenesis of mania.

Lithium Carbonate. A large series of studies, reviewed elsewhere, have demonstrated the efficacy of this drug in the treatment of mania. Used in doses of 1.2 to 2.4 grams per day which yield serum levels of 0.9 to 1.5 mill-equivalents per liter, an apparently specific antimanic effect can usually be seen after five to ten days of treatment. Negligible sedative or antipsychotic

effects are produced by lithium carbonate, and some atypical schizoaffective patients appear more psychotic when hyperactivity diminishes.' The ability of lithium carbonate to interact with sodium, potassium, magnesium, and calcium in a variety of biological systems' may be involved in its therapeutic effects.

Lithium treatment of manic patients has been shown to alter exchangeable and residual (cellular plus bone) sodium, total body potassium, and the urinary excretion of sodium and other electrolytes as well as the hormones (e.g., aldosterone) regulating electrolyte balance. Whether these changes are important in relation to the alterations in water and electrolyte metabolism, reviewed above, or have some direct cellular relationship to the transport, storage, and release of biogenic amines, as reviewed elsewhere, has not been conclusively demonstrated. Lithium has been demonstrated in animal brain and human platelet preparations to lead to actions antagonistic to biogenic amine effects, including an increase in amine reuptake, a decrease in amine release, an increase in intra-neuronal amine destruction and an increase in amine turnover, as well as to an antagonistic effect on cyclic AMP production. This series of effects represent the most likely biochemical mechanism of action for the antimanic effect of lithium, based upon the theoretical support from human and animal studies that antagonistic effects on biogenic amine function would be consistent with antimanic efficacy; however, the relationship of these biochemical effects to the prophylactic and

partial antidepressant actions of lithium remains problematic.

Phenothiazines and Butyrophenones. These antipsychotic drugs are effective in some manic patients, particularly in rapidly diminishing severely disruptive behavior. While these drugs have multiple biochemical effects, they possess antagonistic actions on *a*-adrenergic and dopaminergic receptors in brain and in the periphery, which have been suggested to be related to their antipsychotic and antimanic efficacy.

Alpha-methyl-p-tyrosine. This drug is a blocker of dopamine and norepinephrine synthesis via direct inhibition of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, and was found to temporarily decrease manic symptomatology in most manic patients, some of whom showed a consistent pattern of relapse with repeated placebo substitution. In these patients, decreased urinary excretion of dopamine, 3-methoxy, 4-hydroxyphenolic acid (VMA), and 3-methoxy, 4-hydroxyphenylglycol (MHPG) was observed, as well as decreased levels of homovanillic acid (HVA) and MHPG in the cerebrospinal fluid. These clinical and biochemical data are consistent with the hypothesis that mania is associated with an increase in catecholamines. However, alpha-methyl-p-tyrosine is neither as practical a drug to use clinically (because of hypotension and other side effects) nor is it as effective as lithium or the antipsychotic phenothiazines in leading to a complete remission of manic

symptoms.

Affect, Catecholamines and Psychomotor Activation in Mania

Mania has been relegated to the category of the "affective disorders" and has been found to be the differentiating characteristic of "bipolar" compared to unipolar patients among individuals with primary affective disorders. One implication of the studies reviewed in this chapter is that the use of these terms may be imprecise and perhaps misleading, in that the conception of mania and depression as representing "opposite," pathologic extremes of affective expression appears overly simplistic and reductionistic.

While all depressive states share the common effect of sadness, mania appears to be not as well characterized by elation but rather by a state of heightened affective expression overall together with lability of affect. The co-occurrence of marked depressive thought content and behavior (like crying) with elation and heightened anger and other affects in separately varying intensities in the same manic individual suggests that the equation of elated mood with mania represents an overemphasis and oversimplification of the phenomena of mania.

Various models attempting to relate mania, depression, and normality have been proposed: (a) the traditional bipolar model with normality in the middle and mania and depression as pathologic extremes; (b) a continuum

model reflecting the suggested relative severity of these disorders, with normality at the bottom, depression intermediate, and mania at the top; and (c) a triangular, tripolar model that, in its several variants, essentially posits that mania and depression are separate and independent states. These different models all have some firm support, but none fits all of the data, although the least constraining, the triangular model, comes closest to encompassing both the psychological and biological phenomena observed in these patients.

However, several crucial ingredients appear not to have been taken into account in the construction of conceptual models for manic-depressive illness: (a) the phenomena of depression observed in both unipolar and bipolar patients have previously been grouped together for contrast with mania, although depression in bipolar patients is now known to have features different from that in other depressed patients,' while mania only occurs in bipolar patients; and (b) the dimension of psychomotor activity has been underemphasized, while the affective state has been overemphasized, particularly disproportionately in mania.

The Question of the Primacy of Psychomotor Activity in Mania

The data reviewed in this paper, as well as observations dating from the time of Kraepelin, suggest that motor, speech, and cognitive hyperactivity

may be more specifically characteristic of mania than is elation. In fact, it seems more economic to consider mania and depression in the bipolar individual as more primarily representing extremes on the axis of psychomotor activity or arousal, rather than of mood. Depression in bipolar patients is more frequently characterized by psychomotor retardation, social withdrawal, anergia, and hypersomnia, and appears to be a distinctly different syndrome in other respects from depression in non-bipolar patients. Manic hyperactivity, on the other hand, is accompanied by boundless energy, little need for sleep, and a high level of motor, verbal, and cognitive activity, and social interchange. It is of interest that some psychoanalytic interpretations of mania have emphasized its similarity to the elevated mood and omnipotence that attend the practicing period in early development associated with increased motor and exploratory activity.

A case might even be made for considering the psychomotor hyperactivity with its cognitive components of distractibility and associated impairment of memory and judgment as capable of producing a near totally "present time only" pleasure-orientation as a basis for the elated mood. It is also possible that affective expression is regulated by the same mechanism as psychomotor activity, and, as suggested above, mania is associated with heightened expression or amplification of all affects, while phenomena like "not being able to cry" represent suppressed affective expression during depression. Similarly, other mechanisms regulating sleep, "reward" or

pleasure, and other functions may be subject to independent activation, with the resulting combination of effects yielding each individual's manic syndrome.

However, direct evidence to prove the primacy of activity over mood, or vice versa, is lacking. Until more evidence is at hand, it would seem best to consider affect and psychomotor activity as separate dimensions or axes of behavior that can contribute independently to the final syndrome of mania. Some of the complexity in understanding depression may also be related to separate contributions of the affect-regulating mechanisms and activity-regulating mechanisms. For example, the severely agitated depressed patient with a marked motor component to his symptoms may not resemble other depressed patients when studied, but may rather be closer to manic patients in some phenomena.

Catecholamines, Brain Mechanisms, and Mania

On the basis of the impressive evidence linking brain dopamine and norepinephrine to the regulation of psychomotor activity,' sleep, emotion, reward mechanisms, as well as to arousal mechanisms such as the reticular and limbic activating systems, seems especially pertinent to reemphasize the evidence linking brain catecholamines to mania. Methods capable of demonstrating increased catecholaminergic neuronal activity in man have not

yet been devised. Perhaps the direct measure closest to providing a reflection of catecholamine metabolism in the brain, the measurement in the cerebrospinal fluid of levels of the norepinephrine metabolite, MHPG, has suggested an increase in norepinephrine turnover during mania. However, it appears that physical activity alone may produce an equally large increase.

Nonetheless, indirect evidence from drugs with the greatest relative specificity for affecting catecholamines indicate that the precursor of dopamine and norepinephrine, L-Dopa, can precipitate dose-related hypomanic episodes, while the catecholamine synthesis inhibitor, a-methyl-para-tyrosine, can dampen manic symptoms. Collaborative evidence from other psychoactive drugs including the tricyclic antidepressants, MAO inhibitors, antipsychotic drugs, reserpine, amphetamines, and lithium are also compatible with their mania-related effects being mediated via central catecholamines. While evidence for the primary involvement of serotonergic (see above), cholinergic, and other biogenic amine mechanisms in mania exists, as well as other metabolic interactions (see above), the most weighty current evidence implicates brain dopamine and/or norepinephrine as principal mediators of the symptomatology of mania. Cholinergic and serotonergic' modulation or antagonistic "balancing" of some catecholamine effects may also be present.

In attempting to tie together the evidence pointing to the importance of

psychomotor activity and arousal with the evidence implicating catecholamines in mania, it is necessary to consider the localization in the brain of dopamine and norepinephrine and of the brain sites involved in the regulation of activity and arousal. Recent histofluorescence studies have verified and extended regional chemical analyses and indicate the existence of several different noradrenergic and dopaminergic neural pathways.

Most of the cell bodies of noradrenergic and dopaminergic neurons are present in the brainstem, i.e., the medulla, pons, and mesencephalon, but their terminals extend to almost all parts of the brain and spinal cord. The major dopaminergic pathways (the nigro-neostriatal tract) originates in the pars compacta of the substantia nigra and ascends through the mesencephalic tegmentum, crus cerebri, and internal capsule, terminating in the caudate nucleus and putamen; this system is important in the regulation of motor activation and posture. Another dopaminergic neuronal pathway ascends in the median forebrain bundle and terminates in the tuberculum olfactorum, the nucleus accumbens and the nucleus interstitialis striae terminalis. A small dopaminergic pathway extends into the hypophyseal capillary portal area.

A prominent noradrenergic neuronal group also ascends through the median forebrain bundle to terminate in widely distributed parts of the hypothalamus, most areas of the forebrain limbic system (the septal area), the preoptic area, the amygdaloid cortex, the cingulate gyrus, the nucleus

interstitialis striae terminalis, and the neocortex. Their cell bodies are derived from the locus coeruleus in the pons and the reticular formation in the medulla. These noradrenergic neurons give off many collaterals, and it appears that a single neuron may send fibers to brain areas as distant as the cerebellum and the telencephalon. Monosynaptic connections have been described between both the limbic forebrain area and the neocortex and the reticular formation core of the lower brainstem.

Although normally catecholamines are localized in the above-described tracts, it should be noted that altered catecholamine formation, such as that which follows administration of L-Dopa, also affects serotonergic neurons as well as other brain biochemical processes, and since some of these mechanisms may operate in "balance" or permissive ways with catecholaminergic systems, it is possible that catecholamine-mediated behavioral and psychological changes may not be primarily effected through the catecholaminergic tracts themselves.

Nonetheless, there exists a close correlation between the catecholamine pathways and the sites that brain-lesion and electrode-stimulation studies indicate as important in the regulation of psychomotor activity, reward mechanisms, and arousal. These areas include: (a) dopaminergic corpus striatum areas, lesions of which produce slowed psychomotor activity, and Parkinsonian-type symptoms in animals and man; (b) the various

noradrenergic areas included in the limbic- and reticular-activating systems, which are well known for their role in arousal mechanisms; and (c) some specific noradrenergic areas such as those in the septum which appear to function in the mediation of exploratory activity, rage responses, and reward mechanisms.

Arousal, Psychomotor Activation, and Mania

There is very little direct information to relate the neurochemical state of these specific catecholaminergic brain areas to altered behavior in the manic state and to the hypothesized existence of altered arousal or activation regulation in the bipolar patient group. Indirect evidence based upon drug effects provides suggestive evidence to implicate catecholamine pathways, as discussed above, but cannot yield conclusive proof because of the multiplicity of effects of the drugs studied. Lesion studies such as those which relate such manic-like phenomena as "rage," increased exploratory activity, and a lack of response inhibition to septal area destruction in animals' provide interesting models for abnormal behavioral syndromes, but are obviously severely limited by species differences and the non-specificity of even small lesion production.' However, when several separate threads of evidence can be gathered together from different study approaches, a stronger line of argument is produced. For example, there already exists a body of data suggesting that hyperarousal may be present in some schizophrenic

individuals. This theory is based in part on psychophysiologic evidence and also on indirect data and models constructed from phenothiazine drug effects.' In some ways, an even stronger case can be made for hyperarousal in mania as some similar psychophysiologic alterations occur in mania and as phenothiazines are effective antimanic drugs as well. In addition, the L-Dopa and antidepressant drug-related switches into mania described above also would be compatible with an inherent hypersensitivity of the bipolar individual to these drugs, all of which have activating effects.

From this viewpoint, manic and schizophrenic individuals may be postulated to share a common state of hyperarousal that predisposes them to maladaptive responses to further psychologically or pharmacologically based arousal. The specificity of the responses in these patients and in other individuals susceptible on different bases (e.g., brain damage) to impaired stimulus regulation is suggested to lie in other aspects of the personality structure.

The information from the cortical evoked response studies of bipolar patients provides direct evidence of altered stimulus-intensity modulation compatible with hyperarousal in these individuals, compared to normal people and especially to unipolar patients. The greater EEG augmentation responses in reaction to increasing intensities of light in bipolar patients is increased further during hypomanic and manic episodes and in response to L-

Dopa administration. In contrast, successful treatment of manic episodes with lithium carbonate and with the catecholamine synthesis inhibitor, a-methyl-para-tyrosine, is associated with decreased evoked response amplitudes in these patients.

If the averaged EEG responses evoked by light can indeed be considered an index of stimulus intensity modulation as has been suggested,'' an interesting model of maladaptive activation regulation is suggested. The bipolar manic-depressive patient in this model would appear to be operating in a state of positive feedback as evidenced by sensory input amplification. In control systems theory, positive feedback usually implies the liability of exaggerated over-swings and a susceptibility to being driven by external stimuli. Such a state is clearly analogous to many features of the manic-depressive condition, including lability in mood and activity as well as other characteristics of mania such as distractibility. If, as has been suggested above, activation is alterable by catecholamine-mediated changes, an impaired control mechanism, regulating activation responsiveness to stimulate intensity in these patients, might well be found in the cellular events concerned with catecholamine synthesis, storage, release, reuptake, metabolism, and receptor function. Several examples of the most likely types of changes have been discussed elsewhere.

For future exploration remains the more precise testing of this and

other postulated mechanisms and models of the manic state. Of particular interest is the interaction between the apparently inherited susceptibility to mania and the precipitation, as well as different manifestations, of the bipolar disorder in individual instances. Indeed, the question of whether the inherited factor may lie directly in biogenic amine metabolic pathways, or neural synaptic membranes, or in other brain mechanisms only indirectly affected by psychologic or biochemical activating agents is only beginning to be the subject of speculation. Pharmacologic and other animal models for as complex a human behavioral phenomenon as mania are some distance from meaningful utility. It appears that continuing, clinically based research studies remain the proving ground for hypotheses concerning human behavior and its disorders, including mania.

Conclusions

The review has focused on recent studies of mania and of the individuals who develop mania—the group with the so-called "bipolar-affective disorders." Some evidence indicating that mania and depression are "opposite" bipolar states in some ways only, and clearly not in others, was reviewed. Other evidence suggesting that mania represents more a disorder of activity than of affect was also considered.

Whether mania, schizoaffective states, and some or all forms of

schizophrenia may be related in some way requires reinvestigation. Some of the evidence reviewed suggests that these disorders can be placed along a continuum, and other evidence indicates that they share some clinical and biologic phenomena, although the majority of family-history studies continue to suggest a low cross-incidence in the same family of schizophrenia and the affective disorders considered together.

Mania is the definitional characteristic of the bipolar subgroup of depressed patients. These individuals differ from other (unipolar) depressed patients in some clinical characteristics seen during depression and in remission. They also differ in familial incidence ("genetic") patterns; while an X-linked mode of genetic transmission has been suggested, current evidence is more compatible with a polygenic mode. Differences in psychophysiologic and biologic studies, ranging from EEG and cortical evoked response data to the activity of biogenic amine metabolizing enzymes, have also been observed. In addition, bipolar patients have been demonstrated to manifest a differential susceptibility to drugs such as lithium, L-Dopa and imipramine.

Information from animal studies concerning the mode of action of drugs that suppress and precipitate mania points toward the mediation of these effects in man via changes in central neurotransmitter amines, especially norepinephrine and dopamine. A contributory role of other neurotransmitters, especially the cholinergic and serotonergic systems, may

also be integrated with the catecholamines in the regulation of psychomotor activity, arousal, and affective expression.

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