postulates. Several facts implicate this bacterium as the causal agent: (i) the bacterium was found in the xylem tissue where the causal agent of Pierce's disease is known to be (*7*); (ii) the correlation between symptoms and occurrence of the bacterium was high; (iii) the bacterium was never found in plants in which the disease had been controlled with tetracycline antibiotics and (iv) the exclusion of leafhopper vectors prevented the occurrence of both the symptoms of Pierce's disease and the bacterium.

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Urinary Catecholamine Metabolites during Behavioral Changes in a Patient with Manic-Depressive Cycles

Abstract. *3-Methoxy-4-hydroxyphenylglycol and normetanephrine were analyzed in daily urine specimens of a patient with manic-depressive cycles who was studied longitudinally. The quantities of these catecholamine metabolites excreted into urine were decreased during periods of depression as compared with periods of mania. Urinary excretion of 3-methoxy-4-hydroxyphenylglycol varied cyclically with a period length of approximately 20 days. Changes in this metabolite, and perhaps in normetanephrine, preceded the affective and behavioral shifts.*

The concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG) in urine was found to be significantly decreased in a group of depressed patients as compared with normal controls (*1*). The excretion of this metabolite was decreased in depressed patients and increased in manic patients (*2*). Bond *et al.* (*3*), in a longitudinal study of two patients with manic-depressive illness, also reported that urinary MHPG excretion was significantly higher during the manic phases and lower in the depressed phases. They suggested that the increase in the urinary excretion of MHPG precedes the switch into mania and that the amount of this metabolite reflects a cyclic variation in brain norepinephrine turnover, with decreased turnover triggering the episode of depression. Because of the suggested relation between brain norepinephrine and the affective disorders (*4*), that is, mania and depression, urinary MHPG determinations are of particular interest because this metabolite is the principal product of brain norepinephrine degradation in several species of mammals (*5*, *6*). Early reports indicated that approximately 25 to 30 percent of urinary MHPG in dogs is derived from the metabolism of brain norepinephrine (*5*). However, this figure may be too conservative, because it has been found that approximately 30 to 60 percent of urinary MHPG in nonhuman primates may be derived from the metabolism of brain norepinephrine (*7*).

Urinary norepinephrine and normetanephrine, which are derived from pools of norepinephrine outside the central nervous system (*8*), were also reported to be altered in patients with manic-depressive illness. Strom-Olsen and Weil-Malherbe (*9*) found that urinary excretion of norepinephrine and epinephrine was greater during the manic phase in patients with manic-depressive disorders. Bergman (*10*) reported elevated excretion of norepinephrine and epinephrine in a series of manic patients, whereas no significant changes in the excretion of either amine were observed in patients with endogenous depressions (retarded depressions were not separately characterized). Shinfuku *et al.* (*11*) reported increases in urinary excretion of norepinephrine during mania in a single patient with regular manic-depressive mood changes. Greenspan *et al.* (*12*) found that excretion of norepinephrine and normetanephrine was greater during hypomania than during normothymic periods or during periods of retarded depression. In a longitudinal study of depressed patients, Schildkraut *et al.* (*13*) observed a gradual rise in normetanephrine excretion during the period of definitive clinical improvement in depressed patients treated with imipramine. Bunney *et al.* (*14*) measured urinary catecholamines daily in a group of patients. Norepinephrine and dopamine were elevated before and during the manic episode. In particular, norepinephrine was significantly increased 1 day before the shift from depression to mania. In contrast, MHPG was not elevated just before or during the manic episode. In considering changes in catecholamine excretion, Bunny *et al.* commented that the days just before the manic episode may represent an initial phase of the mania.

Although the cited studies are in essential agreement as to the changes in urinary norepinephrine and its metabolites during shifts between depression and mania, they do not indicate whether these changes are secondary to the behavioral change or whether they reflect a change in catecholamine disposition and metabolism which is related to affective illness. We report longitudinal data on the urinary excretion of normetanephrine, which is derived from peripheral adrenergic pools, and of MHPG, a significant fraction of which may derive from norepinephrine metabolism in brain, by a patient who switched twice from depression to mania and once from mania to depression.

The patient was a middle-aged, married woman who at the time of admission had been suffering from a manic-depressive illness for 5 years. The illness first manifested itself as a severe depression of 3 months' duration, with spontaneous recovery occurring early in a pregnancy. The patient has since had several episodes of depression or mania (or both) of sufficient severity to require hospitalization. In a depressed phase the patient generally looks sad, expresses feelings of guilt, has psychomotor retardation, and may be actively suicidal, and while in a manic phase she is elated or boisterous, angry, and at times combative. During periods spent outside the hospital there was

a tendency toward a cyclical occurrence of alternating periods of moderate depression and mild hypomania, with a complete cycle taking about 3 weeks. At various times she had received most of the organic therapies with only temporary benefit. The patient had been treated with lithium carbonate as an outpatient, but management was difficult. Finally she made a serious suicidal attempt with an overdose of lithium, which required the hospitalization reported here.

Throughout this study the patient was maintained on a diet free of coffee, tea, colas, vanilla, bananas, cheese, oranges, and chocolate; and no drugs, including hypnotics, were given. Urine for 24-hour periods was collected throughout the hospitalization, but if nursing observations or creatinine values suggested that collection was incomplete, the urines were discarded (*15*). Urines were assayed for MHPG by the method of Dekirmenjian and Maas (*16*), for normetanephrine by the method of Taniguchi *et al.* (*17*), and for creatinine by a modification of the method of Bonsnes and Taussky (*18*). All biochemical assays were done without knowledge of the patient's clinical state.

While in the hospital the patient switched from a severe, guilt-ridden, retarded depression into a moderately severe manic state, followed by 5 days of mild hypomania and 2 days of more severe mania. She then became depressed for 13 days, and another period of mania followed. Descriptive comments excerpted from notes made by nurses, attendants, and physicians are tabulated in Table 1, and these time periods and behaviors may be compared with the changes in the biochemical variables.

The pattern of excretion of MHPG into urine in relation to the patient's psychopathological state is shown in Fig. 1a. The mean MHPG excretion during the peroids of depression was 805 ± 42 μg in 24 hours. In comparison, average 24-hour MHPG excretion for normal women ($N = 12$) was 1300 μg, with the 95 percent confidence interval being 1137 to 1463 μg. The mean 24-hour MHPG excretion by this patient during the manic phases was 1182 ± 49 μg, which is within the normal range. The highest 24-hour MHPG value (1520 μg), which is above the 95 percent confidence interval for normal women, coincided with the severest manifestation of the manic behavior. There appears to be a periodicity to the MHPG excretion, with a cycle lasting approximately 20 days. This is of particular interest in view of the patient's history outside the hospital of alternating periods of hypomania and moderate depression occurring during a 3-week period. Finally, comparison of the biochemical data (Fig. 1) and the patient's behavioral state (Table 1) shows that the changes in the MHPG excretion preceded the behavioral changes. For

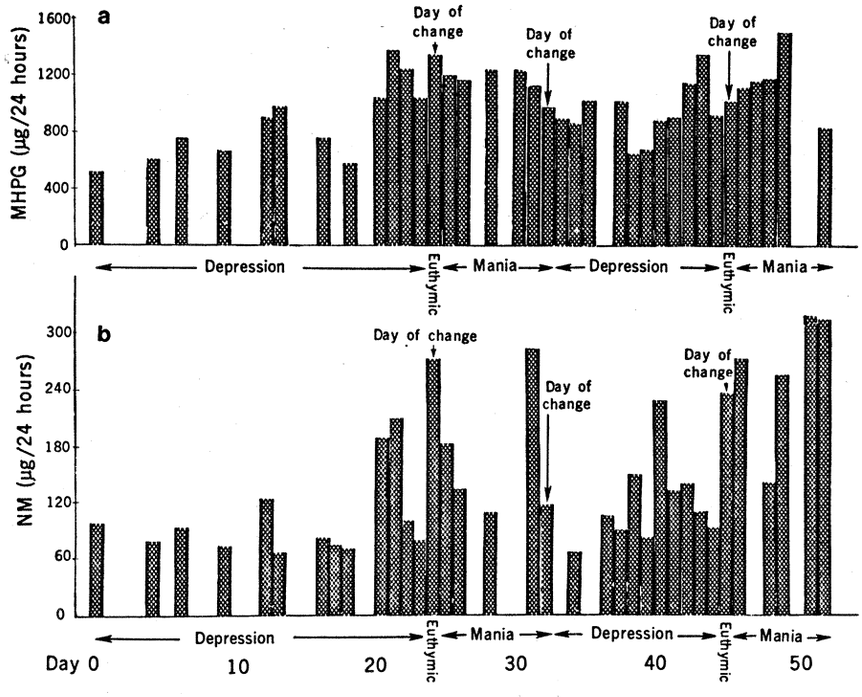

Fig. 1. Excretion of (a) 3-methoxy-4-hydroxyphenylglycol (*MHPG*) and (b) normetanephrine (*NM*) in 24-hour urine samples during two switches from depression to mania. Values represent means of two or three determinations on the same sample.

Table 1. Description of the patient's behavior during the period of study, with particular emphasis on the periods of behavioral changes. The behavioral descriptions are excerpted from notes of nurses, attendants, and physicians.

Depression Days 0 to 23	Looks sad, preoccupied, cries frequently. Expresses death wishes and suicidal thoughts. Isolated most of the time, indifferent to unit activities. Slow in speech and movements. Falls asleep, at times, in meetings.
Euthymic Day 24	Had a congenial, pleasant visit with family members, says she enjoyed herself. Does not appear depressed, talks easily with staff members.
Mania Days 25 to 31	This period characterized by two episodes of mania separated by a 5-day interval in which she appeared calmer and normally engaged in ward activities. Exhibited pressure of speech and flight of ideas on the morning of day 25. Actively showed recent purchases to everyone. Great deal of talk about money matters and how much she spends. Less active in the evening. Appeared in good spirits from days 26 to 30, was personable and talkative. Judged to be either euthymic or mildly hypomanic. Became hyperactive and combative on day 30 while on leave from the hospital. Returned early on day 31 apparently angry with her husband and staff members.
Depression Days 32 to 45	Looks sad, facial expression of pain and fear. Needs encouragement to initiate activities and to talk. Seclusive, indifferent to the environment.
Euthymic Day 46	Morning: Happy to see her family, had pleasant visit with them. Pleasant interactions with patients and staff. Evening: Calm, verbalized her good feelings for family visit. Regretted that she becomes manic but remarked that it helps pass the time and keeps her from being bored.
Mania Days 47 to 53	Day 47: Up all night, appeared in good spirits, superficial conversation. Dressed nicely for breakfast, talkative and seductive, moderately hyperactive. Less active in the evenings, appears happy. Needs close observation. Days 48, 49, and 50: Exhibits behavior similar to other manic episodes, such as riding up and down hall on wheel chair, fighting with staff, destroying valuable belongings. Escapes from unit, causing problems on other wards.

example, during the first shift from depression to mania the MHPG excretion was increased on days 20 through 23, 4 days before the day of behavioral change. Nursing notes during this 4-day period indicate that the patient was nonverbal, sat rigidly in her chair for long periods, and appeared retarded in movements and thought processes. It may also be that the switch from mania to depression was preceded by a beginning decrement in MHPG excretion (Fig. 1). While these changes in MHPG in relation to manic and depressive periods may be coincidental (*19*), they do indicate that the MHPG excretion is not simply a derivative function of the patient's clinical state (namely, more activity during mania), for in this case there would be a close temporal relation between increase in urinary MHPG and the switch from depression to mania. The pattern of MHPG excretion, including changes preceding the behavioral shifts, is unaltered when values are expressed as micrograms of MHPG per milligram of creatinine (not shown). The changes in MHPG excretion and shifts in the affective state are in the expected direction, and the data are in agreement with the comments made by Bond *et al.* (*3*) as well as with the report by Schildkraut *et al.* (*20*) that urinary MHPG excretion is increased during amphetamine-induced hypomania and decreased during the depression which follows amphetamine withdrawal and that the changes in MHPG excretion appear to precede the behavioral shifts.

The pattern of excretion of normetanephrine in relation to the affective shifts is shown in Fig. 1b. The mean normetanephrine excretion by this patient during depressive periods was 99 ± 11 μg in 24 hours, whereas average 24-hour excretion for normal women ($N = 12$) was 191 mg, with the 95 percent confidence interval being 154 to 223 mg (*21*). The mean 24-hour excretion of normetanephrine during the manic phases was 206 ± 22 mg. The relation between urinary normetanephrine and the shifts in the patient's clinical state are less clear than in the case of MHPG. Urinary excretion of normetanephrine was increased on 2 of the 4 days immediately preceding the first switch from depression into mania. During the first manic episode, the urinary excretion increased on the day of behavioral change, but excretion was markedly decreased on the next day despite the moderate amount of activity (Table 1). While these data are generally consistent with the possibility that urinary normetanephrine changes as a function of activity, they also indicate that changes in its urinary excretion may precede the switches from depression into mania and vice versa.

During the second switch from depression into mania normetanephrine excretion was consistently low during the depressive phase (except for 1 day) and increased the day of behavioral change.

In conclusion, the data presented here are considered to support and be consistent with the catecholamine hypothesis of the affective disorders (*4*).

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Sleep and Memory

Abstract. *Two experiments demonstrated that memory over an interval with relatively high amounts of rapid eye movement (REM) sleep was inferior to memory over an interval with relatively high amounts of stage 4 sleep. The results suggest that, at least for humans, REM sleep does not facilitate memory consolidation and that stage 4 sleep may be beneficial to memory.*

Memory for verbal habits is facilitated by sleep occurring during the retention interval (*1*). This simple empirical fact has for some time served as the foundation experiment for an interference theory of forgetting. If forgetting is due to interference from learning taking place during the retention interval, then prevention of this interference, by putting subjects to sleep, would be expected to facilitate recall, and it does just that. We now present evidence which suggests that sleep does not facilitate memory solely by reducing interference.

Physiologists and psychologists interested in sleep and dreaming have attempted to link the beneficial effects of sleep on memory to one particular stage of sleep, rapid eye movement (REM) sleep (*2*). The most general statement of this hypothesis implies that REM sleep is responsible for, or facilitates, memory consolidation. Such a hypothesis has been supported by observations that REM deprivation increases the time interval over which a memory remains susceptible to electroconvulsive shock (*3*) and by a report that REM deprivation during the retention interval interferes with memory for prose passages (*4*). Our own data, on the contrary, suggest that it is delta-wave sleep, particularly stage 4 sleep, that is most beneficial to memory.

The basic paradigm for investigating the effect of REM sleep on memory has involved REM deprivation during the retention interval, an operation