Brit. J. Psychiat. (1966), **112**, 149–156

Mood, Motility and 17-Hydroxycorticoid Excretion; A Polyvariable Case Study*

By MELVIN SCHWARTZ, ARNOLD J. MANDELL, RICHARD GREEN and RICHARD FERMAN

Since the initial observations of a relationship between depression and an increase in urinary adrenal glucocorticoids in psychiatric patients by Reiss (1953) and Rizzo *et al.* (1954), there have been a number of studies confirming this relationship using various chemical techniques (Board *et al.*, 1957; Bunney *et al.*, 1964 and 1965; Gibbons, Gibbons, Maxwell and Wilcox, 1960; Gibbons and McHugh, 1962; Gibbons, 1964; Kurland, 1964a and 1964b; Pryce 1964). One of the questions that immediately comes to mind in reviewing this work has to do with the specificity of this relationship. Perhaps the rise of urine corticoids in depression is a non-specific response to disturbance, as has been demonstrated in various forms of psychological stress (Hamburg, 1962) and in severe psychiatric disturbances such as acute schizophrenic episodes (Sachar *et al.*, 1963). On the other hand it is tempting to hope that there may be a more specific relationship demonstrable between the complex psychobiological phenomenon of depression and some kind of neuroendocrine activation analagous to a syndrome like "periodic hypothalamic discharge" (Wolff *et al.*, 1964). This syndrome is manifested by periodic episodes (lasting several days) of withdrawal and depression associated with marked elevations in 17-hydroxycorticoid excretion. Mandell *et al.* (1963) have recently demonstrated that subthreshold stimulation of limbic sites intimately related to hypothalamic modulation produces marked changes in plasma 17-hydroxycorticoids in man. Limbic areas have been related to affectual phenomena on a speculative basis since the classical papers of Papez (1937).

Besides the question of specificity, there is another uncontrolled variable of importance to an understanding of the modulation of adrenal cortical activity and which also appears to be of potential importance in affect disturbance, namely motility. Frankl and Csakey (1962), Prokop (1963) and others have demonstrated a relationship between activity level and physical work and adrenal cortical activity and morphology.

The presence on our wards of an unusual manic-depressive patient with regular 40 to 50 day cycles containing periods of both mania and depression gave us an opportunity to study both the specificity and motility issues in a longitudinal way, using the subject as her own control. In the following case study, we have attempted to correlate daily objective and subjective mood measures with objective measures of motility, in addition to serial 24 hour urinary 17-hydroxycorticoid levels. It appears that if one factors out the depressive mood indicators during both manic and depressive periods, this patient demonstrates the relationship between the depressive factor and adrenal hyperactivity. However, there was no difference in mean 24 hour 17-hydroxycorticoids between clinically observable manic and depressive periods, and moreover the "crisis-associated" rises in 17-hydroxycorticoid excretion attributed by Bunney (1964 and 1965) to depression occurred in both the manic and the depressive phases. In addition, there are indications that these relationships may be contaminated by motility factors as

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Supported by NASA Grant NsG 237-62 under the aegis of The Space Biology Laboratory, Brain Research Institute.

https://doi.org/10.1192/bjp.112.483.149 Published online by Cambridge University Press

well as by the non-specific influence of "felt discomfort", as suggested recently by Sachar *et al.* (1963).

Methods

The Patient

For this study, one classic cyclic manic depressive patient was studied longitudinally over a 44 day period during one complete cycle. She fitted the diagnostic criteria enumerated by Kallmann (1953) in that she showed periodicity of acute self-limited mood swings before the fifth decade of life and no progressive or residual personality deterioration before or after psychotic episodes of elation or depression. The depression or elation was sufficiently disabling to require hospitalization.

M.N. was first hospitalized at U.C.L.A. on February 1st, 1962. She is a 48-year-old widowed female department store buyer, and is described as a woman who always tended to spend money freely. Friends noted nothing unusual about her behaviour until October, 1961. Just before this time, she failed in a dress business; she had used up a small inheritance, and was having difficulty with her boy friend. About October 1961, she started drinking, and at the same time she was making plans for a cross-country trip. In early December 1961, she lost control of her car and badly damaged it. She immediately rented another car, complete with chauffeur, put a down payment on an expensive apartment and moved into a plush hotel. Her sleep habits became quite erratic. She would drive to her friends three or four times during the early morning hours, and gave gifts expensively or inappropriately. Admission to hospital was now arranged. This was the patient's second admission. Approximately twelve years previously, two years after the death of her third husband, there had been an episode of manic behaviour for which she had been hospitalized for three months.

During her stay at U.C.L.A., M.N. experienced frequent short recurring cycles of manic behaviour followed by depressive episodes and relatively non-psychotic intervals. During manic episodes, when she would frequently suffer from asthmatic symptoms as well (Green, 1965), the patient was grandiose, assaultive, profane in her language and generally uncontrollable except by excessive amounts of medication, sedation and/or electro-convulsive therapy. During depressed periods she manifested intermittent agitation and marked psychomotor retardation. She would be nearly mute, and was frequently unwilling to eat and expressed ideas of worthlessness and sin. During her non-psychotic periods she appeared as an energetic, cheerful, pleasant woman who showed no residua of psychotic ideation and who was able to make reasonable plans for renewing her vocational interest outside the hospital.

The study was begun eight months after the patient's admission. During the study, an effort was made to keep her off all medication. She received E.S.T. on four occasions to curb uncontrollable mania or to alleviate severe depressed states when she could no longer participate in the study. The 24-hour urine specimens for these days were omitted from the corticoid data. Sodium Amytal was given intramuscularly on four occasions because of excessive destructive behaviour.

The Variables Studied

Multiple parameters were studied in the patient:

1. Objective counts of gross movement patterns.
2. Ability to perform fine psychomotor tasks.
3. Urinary Porter–Silber chromagen levels.
4. The patient's rating of her mood.
5. The nurses' rating of the patient's mood.

(1) The measurement of gross movement patterns was accomplished with the use of an activity counter. Briefly, this consists of a five digit counter, connected to a Y-shaped mercury switch. The switch is encapsulated in a belt which is worn round the waist. The switch is placed in the mid-axillary line and rests against the iliac crest. Gross body movements activate the mercury switch and register on the counter (Fig. 1). The patient put on the belt containing the mercury switch and counter on arising each morning and took if off when retiring for the night. Readings from the counter were recorded by the nursing staff four-hourly and reported as counts per 24 hours.

https://doi.org/10.1192/bjp.112.483.149 Published online by Cambridge University Press

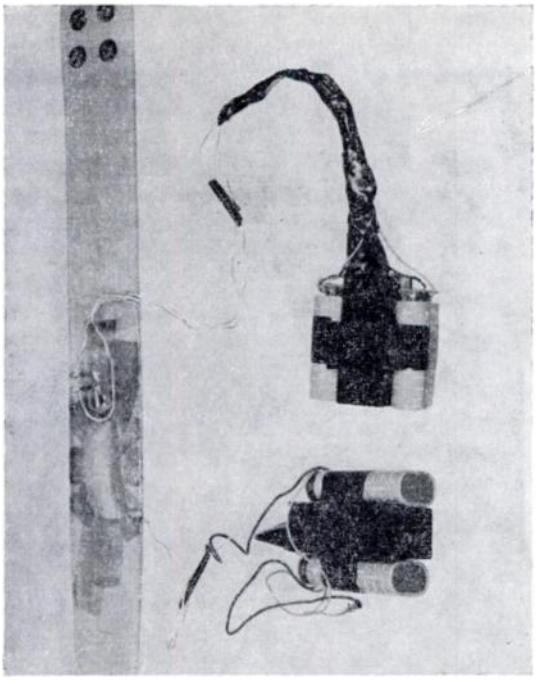


FIG. 1.—This picture of the activity counter (devised by Dr. Ferman) shows the Y-shaped mercury switch attached to the belt which is to be worn around the waist, the switch in the mid-axillary line. Gross body movements move the mercury to close the circuit and register on the counter. See text.

(2) Fine psychomotor task performance was evaluated by having the patient, for a period of 15 seconds, pick up one at a time as many red coloured sticks as she could from a collection of 120 sticks of five different colours (Task I).

In addition, the patient was asked to press and release with her finger the key of a commercial digital counter (of the type used in counting blood cells) as often as possible during a 15 second period. The patient's score was then read from the number on the counter at the end of the trial (Task II). Several practice sessions were allowed, and these tests were performed daily in the mid-morning.

(3) 24-hour urines were collected daily, and creatinine levels were taken to determine the completeness of the collection procedure. Urine 17-OH corticoid levels were determined by the method of Silber and Porter. Values were reported as mg. corticoids per 24 hours.

(4) Mood changes were measured by the patient by means of a self-administered mood test. The requirements for this test were that it could be obtained rapidly and repeatedly over a period of several weeks. This scale was adopted from a combination of the Clyde Mood Scale and the Nowlis Mood Test and was scored in categories as dictated by their standardization data. The scale was found useful, and correlated well to clinical state in a separate study (Ferman, 1965).

The patient rated herself at the same time each day on a number of items describing subjective feelings at the moment. These items were divided into a manic and depressive scale. Ratings were 0 to 4+ on each item. Manic items were: boastful, defiant, impulsive, rude, bossy, nagging, demanding and angry. Depressive items were: lonely, depressed, downhearted, sad, blue, regretful, tired and sluggish. For scoring purposes depressive items were given negative values and manic items positive values. A sum of the values for each scale was determined. Depressive sums were deducted from manic sums. Negative values were eliminated by adding a constant to each score. In addition, the patient rated herself daily on 8 items comprising the anxiety subtest of the scale. The items were: afraid, worried, anxious, upset, apprehensive, "clutched up," fearful and insecure. Ratings were 0 to 4+ on each item. Scoring was achieved by determining daily sums.

(5) Nurses' ratings of the patient's mood were obtained from a behaviour rating form which the nursing staff filled out each day. This form consisted of 9 manic items and 9 depressed items. The patient was evaluated every day in terms of each item on the list.

These items were: Manic scale—vulgar, loosely creative, distractable, prankish, impulsive, combative, angry, irritable, restless. Depressed scale—lacking initiative, brooding, preoccupied, sad, weeping, somatic complaints, indifference, apprehensive, motionless. Each was rated from 0 to 4, 4 being the most severe. The patient then received a daily manic rating, a daily depressive rating and a net mood rating which was the difference between the two

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components of the overall mood. Two psychiatrists independently observed the patient, and their clinical observations were in general agreement with the nurses' objective rating of the patient throughout the study.

Statistical Analysis

The analysis was oriented toward a descriptive picture of the interactions of these variables through the three phases of the patient's clinical course, using a multiple correlation technique. The single case circumstance prevents a very adequate approach to the question of significance, so that it must be kept in mind that apparently significant

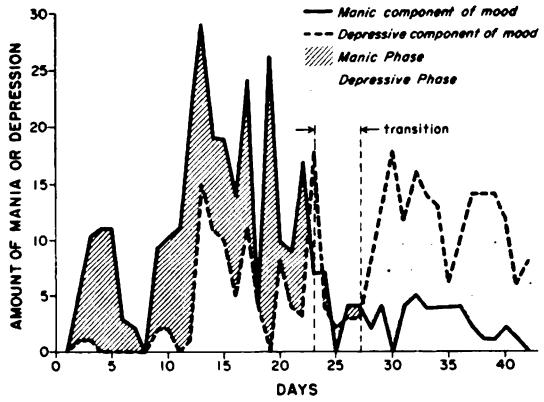


FIG. 2.—A simultaneous plot of "manic" and "depressed" items (here called "amount") during the manic phase and the depressed phase of the 42 day cycle. When compared with Fig. 3, it will be noted that the peaks of excretion of Porter–Silber chromagen follow the number of depressed items, even through the manic phase.

relationships may be due to chance. The manic and depressed phases are clearly seen from the plot of the nurses' rating of the patient's mood (Fig. 2). The first 22 days of the study were clearly manic; days 23 to 27 were transitional; and days 28 to 44 were considered as the depressive phase. The corticosteroid concentrations were handled statistically as the logarithms of the concentrations in order that the steroid values might be related to the other variables in a more linear fashion. Since marked changes took place in as few as 2 or 3 days, no interpolations were made for days on which data were missing. In computing the correlations, only those days on which measurements of both variables had been made were included in the computations.

The correlation between each pair of variables x and y was estimated on an IBM 7094 computer, using the product-moment technique.

RESULTS

Table I is a summary of the relationships between variables. The numbers in parentheses refer to the number of measures available for use in the computation. There are several relationships which appear interesting. No. 2 (depressed items) is consistent with the positive correlation between depression and glucocorticoid excretion reported by several workers. This relationship is similarly seen in No. 5 (ratings by observers) in that the nurses' net rating of the patient as depressed correlated with an increase in 17-hydroxycorticoid excretion. Both of these relationships were obtained by correlating items from the depressive scale throughout both the manic and the depressed clinical phases.

Figure 3, however, indicates that there was no significant difference between the mean 24-hour 17-hydroxycorticoid excretion in the clinically manic and in the depressive phases. Of interest is the almost weekly occurrence of a

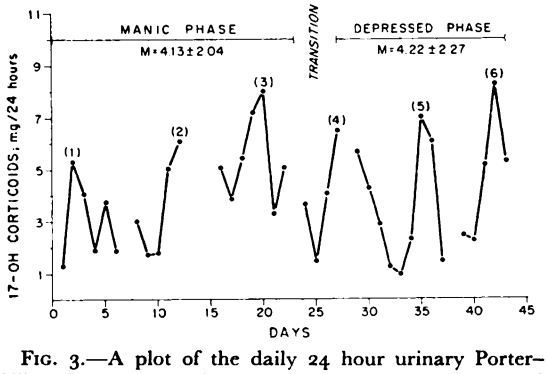


FIG. 3.—A plot of the daily 24 hour urinary Porter–Silber chromagen levels. Points that are missing correspond to the days that EST was used to abort a clinically dangerous state. See text.

https://doi.org/10.1192/bjp.112.483.149 Published online by Cambridge University Press

TABLE I

Variables Correlated		Manic Phase (Day 1–22)	Late Manic Phase (Day 9–22)	Depressed Phase (Day 28–42)
1. Manic component of mood	Gross Motor movement	−0·52 (20 points)	−0·63 (13 points)	0·62 (13 points)
2. Depressed component of mood	17-OH steroid level	0·56 (14 points)	0·76 (8 points)	0·57 (10 points)
3. Depressed component of mood	Psychomotor Task No. 1	−0·27 (12 points)	−0·37 (9 points)	0·69 (9 points)
4. Depressed component of mood	Psychomotor Task No. 2	0·06 (12 points)	0·07 (9 points)	0·68 (9 points)
5. *Nurse's evaluation of patient's mood	17-OH steroid level	−0·06 (15 points)	−0·61 (8 points)	−0·65 (13 points)
6. Psychomotor Task No. 1	Psychomotor Task No. 2	0·80 (12 points)	0·85 (9 points)	0·64 (9 points)
7. Patient anxiety	Depressed component of mood	0·67 (22 points)	0·63 (14 points)	0·82 (7 points)
8. Gross Motor movement	Depressed component of mood	0·40 (20 points)	0·51 (13 points)	0·87 (7 points)
9. Gross Motor movement	Patient's anxiety	−0·34 (20 points)	−0·33 (14 points)	0·90 (7 points)
10. Psychomotor Task No. 1	Patient's anxiety	0·09 (12 points)	0·16 (9 points)	0·79 (5 points)
11. Psychomotor Task No. 2	Patient's anxiety	0·31 (12 points)	0·34 (9 points)	0·91 (5 points)
12. Manic component of mood	Patient's anxiety	0·64 (22 points)	0·67 (14 points)	0·22 (7 points)

*The higher the score, the more manic and vice versa.

marked rise in 24-hour corticoid values through both the manic and depressive phases. The following are typical excerpts from ward staff notes from each of these peak days (Fig. 3): (1) "Upset about poor management of beach outing; argument about whether to go; hyperactive, and voluble." (2) "Striking staff with fists in response to newly-introduced possibility of transfer to a State Hospital." (3) "Up all night; physically violent; vulgar; hyperactive; talks of killing various members of the staff." (4) "Guilty ruminations; unable to dress or eat; feels her picture will be in the paper as a criminal; immobile; apologetic." (5) "Apathetic; unable to dress; sleepless." (6) "Lethargic, sad, lacking initiative; worried." These marked rises in corticoid values have been called "depressive crises" by Bunney (1964; 1965), and therefore it is of interest that in our patient they occurred on days of severe disturbance during both manic and depressive clinical states; it may be, therefore, that they are not specifically related to depression.

A relationship which emerged in this study, and which was not obvious but suspected before the design of the experiment, concerns

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the apparent increase in motility, as measured by the counter, with depression and its relative decrease during the manic phase (Nos. 1 and 8; Table I). In another study using this gross motor movement counter on patients with affect disorders (Ferman, 1965), two out of five patients showed a similar significant increase in counts during the depressive phase compared with the manic phase. The other three showed no relationship between mood state and motility. This would indicate that either the measurement technique is inadequate and we are seeing random deviations, or that the gross motility pattern in response to affective state is not stereotyped in manic-depressive patients, some patients increasing their gross motor activity during a depressive phase. The subject of our study, as well as other hypomanics, often appear to give the impression of increased motor activity by their flight of ideas, disorganization, and volubility. Gross motor movement appeared to increase as a function of felt discomfort (No. 9) which was correlated with the depressed component of mood.

Another theme which appears in the data and has been suggested by the work of Rizzo *et al.* (1954) and Sachar *et al.* (1963) concerns the interaction of a general subjective discomfort factor which we have called "anxiety" with both the manic and depressive mood component (Nos. 7 and 12), more marked during the depressive phase (No. 7). Although we expected higher corticoid correlations with this item, it may play some role in the corticoid data, operating via the observed mood components.

It is of interest that the psychomotor tasks correlated well with each other (No. 6) and appeared to be driven by the "anxiety" factor (Nos. 10 and 11) and increased during the depressive phase. This suggests an increased capacity to carry out movements during the depressed phase (Nos. 3 and 4) and is consonant with the apparently paradoxical relationship between mood indicators and gross motor movement counts reflected in No. 1.

Although the manic items correlated negatively with motility in the manic phases, they correlated positively in the depressive phase. This, plus our failure to find the direct correlation of 17-hydroxycorticoid excretion with motility, in spite of the depression-corticoid and depression-motility positive relationships, introduces some difficulty in integrating these relationships understandably; it also suggests the effects of other, unmeasured relationships.

An interesting point was noted that if the first eight days of the study were omitted, most of the correlation coefficients for the manic phase were markedly increased (Table I—Column 2). In fact, two new correlations became apparent. Gross motor movement correlated positively with the depressive component even during the manic phase (No. 8) and steroids moved inversely with mood during both depressive and manic phases (No. 5). As mood rose (increased mania), steroid levels dropped.

The significance of this finding, if any, is conjecture. Upon reviewing the clinical picture, it was noted that during the first eight days of the study, there were either minimal features or no features of depression present. Whether depressive affect serves as a driving mechanism is a moot point and warrants further study.

Discussion

Although certainly no definitive deductions can be made from an intensively studied single case, the very frequent, short, predictable and yet marked mood states presented by this patient appeared to us to offer an opportunity to study some previously reported relationships between variables within a relatively brief period of time, without the problem of individual differences. The statistical relationships reported are best viewed as descriptive, with no implications as to their significance.

There appear to be at least two generally descriptive psychological states involved in the increase in 17-hydroxycorticoid excretion associated with depression. One, as indicated by our "anxiety" factor and reported in several studies by Board *et al.* (1957), Gibbons *et al.* (1960), Sachar *et al.* (1963) and others, appears to be an "internal suffering", "felt discomfort", "decompensation", what Hamburg (1962) calls "distress", which may be more marked in the depressive phase than in the manic phase. The other may be more affect-specific; this has been

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suggested by Bunney *et al.* (1965) and Kurland (1964). Their reports of significantly large corticoid elevations in advance of or closely accompanying clinical depressive episodes have been interpreted in this way.

In addition, it is of interest that the mean daily corticoid excretion was the same in both the clinically manic and the depressive phase and that crisis-associated augmentation of urine corticoids had both manic and depressive behavioural correlates. One could speculate that the underlying depressive component was variably operative during mania and might be the pertinent affect in the periodic elevations during mania. A comparison between the depressive factor (Fig. 2) and corticoid excretion (Fig. 3) profiles, as well as the results of the correlation computations (Table I), are consistent with this view.

Our pilot data suggest that motility may be a factor that should be monitored in mood-corticoid studies. Clinical impression of a patient's motility level may not be a sufficient control for this variable. Relationship 9 indicates that the gross motility level may be related to felt discomfort of a non-specific sort. Certainly it would appear that motor responses are person-specific; agitation is a frequently seen clinical concomitant of depression.

The use of fluctuating metabolic variables, correlated with clinical state, appear to have continuing great promise in biological approaches to the pathophysiology of mental disease. As biochemical sophistication grows, and such phenomena as corticoid-produced enzyme induction become possible to study in intact man, the 17-hydroxycorticoid correlations with acute transitional states in affect disorders will assume greater potential meaning.

Summary

A repeated measurement, polyvariable study of a manic-depressive patient throughout one cycle has: (1) added evidence in favour of the previously reported relationship between depression and increased urinary excretion of 17-hydroxycorticoids, with, however, the introduction of the possibility that it is not as specific as previously reported in that the manic state is also associated with periodic elevations in corticoid excretion; (2) suggested the possibility that non-specific "discomfort" and motility parameters warrant attention and control in such studies.

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(*Received 4 March, 1965*)

https://doi.org/10.1192/bjp.112.483.149 Published online by Cambridge University Press