METABOLIC VARIATIONS IN MANIC-DEPRESSIVE PSYCHOSIS

By

J. DAWSON, M.Sc., M.B., Ch.B.

R. P. HULLIN, Ph.D., M.Sc., A.R.I.C.

Lecturers, Department of Biochemistry, University of Leeds

and

BEATRICE M. CROCKET, M.B., Ch.B., D.Psych.

Department of Psychiatry, University of Leeds

In previous investigations of changes observed in the blood levels of acetylmethylcarbinol and butane-2:3-diol in patients with manic-depressive psychosis (Dawson *et al.*, 1954), the blood levels of a large number of patients in one mood phase were compared with the levels in another group of patients in a different mood phase. This procedure showed that the differences between the various mood phases were statistically significant. A lack of correlation in time between the chemical changes and the alteration in mood might account for the limited degree of correlation obtained. Thus, if the chemical change preceded the mood change, some of the data would not correspond with the observed mood state during which the blood sample was taken.

Another uncontrolled factor in the previous investigation was the diet; whilst all the blood samples were taken after a 12 hour fast, there was a large difference in the previous dietary history of the patients due to their mental state. Again, only blood levels were investigated and these might have been considerably affected by alterations in kidney activity.

For all these reasons, a different approach to the problem was made, and a small number of patients has been studied closely through a series of mood changes so as to enable us to determine the time relationship, if any, between the change in mental state and the chemical change. The patients were segregated into a small ward where their food intake was determined and 24-hour urine collections made; whilst in the unit, patients were maintained without sedation and without electroconvulsant therapy.

On the basis of the previous work, it was concluded that the variations observed in the blood levels of acetylmethylcarbinol and butane-2:3-diol did not, in themselves, determine a change in mood but were indicators of some other, more fundamental alteration in the metabolic state of the subject. Consequently, changes in extracellular fluid volume as estimated by determinations of the thiocyanate space, were also investigated with these patients. Estimations of urinary constituents were also made to determine the effect of the kidneys in influencing blood levels.

Organization of the Ward

This consisted of a dormitory with accommodation for 4 patients, a room for nursing staff, an office for the psychiatrist and a day room in which the patients could read, listen to the wireless or do handicrafts. Two special nurses

https://doi.org/10.1192/bjp.102.426.168 Published online by Cambridge University Press

were appointed to the unit, with a third who acted as relief during the days when the permanent staff was off-duty. The unit nurses were responsible for the ward from 6 a.m. to 10 p.m. and kept careful, detailed notes on the behaviour and affect of all patients in the ward; they also attended to the patients' meals, weighing the food provided and any left, measuring the fluid intake and supervizing, as far as possible, the collection of 24-hour samples of urine. During the night, the research unit was supervised by the nursing staff on duty in the admission hospital, of which it was a part.

Patients were weighed twice a week. The special diet, selected to provide an intake of approximately 2,400 calories, was supplied from the main kitchens; it was not difficult to prevent the patients from obtaining additional food, as the unit was separated from the rest of the hospital.

Selection of Patients

The ideal patient for this investigation should be a young adult (under 40), of average intelligence exhibiting alternating manic and depressive mood changes, with intermittent normal periods, and showing minimal personality or intellectual deterioration. Such cases are rare today in the mental hospital ward and to supplement our clinical material, older patients were included who had shown spontaneous remission from previous manic or depressive episodes. The criteria for selection in this group were (*a*) no evidence of marked deterioration in intellect or personality, (*b*) a reliable history of more than one previous attack of mania or depression of relatively short duration with remission without the use of electroconvulsant therapy, (*c*) the occurrence of the first attack of mania or depression before the involutional period. The inclusion of this type of patient has given us data on some individuals who remained in the same mental state throughout the investigation; these data are reported to demonstrate that no significant chemical change occurs during the unaltered mood state.

Psychiatric Assessment

A full psychiatric history was obtained, where possible, from the patient and near-relatives. Psychological testing was used to augment clinical estimation of general intelligence and to compile a personality profile of each patient. The mood change, whilst the patient was in the unit, was determined by reference to a daily clinical assessment by the psychiatrist, and a detailed nursing report on the activities and behaviour of each patient. In order to delineate minor fluctuations of mood and to try to forecast the appearance of overt mood changes, this was supplemented by a monthly routine Rorschach test.

Collection of Material for Chemical Analysis

Blood samples (10–15 ml.) were obtained twice weekly from fasting patients for the determination of acetylmethylcarbinol (AMC), butane-2:3-diol (BD), glucose and pyruvate. Thiocyanate space determinations were made weekly.

Twenty-four hour collections of urine were made as a routine procedure and analysed every other day for AMC, BD, creatinine and uric acid.

Methods

AMC and BD were determined by the method of Happold and Spencer (1952) adapted for blood by Dawson, Hullin and Pool (1954). Similar methods were used for the urine analysis, the protein precipitation stage being omitted. Blood glucose was estimated by the method of Hagedorn and Jensen (see Hawk

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https://doi.org/10.1192/bjp.102.426.168 Published online by Cambridge University Press

TABLE I

Variations in the Blood Levels of Glucose, Pyruvate, Acetylmethylcarbinol (AMC), Butane-2:3-diol (BD) and in the Thiocyanate Space (TS) of Subjects With and Without Mood Changes

Blood Levels are Recorded as mg. 100 ml. ± Standard Error of the Mean; Thiocyanate as litres/Kg. Body Weight

Subject	No. of Blood Determinations	Mood	Glucose	Pyruvate	AMC	BD	BD/AMC	AMC+BD	No. of T.S. Determinations	T.S.
Patients without mood changes:										
J.H. ..	14	Normal ..	80±1·7	0·78±0·02	0·031±0·004	0·323±0·018	15·1±3·3	0·354	7	0·293±0·008
A.R. ..	12	Normal ..	87±2·0	0·83±0·05	0·034±0·006	0·305±0·011	12·8±3·1	0·339	7	0·309±0·010
G.J. ..	40	Mania ..	80±1·0	0·82±0·05	0·034±0·003	0·314±0·019	13·0±1·6	0·348	20	0·305±0·005
H.H. ..	16	Depression ..	83±1·3	0·81±0·05	0·039±0·003	0·259±0·020	8·0±1·2	0·298	6	0·282±0·008
Patients with mood changes:										
H.A. ..	37		81±1·0	0·98±0·01	0·037±0·008	0·411±0·040	21 ±2·1	0·448	18	0·385±0·013
C.B. ..	33		79±1·0	1·05±0·12	0·030±0·006	0·300±0·028	18 ±2·4	0·330	15	0·356±0·017
W.S. ..	17		75±1·5	0·81±0·03	0·026±0·005	0·403±0·034	18 ±3·4	0·429	9	0·337±0·014
F.K. ..	13		90±2·5	0·89±0·04	0·050±0·008	0·214±0·021	8·5±2·2	0·264	7	0·300±0·014

et al., 1947), and pyruvate by the method of Friedemann and Haugen (1943). Thiocyanate space determinations were made using the method of Lavietes *et al.* (1936), the correction for red-cell thiocyanate being omitted. The actual serum thiocyanate estimations were made by the method of Bowler (1944).

Uric acid in urine was determined by the method of Benedict and Franke (1922) whilst urinary creatinine was estimated by the modification of the Jaffe colour reaction suggested by Folin and Wu (1919).

Results

Table I has been constructed by dividing the patients into two groups; those patients whose mood remained constant during the whole of the period studied and those who had mood swings whilst being investigated. If the latter group showed a larger standard error of the mean of the various chemical determinations for the whole period of investigation then it could be inferred that a greater variation exists in patients suffering from mood changes. Only in the results for thiocyanate space and butane-2:3-diol, does a larger coefficient of variation exist in the group with mood swings. This variation is probably reduced by the small period of time relative to the total period under study during which the actual mood change was operating.

As the table shows, there is no large difference between any of the mean values for the group with mood changes compared with the group of patients with constant mood. It may be concluded from this treatment of the data that, if any chemical change occurs, it persists only for a relatively short time in relation to the change in mood. The exception may be that of thiocyanate space which does vary more in mood swingers than in the group with constant mood.

Similar treatment of the results of urine determinations (Table II) did not show a larger variation in the group with mood changes and provided no evidence to support the view that a change in mood is associated with any variation in the urinary excretion of AMC or BD.

Table II

Variations in the 24-Hour Urinary Excretion of AMC, BD and Uric Acid of Subjects With and Without Mood Changes. (Units: mg./g. Creatinine ± S.E.M.)

Subject	No. of Determinations	Mood	AMC / Creatinine	BD / Creatinine	Uric Acid / Creatinine
(*a*) Patients without mood change:					
J.H. ..	14	Normal ..	1·18±0·11	8·6±0·65	180± 4
A.R. ..	19	Normal ..	0·82±0·07	11·4±1·00	230±10
G.J. ..	52	Mania ..	2·60±0·22	17·1±0·80	160±24
H.H. ..	18	Depression ..	1·06±0·02	10·9±0·47	190± 8
(*b*) Patients with mood changes:					
H.A. ..	50		0·71±0·06	9·2±0·48	246± 7·4
C.B. ..	53		0·71±0·05	10·3±0·53	232± 5·4
W.S. ..	21		1·03±0·10	8·4±0·41	184± 4·8
F.K. ..	12		0·59±0·05	7·45±0·50	189±11·5

The results for patients showing changes of mood are next classified into the depressed, manic or normal interphases in order to see whether any change

https://doi.org/10.1192/bjp.102.426.168 Published online by Cambridge University Press

https://doi.org/10.1192/bjp.102.426.168 Published online by Cambridge University Press

TABLE III

Variations in Blood Levels of Glucose, Pyruvate, AMC, BD and Thiocyanate Space (T.S.) of Subjects During the Normal, Depressed and Manic Phases of Manic-depressive Psychosis. (Units as in Table I)

Subject	No. of Blood Determinations	Glucose	Pyruvate	AMC	BD	BD/AMC	AMC+ BD	No. of T.S. Determinations	T.S.	T.S. (litres)
Normal phases:										
H.A. ..	9	82±2·3	0·84±0·12	0·028±0·007	0·298±0·028	24·8±5·0	0·326	5	0·445±0·032	22·9±2·3
C.B. ..	15	79±1·4	0·97±0·05	0·028±0·007	0·267±0·023	18·1±3·6	0·295	7	0·417±0·023	26·6±1·9
W.S. ..	13	74±1·4	0·80±0·04	0·033±0·005	0·417±0·037	11 ±1·4	0·450	7	0·327±0·016	23·6±1·1
F.K. ..	6	88±4·2	0·84±0·02	0·049±0·009	0·200±0·025	6 ±2·5	0·249	3	0·32	21·5
Manic phases:										
H.A. ..	15	78±1·4	0·98±0·07	0·036±0·008	0·541±0·065	21·3±2·8	0·577	7	0·342±0·018	15·7±0·8
C.B. ..	17	76±1·2	0·80±0·04	0·016±0·001	0·363±0·037	23·4±4·2	0·379	6	0·311±0·012	20·9±0·7
W.S. ..	4	74±2·9	0·73±0·07	0·010±0·00	0·391±0·064	38 ±6·6	0·401	2	0·287	20·8±0·2
F.K. ..	2	101	1·06	0·074	0·172	3·5	0·246	1	0·27	17·3
Depressed phases:										
H.A. ..	15	83±1·4	0·99±0·07	0·047±0·021	0·277±0·033	16·3±3·2	0·324	7	0·393±0·003	17·8±0·1
C.B. ..	7	84±3·7	1·71±0·55	0·069±0·025	0·304±0·087	11 ±3·8	0·373	2	0·302	19·6
F.K. ..	5	90±2·9	0·87±0·06	0·026±0·005	0·274±0·030	13 ±4·1	0·300	3	0·290	18·1±0·5

The test of significance adopted was the analysis of variance; the following results were obtained when the thiocyanate space values for the different mood phases were treated in this way.

H.A. Between normal, manic and depressed phases. Probability that difference due to random variation $p<0·05$.
C.B. Between normal and manic phases. $p<0·01$.
W.S. Between normal and manic phases. $p<0·05$.
F.K. Number of estimations in different phases was too small for satisfactory statistical analysis.

takes place in the chemical constituents of the blood in the various mood states. It is assumed in this treatment that any chemical change is closely associated in time with the mood state.

The results, shown in Table III, demonstrate that the thiocyanate space, either as an absolute determination or as a fraction of the body weight, is at a maximum during the normal interphases. The mean thiocyanate space values during mania are not significantly different from those in depression.

Patient W.S., the only one of the group to have only one short mood change, shows a significant difference between the blood AMC level in mania and normality and consequently is the only patient in the group whose blood BD/AMC ratio is significantly increased in mania. In contrast, patient F.K. who had a series of rapid fluctuations in mood, shows the opposite of this change in mania. The other two patients, H.A. and C.B., who had long periods of either mania or depression with relatively long periods of normal mood, do not show any very significant chemical change.

This method of treatment of the data assumes that, if the mood change persists, so must any chemical change, and does not allow of the possibility that the chemical changes might be out of step with the mood changes. The results in Table III indicate that the thiocyanate space alterations are associated in time with the changes of mood. The changes in urinary excretion of AMC, BD and uric acid associated with the mood of the patient are shown in Table IV.

TABLE IV

Variations in the 24-Hour Urinary Excretion of AMC, BD, and Uric Acid of Subjects During the Normal, Depressed and Manic Phases of Manic-depressive Psychosis (mg./g. Creatinine)

Subject	No. of Estimations	AMC / Creatinine	BD / Creatinine	Uric Acid / Creatinine
Normal phases:				
H.A.	12	0·8 ±0·20	12·8±2·1	260± 6
C.B.	19	0·6 ±0·05	10·4±0·8	230± 5
W.S.	13	1·24±0·14	8·3±0·5	180± 6
F.K.	6	0·75±0·10	7·3±0·97	190±17
Manic phases:				
H.A.	24	1·1±0·20	9·3±1·8	240±14
C.B.	26	0·8±0·10	9·0±0·4	260± 7
W.S.	6	0·5±0·12	8·4±0·7	190± 7
F.K.	1	0·5	6·9	140
Depressed phases:				
H.A.	21	0·5±0·05	7·7±0·4	240± 6
C.B.	12	0·6±0·04	13·6±2·2	190±10
F.K.	6	0·42±0·02	7·7±1·4	170±14

The excretions are expressed as a ratio of creatinine excretion to minimize the error due to urine loss, assuming that the creatinine excretion would be approximately constant from day to day. No clear picture emerges of specific differences in the excretory pattern between the various mood states.

The data has been examined so far on the assumption that any chemical changes are associated simultaneously with the mood changes and that they

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persist as long as the mood change persists. This is true for thiocyanate space but not for the other chemical estimations which have been made. The next development was to consider the possibility that the chemical change precedes the mood change and does not persist for the whole period of the altered mood. The group of patients studied could be subdivided on the basis of the periodicity of mood changes. Two patients (H.A. and C.B.) had long periods of mania and depression with relatively long, normal interphases ("slow-swingers") whilst the other two (F.K. and W.S.) had only short periods of mania and depression with limited normal interphases. It might well be that the periodicity of the chemical changes was likewise different in the two sub-groups. On empirical grounds, we assumed that in cases of short periodicity the chemical changes preceded the mood changes by 1 week whilst in the two patients with more infrequent changes the time interval between chemical and mood changes was 3½ weeks. The results were then re-grouped on this assumption by moving the time scale with respect to the chemical data so that every mood change was located either 1 or 3½ weeks before it actually occurred. Subject to this change, the results were again classified according to the various mood states (Table V). Thiocyanate space values were not treated in this way since the change in this factor actually corresponds in time with the mood change and does not so correspond if the time scale is moved.

TABLE V

Variations in the Mean Blood Level Values of Glucose, Pyruvate, AMC and BD in Cases of Manic-depressive Psychosis for the Period (a) *3·5 Weeks*, (b) *1 Week Preceding the Onset of the Mood Phase to the Corresponding Time Before the End of the Phase.* (*Units as in Tables I and III*)

Subject	No. of Estimations	Glucose	Pyruvate	AMC	BD	BD/AMC	AMC+BD
Normal phases:							
(*a*) H.A. ..	9	78·5	0·86	0·034	0·465	15·4	0·499
(*a*) C.B. ..	11	80·6	1·00	0·029	0·237	11·4	0·266
(*b*) W.S. ..	14	76	0·82	0·045	0·391	15·6	0·436
(*b*) F.K. ..	4	97	0·96	0·067	0·174	3·5	0·241
Manic phases:							
(*a*) H.A. ..	7	81·3	0·99	0·013	0·345	32·3	0·358
(*a*) C.B. ..	12	78·7	0·87	0·016	0·317	27	0·333
(*b*) W.S. ..	4	77	0·72	0·023	0·372	24·3	0·395
(*b*) F.K. ..	2	95·5	0·97	0·015	0·266	20·5	0·281
Depressed phases:							
(*a*) H.A. ..	14	81·5	1·08	0·040	0·484	18·8	0·524
(*b*) F.K. ..	5	85·4	0·81	0·048	0·208	7	0·256

The data was treated by the analysis of variance. The probability that the decreased AMC blood level in the manic phases was due to random variation was $<0·01$ for patient H.A. and $<0·05$ for patients C.B., W.S. and F.K.

Considering the greater BD/AMC ratio of the manic phases in a similar manner gave values of $p<0·01$ for patients H.A., C.B. and $<0·05$ for patients F.K. and W.S.

The re-arranged results demonstrate that, in the manic phase, the AMC blood level is significantly lower in every case than in the normal phase;

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corresponding to this, the blood BD/AMC ratio is also increased in the manic phase. The results during depression would seem to indicate that the AMC values are not significantly different from normal values. The BD values show no consistent change between the mood states; similarly, neither the blood glucose nor pyruvate levels show any consistent alteration.

The urinary excretions treated in the same way are presented in Table VI.

TABLE VI

Variations in the Mean 24-Hour Urinary Excretion of AMC, BD, and Uric Acid in Cases of Manic-depressive Psychosis. The Data Tabulated under any Mood State Include Results Obtained During the Period (a) 3·5 Weeks, (b) 1 Week Preceding the Onset of the Mood Phase but not those During the Corresponding Time Interval at the End of the Phase. (Units: mg. per g. Creatinine)

Subject	No. of Estimations	AMC / Creatinine	BD / Creatinine	Uric Acid / Creatinine
Normal phases:				
(*a*) H.A.	15	0·95	9·2	276
(*a*) C.B.	19	0·80	10·5	248
(*b*) W.S.	16	1·07	8·2	188
(*b*) F.K.	3	0·77	8·6	193
Manic phases:				
(*a*) H.A.	9	0·38	7·4	231
(*a*) C.B.	26	0·61	10·7	222
(*b*) W.S.	4	0·92	9·1	170
(*b*) F.K.	3	0·40	7·4	176
Depressed phases:				
(*a*) H.A.	25	0·74	9·85	226
(*b*) F.K.	5	0·40	6·5	168

The test of significance was the analysis of variance. The probability that the decrease in uric acid/creatinine values observed in both the manic and depressed phases might be due to random variation was $<0·01$ for patient H.A., and $<0·05$ for patients C.B. and W.S. The small number of determinations obtained in each phase for patient F.K. did not permit satisfactory statistical analysis.

There is a marked fall in the urinary AMC excretion during the manic phase; this is associated with a decreased blood level so the altered urinary excretion is not responsible for the altered blood level but is probably caused by it. The AMC excretion is also reduced in depression.

There is no consistent alteration in the BD excretion pattern but the uric acid/creatinine ratio is reduced both in mania and depression. These observations could not be discerned from the urine results when treated on the assumption that the chemical and mood changes occur simultaneously.

DISCUSSION

Previous work by Dawson *et al.* (1954) has shown that the blood AMC level is reduced below normal in the manic phase. This conclusion emerged from a statistical study of results derived from a large number of subjects from whom only one or two blood samples were taken. The observation could not be demonstrated in every individual case and there was quite a large degree of variation in the extent of the reduction. It was possible that the variation might be due to a lack of correlation in time between the mood state and the blood level of AMC. In this series of patients, we have been able to demonstrate that the

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blood changes are not simultaneous with the mood changes but occur prior to them. The period between the alteration in blood values and mood change varies from subject to subject and appears to be related to the pattern of mood variation.

The two patients with long periods of mania, depression and normality (the so-called "slow-swingers") seem to exhibit a change in blood level from 3–4 weeks before the mood change is observed. In these patients the chemical change has to persist for quite a long period before the mood state changes. There is little evidence that the magnitude of the blood change determines the length of time it has to operate before the onset of mood alteration.

Statistically there does not appear to be any characteristic alteration in blood AMC level in depression as compared with that in the normal interphases. This may, in part, be due to the difficulty of accurately timing the onset of mood change, particularly in the "slow-swingers". Our general impression is that the blood AMC level is increased at the beginning of a depressed phase but it is very difficult in some of these patients to determine exactly when depression ends and normality begins.

The blood BD levels do not indicate any specific effect and may be regarded as resulting from non-specific reduction of the AMC. Since the BD levels do not vary significantly, the BD/AMC ratio is markedly increased prior to and during the early part of a manic phase.

The clearance rates of AMC and BD by the kidney indicate that 95 per cent. of these compounds filtered in the glomerular filtrate are re-absorbed by the renal tubules, suggesting that when the blood level falls AMC excretion in the urine will be decreased. This reduced excretion of AMC has been demonstrated so it is unlikely that the kidney is responsible for the reduction in blood level observed. The blood level of BD prior to and during the initial part of a manic attack is not so clearly altered and the BD urinary excretion values for this period are correspondingly variable.

Pyruvate is the immediate precursor of AMC and Dawson and Hullin (1954) showed that pyruvate, when injected, will increase the AMC blood level. In the patients studied however, alterations of blood pyruvate level seem to play no part in producing the variations in AMC level; neither is the latter determined by the blood glucose level. This is in spite of the demonstration in the earlier communication (Dawson *et al.*, 1954) that the blood AMC level is different during the absorptive phase of digestion from that in the fasting state.

The thiocyanate space determinations in subjects with constant mood do give relatively constant values. The values for fluid in this space as a percentage of the total body weight are high when compared with the results of other workers, largely due to the omission of the correction for the thiocyanate which has entered the red blood cells. This simplification of the procedure does not however invalidate the finding of a marked reduction in thiocyanate space associated with the manic and depressed phases, the change not occurring before the mood change. The observed reductions are towards values which are more nearly normal for the body weight and sex and it is during the mentally normal interphases that the most abnormal values for thiocyanate space are found. The changes observed may be due to a true increase in the extracellular fluid volume or to an alteration in the permeability of cells with respect to the thiocyanate ion. Further work is necessary to decide which of these two mechanisms is operating to produce the increase in thiocyanate space seen in the normal interphases.

The urinary uric acid/creatinine ratio is reduced in both mania and

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depression. This reduction can only be shown when the same slipped time scale is used as is used for the correlation of blood AMC level with mood state. If the ratio can be taken as an index of adrenal cortical activity, then there is reduced activity of this endocrine organ prior to the onset of a manic or depressed phase as compared with that preceding a normal phase.

It is interesting to speculate that the chemical changes we have observed might in fact be produced by alterations in activity of the adrenal cortex. There is no evidence that the reduced AMC blood level will itself produce a mood change. Similarly it is difficult to understand how the abnormally large thiocyanate space could be responsible for the production of a normal interphase. However, it does seem possible that an alteration in adrenal cortical activity could be responsible both for the chemical changes and, in susceptible subjects, for the disturbance of affect.

Further work is proceeding to evaluate the biochemical significance of electroconvulsant therapy in the treatment of disturbances of affect (with reference to any possible correlation between chemical change and the achievement of a more stable mood state with treatment). Additional investigations are necessary in order to implicate the adrenal cortex in the pathogenesis of mania and depression and the associated changes in blood AMC and thiocyanate space.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the technical assistance of Mrs. Beryl Taylor and the invaluable help of the nursing staff in charge of the patients in the research unit at Menston Hospital, particularly Messrs. McKinley, Ryder, Crookes and Matthews.

Our thanks are also due to the Menston Hospital Management Committee both for financial assistance and for providing the facilities.

SUMMARY

(1) The blood levels of acetylmethylcarbinol, butane-2:3-diol, pyruvate and glucose have been determined at twice-weekly intervals in a group of patients exhibiting alternating manic and depressive mood changes and in a group of subjects without mood variation while under observation. In addition, the thiocyanate space and 24-hour urinary excretions of acetylmethylcarbinol, butane-2:3-diol, uric acid, and creatinine have also been estimated at frequent intervals.

(2) An increase in the thiocyanate space is associated with the normal inter-phases in the group showing alternating manic and depressive mood changes. The variation in thiocyanate space in the group without a mood change during the period of investigation is within normal limits.

(3) A decrease in both the blood level and urinary excretion of acetylmethylcarbinol precedes and is associated with the early part of a manic phase. The relationship in time between the chemical change and the mood change is determined by the periodicity of the cycle.

(4) The uric acid/creatinine ratio is decreased before and in association with the initial part of both manic and depressed phases.

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