Psychological Reports, 1965, 17, 563-582. © Southern Universities Press 1965
Monograph Supplement 2-V17

DIFFERENCES IN INTERMEDIARY METABOLISM IN MENTAL ILLNESS

GEORGE WATSON[1]
Lancaster Foundation for Scientific Research, Pasadena

Summary.—Exploratory tests of the hypothesis that enzymatic blocks due to unsuspected co-factor deficiencies might be a causal factor in functional mental illness revealed that treatment with certain vitamins or minerals in some instances could apparently make mentally ill *Ss* more ill. Extensive clinical tests led to separation of the principal vitamins and minerals into groups in terms of whether or not they would improve or worsen the condition of a given *S*. Two basic types of mentally ill *Ss*, Types I and II, and two corresponding types of vitamins and minerals were tentatively established. Blood studies revealed statistically significant differencees between *Ss* classified as Type I or as Type II, the greatest differences being found in the plasma pH and in the dissolved $CO_2 + H_2CO_3$. Preliminary exploration of the effect of treatment indicates these variables co-vary with psychological status of *S* when given appropriate vitamins and minerals. Since Type I *Ss* showed an *increase* in dissolved $CO_2 + H_2CO_3$ with treatment, it is suggested that they are *slow oxidizers*, and Type II *Ss* who show a *decrease* are *fast oxidizers*.

Several types of anomalies involving intermediary metabolism have been reported in schizophrenics, including nitrogen retention in periodic catatonia, ketonuria, abnormal glucose tolerance, as well as others (9). These findings, although not characteristic of schizophrenia in general, nevertheless suggest that in some mentally ill patients biochemical lesions may exist in the mechanisms for energy release from nutrients, since nitrogen retention, ketonuria, and abnormal glucose tolerance reflect abnormalities in protein, fat, and carbohydrate metabolism.

This possibility appears to gain support from the discovery that mental illness may be induced in emotionally healthy volunteer *Ss* when they are placed on an experimental semi-starvation diet (7). Although mental illness induced in this manner probably does not result from a metabolic defect, but rather from a caloric deficit, the end-result may be the same, namely, an insufficient production of energy resulting in impaired functioning of the central and peripheral nervous systems.

The report that starvation-induced neuroses and psychoses cannot be differ-

[1]The author wishes to express his very deep gratitude to Prof. Andrew Comrey of the University of California at Los Angeles for his continuing advice and help in this research in matters of experimental design, analysis and presentation of data, in the preparation of the manuscript, and in many other ways, not the least of which has been his continuing support and encouragement. The author also acknowledges with deepest appreciation the medical and technical supervision of this research and the continuing aid and constant support provided by Dr. W. D. Currier, Medical Director of the Lancaster Foundation, without whose dedication and help the present study could not have been completed.

entiated clinically from "functional" mental illness—which many believe to originate in psychological conflict and trauma—is particularly striking (1).

It has long been known that a deficiency of a single vitamin, nicotinic acid, can cause psychosis, and that this illness can be cured by administering niacin or its amide. Other vitamins in addition to niacin also have been implicated in the etiology of specific mental disorders (8). Since several of the vitamins and some of the trace minerals function as coenzymes or as constituents of enzymes in both the Embden-Meyerhoff (glycolytic) and Kreb's (tricarboxylic acid) metabolic pathways, if mental illness can result from malfunctioning of such energy producing systems, it appears that the deficiency of one or more vitamins and/or minerals could play either a primary or secondary role in the etiology of some neuroses and psychoses.

Experiments designed to explore the hypothesis that enzymatic blocks due to unsuspected co-factor deficiencies might be a causal factor in functional mental illness produced an altogether surprising result, namely, that treatment with vitamins and minerals in many instances could apparently make mentally ill patients more ill (11). For example, it was frequently found that two *Ss*, paired as closely as possible for age, sex, duration of illness, clinical symptoms, and psychological test scores, would respond differently to an identical combination of vitamins and minerals, one improving markedly with the other becoming much more ill. In the latter case, discontinuing the treatment generally resulted in improvement within a few days.

Consequently, it appears that certain vitamins and minerals may benefit some mentally ill *Ss* but seem to worsen the condition of others with similar symptoms. This finding led to trial-by-error clinical tests to determine whether it would be possible to separate the principal vitamins and minerals into groups in terms of the criterion of whether or not they would worsen or improve a major symptom such as anxiety, depression, or paranoid reaction in a given *S*. For example, an *S* whose dominant symptom was anxiety was instructed to take a tablet of thiamine chloride (100 mg.) both during an attack of panic and when he felt relatively secure. Trials such as this with thiamine showed that in some *Ss* noticeable relief from anxiety apparently was afforded during an attack and that periods of anxiety apparently became more widely separated. On the other hand, thiamine seemed to produce the opposite result in other *Ss* presenting a similar clinical picture of anxiety neurosis. Since clinical trials such as this with thiamine were alternated with placebos without *S*'s knowledge, it appears that vitamin B_1, for example, can worsen the symptoms of anxiety in some *Ss* as well as bring relief to others.

Extensive exploratory trials of this kind with the principal vitamins and minerals were performed over a period of several years, utilizing over 200 mentally ill *Ss* who exhibited a very wide range of psychological disorders. This re-

TABLE 1

PRINCIPAL VITAMINS AND MINERALS CLASSIFIED IN TERMS OF FAVORABLE/UNFAVORABLE RESPONSE CRITERION IN TYPES I AND II MENTALLY ILL *Ss*

Type I	Type II
Vitamin D	Vitamin A
Vitamin K	Vitamin E
Ascorbic Acid	Vitamin B_{12}
Biotin	Nicotinamide
Folic Acid	Pantothenic Acid
Pyridoxine	Choline*
PABA	Inositol*
Niacin	Citrus Bioflavonoid Complex*
Riboflavin	
Thiamine	
Iron	Calcium
Potassium	Iodine
Magnesium	Phosphorous
Copper	Sodium
Chloride	Zinc
Manganese	

*This substance is arbitrarily classified as a "vitamin" for the purposes of this discussion.

search resulted in the tentative establishment of two basic types of mentally ill *Ss* and two basic classes of vitamins and minerals (Table 1). *Ss* were designated as "Type I" if they appeared to respond favorably to "Type I" vitamins and/or minerals and unfavorably to "Type II" vitamins and/or minerals. *Ss* were designated as "Type II" if they appeared to respond favorably to "Type II" vitamins and/or minerals and unfavorably to "Type I" vitamins and/or minerals.

Blood studies showed large and significant statistical differences between patients who were retrospectively classified as Type I ($N = 12$) or Type II ($N = 12$) in terms of the success of treatment with the corresponding Type I or Type II vitamins and minerals. Table 2 summarizes the before-treatment values for venous plasma pH, dissolved carbon dioxide plus carbonic acid, total lipids, and fasting blood sugar in 24 *Ss*, 12 in each group, showing significant differences between the group means for pH, $CO_2 + H_2CO_3$, and lipids, while the blood sugar difference is not quite significant at the 5% level.

These particular tests proved to be the most promising of many that were investigated for their possible relationship to the Type I-Type II classification of *Ss*. Since the greatest differences between the two types of *Ss* were found in the plasma pH and dissolved carbon dioxide, a small pilot experiment was undertaken to explore the hypothesis that these variables were related both to the Type I-Type II classifications as well as to the psychological conditions of the

TABLE 2

DIFFERENCES IN VENOUS PLASMA pH, DISSOLVED $CO_2 + H_2CO_3$, TOTAL LIPIDS, AND FASTING BLOOD SUGAR BETWEEN TYPE I ($N = 12$) AND TYPE II ($N = 12$) MENTALLY ILL *Ss*

S	Venous Plasma pH		Dissolved $CO_2 + H_2CO_3$ (mM/l)		Total Lipids		Blood Sugar	
	Type I	Type II	Type I	Type II	Type I	Type II	Type I	Type II
1	7.48	7.37	1.02	1.26	880	1315	56	93
2	7.51	7.39	.97	1.23	1150	930	76	59
3	7.51	7.45	.99	1.11	1180	1125	90	105
4	7.55	7.39	.74	1.23	830	1125	86	80
5	7.55	7.42	.74	1.05	500	880	94	53
6	7.50	7.39	.69	1.20	550	1345	108	80
7	7.56	7.36	1.02	1.29	725	1235	122	76
8	7.50	7.45	.91	1.09	665	1035	104	70
9	7.52	7.40	.93	1.22	638	1095	83	96
10	7.53	7.40	.90	1.22	325	1025	76	48
11	7.47	7.39	1.06	1.18	590	685	84	86
12	7.51	7.43	.87	1.09	590	665	108	56
M	7.52	7.40	.91	1.18	719	1038	91	75
	$t = 9.73$*		$t = 6.65$		$t = 3.30$		$t = 1.97$	

*$t_{.05} = 2.074$; $t_{.01} = 2.819$.

mentally ill *Ss* so classified, and that they covaried with the changing psychological status of *Ss* under treatment.

THE EXPERIMENT

Twenty unhospitalized ambulatory *Ss* were selected for an 8-mo. study on the basis of the severity of their illnesses and the length of time they had been ill. Every *S* had an extended history of mental illness for which he previously had been treated without significant success. Twelve had received electroshock therapy, 18 had been under psychotherapy, and all had received one or more forms of psychotropic drugs. Eleven of the 20 were diagnosed by a psychiatrist as psychotic (schizophrenic), while 9 had been diagnosed as neurotic (anxiety, depressive, obsessive-compulsive).[2]

Brief psychological case histories were recorded in an initial interview, together with dietary information in order to determine approximate protein, fat, and carbohydrate intakes. All *Ss* reported that they were eating mixed diets which generally represented the basic food groups. In addition to dietary data, medical histories were also obtained, and routine physical examinations with laboratory tests were given to all *Ss*. The venous plasma pH and the CO_2 content were determined both at the beginning and at the end of the experiment.

[2]Detailed case histories of the individuals who participated in this study will be published elsewhere.

The psychological progress of each *S* was checked by the author clinically in a monthly 30-min. interview, at which time adjustments in medication were made if necessary. *S*s were classified as Type I ($N = 10$) if their initial pH was 7.47 or higher, and as Type II ($N = 10$) if their initial pH was 7.45 or lower. These limits were selected on the basis of previous research (Table 2)

TABLE 3

BEFORE-TREATMENT DIFFERENCES IN VENOUS PLASMA pH, BICARBONATE, AND DISSOLVED $CO_2 + H_2CO_3$ BETWEEN TYPE I ($N = 10$) AND TYPE II ($N = 10$) MENTALLY ILL *S*s

S	Venous Plasma pH		Plasma Bicarbonate		Dissolved $CO_2+H_2CO_3$	
	Type I	Type II	Type I	Type II	Type I	Type II
1	7.55	7.35	13.50	23.50	.48	1.32
2	7.50	7.36	18.50	23.50	.73	1.29
3	7.55	7.38	22.50	24.00	.79	1.25
4	7.55	7.36	17.00	23.50	.60	1.29
5	7.56	7.40	26.00	24.00	.90	1.20
6	7.50	7.35	17.50	22.50	.69	1.26
7	7.55	7.37	18.50	23.50	.65	1.25
8	7.49	7.33	24.00	23.00	.97	1.35
9	7.55	7.36	21.00	22.50	.74	1.23
10	7.56	7.35	20.50	23.50	.71	1.32
M	7.54	7.36	19.90	23.35	.73	1.27
	$t = 5.22^{*}$		$t = 2.94$		$t = 11.75$	

*$t_{.05} = 2.101$. $t_{.01} = 2.878$.

TABLE 4

VITAMIN-MINERAL COMBINATIONS USED IN EXPERIMENTAL TREATMENT OF TYPES I AND II MENTALLY ILL *S*s*

Type I Formula		Type II Formula	
Vitamin B_1	10 mg.	Vitamin A	25,000 IU
Vitamin B_2	10 mg.	Vitamin E	100 IU
Vitamin B_6	10 mg.	Vitamin B_{12}	10 mcg.
PABA	25 mg.	Nicotinamide	200 mg.
Niacin	25 mg.	Pantothenate	50 mg.
Ascorbic Acid	300 mg.	Choline	300 mg.
Vitamin D	2500 IU	Inositol	90 mg.
Potassium Citrate	900 mg.	Bioflavonoids	350 mg.
Magnesium Chloride	100 mg.	Calcium	330 mg.
Copper Gluconate	.6 mg.	Phosphorous	250 mg.
Manganese Oxide	10 mg.	Iodine	.45 mg.
		Zinc Sulfate	10 mg.

*The quantities listed for each type formula represent the basic dosage, which was administered in capsule form, three times daily, after meals. Individual variations in response to treatment occurred, most frequently requiring a reduction in the number of times daily the basic dosage was given.

and represent the lowest pH measured in a Type I *S*, as well as the highest pH determined for a Type II *S*. Before-treatment test values for the two groups are presented in Table 3. The differences between mean values for the Type I and Type II *S*s were statistically significant for all 3 biochemical measures (see Table 3).

The formulas administered to each of the two types of *S*s are listed in Table 4. Type I *S*s were given the formula of Type I vitamins and minerals and Type II *S*s were given the formula of Type II vitamins and minerals.

Results

*S*s were evaluated clinically by the author and placed in one of three categories: (i) clinical remission of symptoms, (ii) marked reduction in intensity of symptoms, or (iii) noticeable reduction in intensity of symptoms.[3]

An *S* was judged to have achieved a clinical remission of symptoms if the major symptoms for which he was being treated were no longer evident. For example, when an obsessive-compulsive neurotic who was a compulsive eater no longer thought about food and no longer consumed huge quantities, she was considered to have shown a clinical remission of symptoms.

An *S* was judged to have achieved a marked reduction in intensity of symptoms if improvement occurred to the point where the manifestations of illness no longer constituted a major problem for him. For example, an *S* was considered as having shown a marked reduction in intensity of symptoms who at the start of treatment presented a severe anxiety neurosis which prevented his driving a car and working, while at the end of the experiment he had obtained a job and drove regularly, although he was still anxiety-prone under stress.

Finally, an *S* was judged to have achieved a noticeable reduction in intensity of symptoms when definite behavioral changes occurred although the illness was still clearly manifest. For example, a withdrawn schizophrenic *S* was judged as showing a noticeable reduction in intensity of symptoms when at the start of treatment he would rarely speak to anyone but his mother and would not voluntarily leave the house, but just prior to the end of the experimental period he had voluntarily taken a trip of several days' duration with members of a radio listeners' club he had joined, after which, however, he exhibited his previous pattern of withdrawal.

Evaluated in the manner just described, every *S* in the experiment showed psychological improvement: 11 out of 20 (55%) were classified as showing

[3]Although previous studies (10, 12, 13) employed both clinical evaluations made by the present author as well as to the Minnesota Multiphasic Personality Inventory, the latter was not used in the present experiment since some *S*s were too disturbed to be evaluated in this manner. However, in all of the previous studies where both clinical judgment by the author and MMPI were used together, each type of evaluation yielded similar confidence levels in assessing psychological change. It should be remarked that in none of the previous experiments was a significant placebo response recorded.

TABLE 5

CLINICAL IMPROVEMENTS IN TYPES I AND II MENTALLY ILL *Ss*

Type I					Type II				
S	Age (yr.)	Sex	Diagnosis	Evaluation*	*S*	Age	Sex	Diagnosis	Evaluation*
1	43	M	Depressive Reaction	+++	1	53	F	Schizophrenic Reaction	+
2	54	F	Schizophrenic Reaction	+++	2	62	F	Schizophrenic Reaction	+++
3	48	F	Schizophrenic Reaction	+++	3	29	F	Anxiety Neurosis	++
4	55	F	Schizophrenic Reaction	+++	4	51	M	Anxiety Neurosis	++
5	27	F	Schizophrenic Reaction	++	5	21	F	Obsessive-Compulsive	+++
6	49	F	Schizophrenic Reaction	++−	6	28	F	Obsessive-Compulsive	+
7	56	F	Anxiety Neurosis	+	7	24	M	Depressive Reaction	+++
8	32	M	Schizophrenic Reaction	++	8	43	M	Schizophrenic Reaction	+++
9	22	F	Anxiety Neurosis	++	9	29	M	Schizophrenic Reaction	+++
10	24	M	Schizophrenic Reaction	+++	10	39	M	Anxiety Neurosis	+

*+++ = Clinical remission of symptoms.
++ = Marked reduction in intensity of symptoms.
+ = Noticeable reduction in intensity of symptoms.

clinical remission of symptoms, 5 out of 20 (25%) were classified as showing marked reduction in intensity of symptoms, while 4 out of 20 (20%) were classified as showing noticeable reduction in intensity of symptoms (Table 5).

These psychological improvements were accompanied by changes in the biochemical variables under study, the initial differences in plasma pH, plasma bicarbonate, and dissolved carbon dioxide plus carbonic acid between Type I and Type II *Ss* disappearing with treatment.

TABLE 6

BEFORE AND AFTER TREATMENT DIFFERENCES IN VENOUS PLASMA pH, BICARBONATE, AND DISSOLVED $CO_2 + H_2CO_3$ IN TYPE I MENTALLY ILL *Ss* ($N = 10$)

S No. and Sex	Age (yr.)	Plasma pH		Bicarbonate (mM/l)		Dissolved $CO_2 + H_2CO_3$ (mM/l)	
		Before	After	Before	After	Before	After
1 M	43†	7.55	7.41	13.50	23.50	.48	1.14
2 F	54‡	7.50	7.44	18.50	24.00	.73	1.09
3 F	48‡	7.55	7.45	22.50	22.00	.79	.98
4 F	55‡	7.55	7.42	17.00	24.00	.60	1.14
5 F	27‡	7.56	7.45	26.00	27.50	.90	1.22
6 F	49‡	7.50	7.43	17.50	24.50	.69	1.14
7 F	56§	7.55	7.46	18.50	22.00	.65	.96
8 M	32‡	7.49	7.42	24.00	25.50	.97	1.22
9 F	22§	7.55	7.42	21.00	20.05	.74	.97
10 M	24‡	7.56	7.42	20.50	24.50	.71	1.17
M		7.54	7.43	19.90	23.80	.73	1.10
		$t = 10.74$*		$t = 3.46$		$t = 8.01$	

*$t_{.05} = 2.262$; $t_{.01} = 3.250$.

Note.—Diagnosis: †Depressive Reaction; ‡Schizophrenic Reaction; §Anxiety Neurosis.

At the start of the experiment the average plasma pH of Type I *Ss* was 7.54, while at the end of the experiment it was 7.43 (Table 6). Type II *Ss* had an average plasma pH of 7.36 before treatment, while after treatment it was 7.46 (Table 7). Thus the initial mean pH values for Type I and Type II *Ss* of 7.54 and 7.36, respectively, were no longer present after treatment, at which time the values for each group were 7.43 and 7.46, respectively. These changes in pH for each type of *S* are statistically significant well beyond the 1% level of confidence, using the t test.

The beginning values for plasma bicarbonate in Type I *Ss* averaged 19.90 millimoles per liter (mM/l) as compared to 23.80 mM/l at the end of the treatment period. Type II *Ss* had an average initial plasma bicarbonate level of 23.35 mM/l and an after treatment level of 24.15 mM/l. Thus the before treatment differences in this variable between Type I and Type II *Ss* of 19.90 mM/l and 23.35 mM/l, respectively, were not present at the end of the experi-

TABLE 7

BEFORE AND AFTER TREATMENT DIFFERENCES IN VENOUS PLASMA pH, BICARBONATE, AND DISSOLVED $CO_2 + H_2CO_3$ IN TYPE II MENTALLY ILL *Ss* ($N = 10$)

S No. and Sex		Age (yr.)	Plasma pH		Bicarbonate (mM/l)		Dissolved $CO_2 + H_2CO_3$ (mM/l)	
			Before	After	Before	After	Before	After
1	F	53‡	7.35	7.47	23.50	23.50	1.32	1.00
2	F	62‡	7.36	7.42	23.50	23.50	1.29	1.12
3	F	29§	7.38	7.47	24.00	26.00	1.25	1.10
4	M	51§	7.36	7.45	23.50	24.50	1.29	1.10
5	F	21§	7.40	7.45	24.00	25.50	1.20	1.13
6	F	28§	7.35	7.45	22.50	25.00	1.26	1.11
7	M	24†	7.37	7.51	23.50	24.50	1.25	.95
8	M	43‡	7.33	7.50	23.00	23.50	1.35	.93
9	M	29‡	7.36	7.42	22.50	22.00	1.23	1.05
10	M	39§	7.35	7.47	23.50	23.50	1.32	1.00
M			7.36	7.46	23.35	24.15	1.27	1.04
			$t = 8.26$*		$t = 2.59$		$t = 6.70$	

*$t_{.05} = 2.262$; $t_{.01} = 3.250$.

Note.—Diagnosis: †Depressive Reaction; ‡Schizophrenic Reaction; §Anxiety Neurosis; §Obsessive Compulsive Neurosis.

ment, when the bicarbonate levels for the two types of *Ss* were 23.80 mM/l and 24.15 mM/l, respectively.

Each type of *S* registered increases in plasma bicarbonate that were significant statistically (see Tables 6 and 7).

The initial concentration of dissolved carbon dioxide plus carbonic acid for Type I *Ss* averaged .73 mM/l, which increased to 1.10 mM/l at the end of the experiment (see Table 6). Type II *Ss* had an average initial level for this variable of 1.27 mM/l, which decreased to 1.04 mM/l at the end of the treatment period (see Table 7). Thus the beginning differences between the two types of *Ss* for dissolved carbon dicxide plus carbonic acid, represented by values of .73 mM/l and 1.27 mM/l, respectively, were not present after treatment, when the levels for this variable were 1.10 mM/l and 1.04 mM/l, respectively. These changes for both Type I and Type II *Ss* are statistically significant ($p < .01$).

Tables 6 and 7 summarize these before and after treatment values for plasma pH, bicarbonate, and dissolved carbon dioxide plus carbonic acid for Type I and Type II *Ss*. In each case the t test for the differences between the correlated means was used.

DISCUSSION

Of particular interest from the viewpoint of intermediary metabolism is that at the beginning of the experiment the Type I *Ss* had an average level of dissolved $CO_2 + H_2CO_3$ that was 43% less than that of Type II *Ss* (.73 mM/l

compared to 1.27 mM/l) ($p < .00001$). That this is apparently a real characteristic of Type I *Ss* rather than an artifact due to classificatory decision in experimental design is suggested by the fact that this difference disappeared with experimental treatment.

In order to discuss possible reasons for these observations, some elementary background information must be considered.

As carbon dioxide and water are the major end-products of the oxidation of all types of food, the amount of CO_2 that is produced by the tissues, as related to the amount of oxygen that is consumed, provides the principal basis for measuring the energy output of the organism.

Carbon dioxide enters the plasma as dissolved gas from tissue cells where it is formed by the processes of intermediary metabolism. In the extracellular fluid a small amount is hydrated to form carbonic acid:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \qquad [1]$$

Carbonic acid ionizes according to the equation:

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad [2]$$

The bicarbonate ion HCO_3^- is normally balanced by sodium. The hydrogen ion concentration of the extracellular fluid is determined by the degree of dissociation of H_2CO_3 and by the amount of available base. These relationships are summarized by the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]} \qquad [3]$$

According to Equation [3], when the bicarbonate concentration is 27 mM/l and the concentration of dissolved carbon dioxide plus carbonic acid is 1.35 mM/l, the plasma pH will be 7.40. When this ratio is based upon a pH of 7.40, a bicarbonate level of 27 mM/l and a dissolved carbon dioxide plus carbonic acid level of 1.35 mM/l, it is considered to represent the theoretical "ideal normal" (3).

Although there are conflicting reports in the literature as to what constitute "normal" ranges for these variables for healthy adults, very close experimental confirmation of the theoretical normal values just cited has recently been obtained in a careful study (2).

Under conditions of normal pH, the volume of carbon dioxide produced divided by the volume of oxygen consumed in a given period allows the calculation of the respiratory quotient (R.Q.), which provides a clue to the type of food being oxidized. For example, the R.Q. of carbohydrate is 6/6 or 1, being oxidized according to the equation:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O \ .$$

The average respiratory quotients for fat and protein are 0.71 and 0.80, respectively, while an "average" mixed diet gives a R.P. of about 0.85. Since the brain has a R.Q. of between 0.9 and 1.0, it depends mainly upon carbohydrate for energy. Approximately 90% of the brain's respiration can be accounted for by glucose consumption, even though it possesses both the anaerobic (glycolytic) and aerobic (citric acid) metabolic pathways, and appears to be capable of oxidizing the same substrates as do other tissues.

The volume of carbon dioxide expired during normal respiration is related to the partial pressure of CO_2 in the alveolar air. Since the blood volume of dissolved $CO_2 + H_2CO_3$ is in equilibrium with the pCO_2 of the alveolar air, the higher the blood level of dissolved CO_2 plus carbonic acid, the larger is the percentage of carbohydrate being oxidized. Conversely, in uncontrolled diabetes, for example, where fat and protein are oxidized instead of carbohydrate, the R.Q may be 0.70, with a proportionate decrease in dissolved CO_2 level.

In addition to the types of food being oxidized, there are a great number of other conditions which can cause deviations in the volume of CO_2 being produced, as well as deviations in hydrogen ion and bicarbonate concentrations. Because of the considerable complexity of this problem, there consequently may be numerous possible reasons for the observed differences between Types I and II mentally ill *Ss* other than the metabolic ones to be considered in what follows. The explanations advanced, however, appear to accord with the observations, whether or not they do account for them.

Possibly the major clue to understanding the results reported in this study lies in the fact that some mentally ill *Ss* apparently can be made more ill by administration of certain vitamins and minerals. Since some of the substances which exert such adverse effects are implicated principally in fat and protein metabolism, while the nervous system depends principally upon the oxidation of carbohydrate, it appears that the manner in which fat and protein are utilized in general intermediary metabolism may exert an indirect effect upon brain respiration. This is known to happen, for example, in diabetes, where circulating blood ketones resulting from the excessive breakdown of fat may actually lower cerebral respiration to the point of coma.

A consideration of the most important metabolic roles played by several of the vitamins that produce untoward psychological reactions in some mentally ill persons suggests that two major types of disturbances in intermediary metabolism may be involved: (i) a differentially slow oxidation of carbohydrates and glucogenic amino acids, resulting in a slow but preferential utilization of fats and ketogenic amino acids, and (ii) a disproportionally fast oxidation of carbohydrates and glucogenic amino acids, together with a slower, but still more rapid than normal, oxidation of fats and ketogenic amino acids.

The Type I *Ss* represent the "slow oxidizers," while the Type II *Ss* represent the "fast oxidizers."

The following discussion of this hypothesis will only undertake to illustrate briefly the lines of reasoning involved, since a more complete analysis would require lengthy treatment.

Among the vitamins in the Type I grouping which appear to worsen the psychological symptoms of Type II "fast oxidizing" *Ss* to the greatest degree are thiamine, niacin, pyridoxine, and riboflavin.

The pyrophosphoric ester of thiamine (TPP) participates in the major oxidative decarboxylations which lead to the formation of carbon dioxide. Probably the most important of these is the decarboxylation of pyruvic acid to acetylcoenzyme A, which can then in turn be oxidized in the tricarboxylic acid cycle to CO_2 and H_2O. In addition to thiamine, niacin as nicotinamide adenine dinucleotide (NAD) also participates in this reaction. The absence of thiamine is known to prevent the breakdown of pyruvate, resulting in incomplete carbohydrate oxidation and in the accumulation of both pyruvate and lactate in the blood.

On the other hand, the administration of relatively large amounts of thiamine or niacin may possibly result in an increase in the rate of decarboxylation of pyruvate to acetylcoenzyme A. If this were to occur in the presence of sufficient amounts of substrate as well as of all of the other co-factors necessary to the operation of the Kreb's cycle at an increased rate, the result would be an increase in the volume of carbon dioxide entering the blood from the tissues.

Pyridoxine (as pyridoxal phosphate), as well as riboflavin (as flavin adenine dinucleotide, FAD), play prominent roles in the catabolism of amino acids. Pyridoxal phosphate is required as a prosthetic group in transamination, as well as functioning as coenzyme in the alternate pathway of amino acid breakdown of decarboxylation. FAD participates in the oxidation deamination of amino acids.

Both the transamination and deamination of amino acids yield keto acids, some of which (such as pyruvic, oxaloacetic, and α-oxoglutaric) are formed from glucogenic amino acids and are oxidized in the same manner as are carbohydrates.

Since pyridoxine and riboflavin are essential to the catabolism of amino acids, some of which are ultimately oxidized in the same metabolic pathways as are carbohydrates, it appears possible that under appropriate conditions excess amounts of either vitamin could accelerate the rate of operation of the tricarboxylic acid cycle by increasing the rate of formation of pyruvic, oxaloacetic, and α-oxoglutaric acids.

On the hypothesis that Type II *Ss* are "fast oxidizers," differing from Type I "slow oxidizers" principally in that they oxidize carbohydrate and glucogenic amino acids at a more rapid rate than do the latter, the administration of vitamins and minerals that play an important role in their breakdown might be expected to result in a further increase in the rate at which such "fast oxidizing" *Ss* pro-

duce carbon dioxide. Such an increased volume of CO_2 would also be expected to elevate disproportionally the dissolved $CO_2 + H_2CO_3$ blood level, since hypothetically it would reflect the increased oxidation of carbohydrate and glucogenic amino acids.

This interpretation of the reason why thiamine, niacin, and other Type I vitamins and minerals aggravate the conditions of Type II *Ss* is suggested by blood tests from five such "fast oxidizing" *Ss* whose psychological conditions were inadvertently worsened when they were administered Type I vitamins and minerals while undergoing experimental treatment (Table 8).[4] These show

TABLE 8

BEFORE AND AFTER TREATMENT DIFFERENCES IN VENOUS PLASMA pH, BICARBONATE, AND DISSOLVED $CO_2 + H_2CO_3$ IN TYPE II "FAST OXIDIZING" MENTALLY ILL *Ss* WHOSE PSYCHOLOGICAL SYMPTOMS WERE AGGRAVATED BY INAPPROPRIATE THERAPY

S	Plasma pH		Bicarbonate (mM/l)		Dissolved $CO_2 + H_2CO_3$ (mM/l)	
	Before	After	Before	After	Before	After
1	7.42	7.39	25.50	23.50	1.22	1.20
2	7.38	7.35	23.00	23.50	1.20	1.32
3	7.45	7.42	21.00	20.50	.93	.98
4	7.44	7.38	28.50	24.00	1.30	1.25
5	7.45	7.35	20.00	22.50	.89	1.26
M	7.43	7.38	23.60	22.80	1.10	1.20
	$t = 3.63, .05>p>.01$		$t = 0.68$, n.s.		$t = 1.25$, n.s.	

decreases in plasma pH with disproportional increases in dissolved carbon dioxide plus carbonic acid. The direction of these changes is the opposite of those that occur when psychological improvement is obtained with appropriate therapy and are what would be expected by the hypothesis under consideration.

In contrast to the "fast oxidizing" Type II mentally ill *Ss* just considered, Type I *Ss* appear to be "slow oxidizers" whose poor utilization of carbohydrate and glucogenic amino acids results in a slow but preferential utilization of fats and ketogenic amino acids. On this hypothesis it would be expected that the intake of vitamins that might tend to favor the increased oxidation of fats and ketogenic amino acids when carbohydrate metabolism is depressed would also tend to worsen the psychological conditions of such *Ss*, principally because the normal oxidation of fatty acids depends upon the breakdown of carbohydrates.

The first step in the oxidation of fatty acids requires their activation to acetylcoenzyme A, utilizing adenosine triphosphate (ATP) as a source of energy. Since ATP is principally formed as the result of the final stages of carbo-

[4]Data on these 5 *Ss* were obtained in exploratory tests which preceded the experiment reported in this paper.

hydrate metabolism, if this is not proceeding normally, fat oxidation is also reduced.

However, assuming that sufficient ATP is available from glycolysis, the acetyl-coA formed in the initial phase of fatty acid oxidation condenses with oxaloacetic acid to form citrate, which is subsequently oxidized to carbon dioxide and water in the Kreb's cycle. When carbohydrate metabolism is faulty there will not be enough oxaloacetic acid to combine with the acetyl-coA being formed. As a consequence, acetoacetic acid is produced, some of which is decarboxylated to acetone, while some is reduced to β-hydroxybutyric acid. Acetoacetic acid, β-hydroxybutyric acid, and acetone are ketone bodies which if formed may be oxidized to CO_2 and H_2O through the citric acid cycle in extrahepatic tissue. Here again, however, it is requisite that carbohydrate oxidation is proceeding normally, otherwise ketone bodies will accumulate in the blood and appear in the urine.

Under the conditions outlined above it is evident that any factor which might tend to increase the oxidation of fatty acids will further increase the need for the efficient oxidation of carbohydrates. With this relationship in view, the question of why Type I "slow oxidizing" *S*s appear to be made more ill by certain vitamins may be considered.

Two of the nutrients in the Type II grouping for which some of the metabolic functions are known and which appear to worsen the psychological conditions of most Type I *S*s are choline and pantothenate.

Choline is used by the body in the synthesis of phospholipids, which are one of the three principal lipid components of the plasma. Since the ingestion of phospholipid causes marked and persistent hyperlipemia (14), the intake of excessive amounts of choline may elevate plasma lipid levels, since this substance is known to stimulate the rate of choline phospholipid synthesis. Elevated lipid levels increase the need for carbohydrate metabolites and in their absence may produce ketosis (14).

Pantothenic acid is a constituent of coenzyme A, which, together with a specific protein apoenzyme, functions in several reversible acetylation reactions in fat, protein, and carbohydrate metabolism. As noted above, the first step in the oxidation of fatty acids is their condensation with coenzyme A to form acetyl-coA, which, under conditions of normal carbohydrate metabolism, condenses with oxaloacetic acid to form citric acid. When carbohydrate oxidation is depressed, however, the acetyl-coA may accumulate faster than it can be utilized, resulting in the formation of ketone bodies. This state of affairs might possibly be aggravated if the intake of excessive amounts of pantothenate resulted in the formation of added coenzyme A, which could then in turn participate in the initial phase of fatty acid oxidation, consequently increasing the need for ATP and oxaloacetic acid.

On the hypothesis that the principal reason why Type I *S*s have dispropor-

TABLE 9

BEFORE AND AFTER TREATMENT DIFFERENCES IN VENOUS PLASMA pH, BICARBONATE, AND DISSOLVED $CO_2 + H_2CO_3$ IN TYPE I "SLOW OXIDIZING" MENTALLY ILL *Ss* WHOSE PSYCHOLOGICAL SYMPTOMS WERE AGGRAVATED BY INAPPROPRIATE THERAPY

S	Plasma pH		Bicarbonate (mM/l)		Dissolved $CO_2 + H_2CO_3$ (mM/l)	
	Before	After	Before	After	Before	After
1	7.47	7.56	25.00	26.00	1.14	.90
2	7.45	7.49	19.00	24.00	.84	.97
3	7.50	7.55	22.00	19.00	.87	.67
4	7.46	7.52	24.50	22.00	1.06	.83
M	7.47	7.52	22.62	22.75	.98	.84
	$t = 6.12, p < .01$		$t = 0.07$, n.s.		$t = 1.52$, n.s.	

tionately low average plasma levels of dissolved $CO_2 + H_2CO_3$ is that their carbohydrate metabolism is depressed, it would be anticipated that the administration of vitamins and minerals that might tend to increase fatty acid breakdown with the consequent increase in demands for carbohydrate metabolites such as oxaloacetic acid would also result in the further lowering of plasma levels of dissolved $CO_2 + H_2CO_3$, with a resulting increase in plasma pH.

Table 9 presents blood tests on 4 Type I *Ss* whose psychological conditions were unintentionally worsened by inappropriate therapy.[5] These show a lowering of dissolved $CO_2 + H_2CO_3$ levels, with a consequent rise in plasma pH. The direction of these changes is in conformance with the hypothesis being suggested.

A cross-check on the interpretation advanced as to why certain nutrients aggravate the psychological conditions of Type I and Type II mentally ill *Ss* is provided by a brief consideration of why other nutrients apparently improve the psychological conditions of some mentally ill *Ss*.

It is being suggested that "fast oxidizing" Type II *Ss* are metabolizing carbohydrates and glucogenic amino acids disproportionately faster than they are oxidizing fats and ketogenic amino acids, and that this differential utilization of carbohydrates appears to be related to their psychological state. Consequently, their mental and emotional symptoms would be worsened by factors that favor the increase of oxidation of such substrates, such as certain members of the B-complex vitamin group included in the Type I formula. However, since the opposite metabolic anomaly is hypothesized for the "slow oxidizing" Type I *Ss*, the vitamins and minerals which worsen the psychological conditions of "fast oxidizers" might be expected to benefit the "slow oxidizers," if, among other factors,

[5]Data on these 4 *Ss* were obtained in exploratory tests which preceded the experiment reported in this paper.

the carbohydrate metabolism is accelerated in one type and depressed in the other type.

This appears to be what happens. "Slow oxidizing" Type I *Ss* whose average initial plasma level of dissolved $CO_2 + H_2CO_3$ before treatment was .73 mM/l showed an after-treatment value of 1.10 mM/l, an increase of approximately 50%, while at the start of treatment these *Ss* had an average level of dissolved carbon dioxide plus carbonic acid which was 43% lower than for the "fast oxidizing" Type II group.

On the other hand, if Type II *Ss* are utilizing carbohydrates and glucogenic amino acids more rapidly than they are fats and ketogenic amino acids, the substances which may tend to further the oxidation of fats in "slow oxidizing" Type I *Ss* ought also to have the same effect in "fast oxidizing" Type II *Ss*, resulting in a lowering of dissolved CO_2 levels with resultant increases in plasma pH and bicarbonate.

Again, this appears to be what occurs. At the beginning of the experiment the "fast oxidizing" Type II *Ss* showed an average dissolved $CO_2 + H_2CO_3$ level of 1.27 mM/l, while at the end of the test this was reduced to 1.04 mM/l, a reduction of 22%. Since this reduction occurred at the same time there was a net increase in the level of total CO_2 (from 24.62 mM/l to 25.19 mM/l), it appears that the reduction in dissolved $CO_2 + H_2CO_3$ reflects an increase in the oxidation of fatty acids and ketogenic amino acids.

The following considerations appear to support such an interpretation. Table 2 presents the before-treatment differences between Type I and Type II *Ss* in fasting total lipids and blood sugar. "Slow oxidizing" Type I *Ss* reveal very significantly lower total lipid values and higher blood sugar levels than do Type II "fast oxidizers," suggesting a differential utilization of fats rather than carbohydrates by Type I *Ss*, while the reverse appears to occur in Type II *Ss*.

Before and after treatment data on these variables for the whole experimental group are not available. However, values for 2 *Ss* from whom before

TABLE 10

BEFORE AND AFTER TREATMENT DIFFERENCES IN VENOUS PLASMA pH, BIBARBONATE, DISSOLVED $CO_2 + H_2CO_3$, FASTING TOTAL LIPIDS, AND FASTING BLOOD SUGAR IN TYPE I AND TYPE II MENTALLY ILL *Ss*

Time	Plasma pH	Bicarbonate	Dissolved $CO_2+H_2CO_3$	Total Lipids	Blood Sugar
		Type I "Slow Oxidizing" *S*			
Before	7.50	17.50	.69	550	108
After	7.43	24.50	1.14	700	86
		Type II "Fast Oxidizing" *S*			
Before	7.36	23.50	1.29	1235	76
After	7.45	24.50	1.10	830	106

and after tests were obtained are given in Table 10. The "slow oxidizing" Type I *S* (Subject 6, Tables 5 and 6) showed a full clinical remission of schizophrenic reaction of 10 years' duration at the same time the CO_2 content increased 40%, with a concomitant increase in blood lipids and decrease in blood sugar. This suggests that an increase in carbohydrate utilization occurred, resulting in increased energy production.

On the other hand, the "fast oxidizing" Type II *S* (Subject 4, Tables 5 and 7) showed a marked reduction in symptoms of anxiety and fatigue, permitting him to work for the first time in several years. Of interest here is an increase in fasting blood sugar with a concurrent reduction in total lipids and dissolved $CO_2 + H_2CO_3$, suggesting an increased utilization of fats as compared to carbohydrates. Of possible significance in this case is that *S*, prior to participating in this experiment, had been treated for hyperinsulinism on the basis of an abnormal glucose tolerance curve. This treatment was claimed by *S* to have been helpful, although the dietary management prescribed did not result in establishing a normal glucose tolerance curve. However, at the end of the test period his glucose tolerance was normal, which suggests that the apparent increase in oxidation of fats might be a factor in his increased energy, since an increase in the utilization of fats would tend to raise and to stabilize his blood sugar level.

Conclusion

This study together with previous experiments (10, 12, 13) suggests that some cases of mental illness apparently may involve impairment of nervous system function due to abnormalities in intermediary metabolism. Normal cellular metabolic balance depends upon several factors, including an adequate supply of nutrients to provide both substrate as well as vitamins and minerals to participate in the synthesis of cellular enzymes, together with hormones such as thyroid and insulin which help regulate the rate of cellular oxidation.

Consequently, anomalies in intermediary metabolism may reflect many different conditions, such as inadequate food intake, poor digestion and assimilation, as well as endocrine disorders. In addition, both physical and emotional stress can disturb normal metabolic functions. Of interest in this connection is the observation that periods of intense psychological stress which several *S*s encountered during the course of the research here reported were found to result in decreases in the rates of oxidation in Type I "slow oxidizers," and increases in the rates of oxidation in Type II "fast oxidizers." This finding suggests that one important etiological factor in the disturbed intermediary metabolism of some of these mentally ill *S*s is psychological stress, which may increase the need for selective co-factors such as represented by the Types I and II vitamins and minerals for the respective types of *S*s.

One of the major difficulties confronting investigators in the field of biological psychiatry has been the failure to obtain a consistent set of deviations

from normal values in blood variables in types of mental illness. Perhaps one of the reasons for this failure is suggested by the results of the present study, namely, that the clinical picture presented by one patient may be very similar to the clinical picture presented by another patient, but the identical symptom complex apparently can accompany entirely different biochemical anomalies. Conversely, such widely divergent clinical pictures as presented by obsessive-compulsive neurosis and periodic catatonia may each be accompanied by similar metabolic disturbances.

In view of these considerations, it appears desirable to supplement or supplant descriptive psychological criteria with a classificatory system based upon similarities and differences in metabolic profiles. Such an approach might help eliminate some of the confusion in research in mental illness, for it is obvious that if we group all "schizophrenics" together and simply average the result of measurements made on an apparently heterogeneous population, possible clues may be obscured by such treatment of the data.

There seems little doubt but that this kind of interpretation of experimental results is common and that it does in fact lead to confusion and controversy. Three examples may be cited.

Hoskins (5) in a study of oxygen consumption in 214 male schizophrenics reported finding an average rate of 88.3% of standard normal. However, an examination of the measurements upon which this average was based shows that the rates of individual patients varied from 55% of normal to 150% of normal, from being representative of what we have termed "slow oxidizers" to being "fast oxidizers." The author himself expresses doubt in his summary whether his results generally reflect "nosological homogeneity."

In another study of metabolism in schizophrenia by Kety, *et al.* (6), comparing 22 patients with normal controls, it is stated that "on the basis of these data a generalized change in circulation or oxygen utilization by the brain of schizophrenics may safely be ruled out. . . ." Cerebral oxygen consumption in schizophrenia is "identical" to that in normal healthy adults. A closer examination of the data upon which these conclusions are offered, however, shows a range of arterial blood pH from 7.30 to 7.50, with the range of dissolved CO_2 + H_2CO_3 extending from .72 mM/l to 1.48 mM/l.[6]

In terms of the language of the present study, 20 out of 22 of Kety's patients are what would have been classified as "fast oxidizers" had they participated in the research here reported. In other words, on the basis of the findings of the present study, Kety, *et al.* did not test a representative sample of the schizophrenic population. They appear to have all but missed the "slow oxidiz-

[6]These values for dissolved CO_2 + H_2CO_3 are not given in the original but were computed on the basis of the pH and the CO_2 content, which are given.

ers" and as a result have apparently reported the coincidence that their experimental group was "identical" to normal controls in brain metabolism.

Confirmation of this suggestion that Kety, *et al.* did not study a representative sample of schizophrenics is found in the contradictory results obtained by Gordon, *et al.* (4). In a study directed at confirming the results of Kety, Gordon tested cerebral oxygen uptake in 24 schizophrenics and found only one to be normal, 3 were above normal, while 21 were below normal. In terms of the present report, if Kety may have failed to include the "slow oxidizers," Gordon appears to have all but missed the "fast oxidizers." On the other hand, Hoskins appears to have found that the term schizophrenic does not signify an homogeneous population, metabolically.

That this is apparently so is illustrated in the study here reported, for 7 out of 11 schizophrenics were Type I "slow oxidizers," with an average plasma pH of 7.53, while 4 were Type II "fast oxidizers," with an average plasma pH of 7.35. However, if we had proceeded upon the assumption that the term 'schizophrenic' signified a well-defined population from a biochemical point of view, we would have averaged these values and obtained a pH of 7.46 for the group, a value which some might interpret to be "normal." If such a "normal" value is now accepted as accurately characterizing the schizophrenic population, it will effectively hide a possibly vital clue, as well as acting to discourage further research in this particular area by other investigators.

REFERENCES

1. BROZEK, J., & ERICKSON, N. K. Item analysis of the psychoneurotic scales of the Minnesota Multiphasic Personality Inventory in experimental semi-starvation. *J. consult. Psychol.*, 1948, 12, 403-411.
2. GAMBINO, S. R. Normal values for adult human venous plasma pH and CO_2 content. *Tech. Bull. Registry Med. Technol.*, 1959, 29, 132-135
3. GOLDBERGER, E. *Water, electrolyte, and acid-base syndromes.* Philadelphia: Lea & Febiger, 1959.
4. GORDON, G. S., ESTESS, F. M., ADAMS, J. E., BOWMAN, K. M., & SIMON, A. Cerebral oxygen uptake in chronic schizophrenic reaction. *A.M.A. Arch. Neurol. Psychiat.*, 1955, 73, 544-545.
5. HOSKINS, R. G. Oxygen consumption ("basal metabolic rate") in schizophrenia. *Arch. Neurol. Psychiat.*, 1932, 28, 1346-1364.
6. KETY, S. S., WOODFORD, R. B., HARMEL, M. H., FREYHAN, F. A., APPEL, K. E., & SCHMIDT, C. F. Cerebral blood flow and metabolism in schizophrenia. *Amer. J. Psychiat.*, 1948, 104, 765-770.
7. KEYS, A., BROZEK, J., HENSCHEL, A., MICKELSON, O., & TAYLOR, H. L. *The biology of human starvation.* Minneapolis: Univer. Minnesota Press, 1950.
8. PETERMAN, R. A., & GOODHART, R. S. Current status of vitamin therapy in nervous and mental disease. *J. clin. Nutrit.*, 1954, 2, 11-21.
9. RICHTER, D. (Ed.) *Schizophrenia, somatic aspects.* New York: Pergamon, 1957.
10. WATSON, G. Vitamin deficiencies in mental illness. *J. Psychol.*, 1957, 43, 47-63.
11. WATSON, G. Note on nutrition in mental illness. *Psychol. Rep.*, 1960, 6, 202.
12. WATSON, G., & COMREY, A. L. Nutritional replacement for mental illness. *J. Psychol.*, 1954, 38, 251-264.

13. WATSON, G., & CURRIER, W. D. Intensive vitamin therapy in mental illness. *J. Psychol.*, 1960, 49, 67-81.

14. WOHL, M. G., & GOODHART, R. S. (Eds.) *Modern nutrition in health and disease.* Philadelphia: Lea & Febiger, 1960.

Accepted August 25, 1965.