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Acetazolamide and Thiamine: An Ancillary Therapy for Chronic Mental Illness

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Abstract. Twenty-four chronic schizophrenic patients were treated successfully with the addition of acetazolamide and thiamine (A + T) to their unchanged existing therapies in a double-blind, placebo-controlled crossover study Therapeutic effects were measured by the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms Overall, 50% of the patients showed improvement on all assessment scales No untoward effects occurred in these patients or in patients in previous studies who have been treated continuously with A + T therapy for as long as 3 years

Key Words. Thiamine, acetazolamide, pyruvate dehydrogenase complex, chronic schizophrenia

This report describes a clinical trial of a new treatment, involving the use of acetazolamide and thiamine (A + T), in a double-blind, two-period, placebo-controlled crossover study with a group of chronic hospitalized schizophrenic subjects who had proved resistant to the usual forms of therapy

The rationale for this treatment with A + T originated in the Cerebral Metabolism Laboratory of the Kline Institute for Psychiatric Research, which for many years used an original arteriovenous technique for determining cerebral metabolism in vivo in human subjects (Sacks, 1969, 1973, 1976, 1983) With over 500 experiments in human subjects (half chronic mental patients and half volunteers), it was originally found that significantly less [C-14] carbon dioxide was produced from [C-14] glucose by mental patients' brains than by those of mentally normal subjects (Sacks, 1959). Later it was determined that much higher specific activity [1-C-14] lactate was made from [3-C-14] glucose by mental patients' brains (Sacks et al., 1981). The most likely explanation of these data was that there were some small lactate compartments in specific brain region(s), in which the decarboxylation of endogenously formed cerebral lactate was partially inhibited As seen in Fig 1, the pyruvate dehydrogenase complex (PDHC) is involved in this key step in cerebral glucose metabolism A lack of this enzyme complex has important consequences. Early in glucose metabolism, pyruvate comes

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into rapid equilibrium with lactate which accumulates unless pyruvate is decarboxylated to acetyl-Co A through the action of PDHC This accumulation of lactate may bring about mental symptoms under certain conditions (i e , lactate infusions induce anxiety symptoms and attacks in some subjects (Pitts and McClure, 1967) Further, lack of PDHC can result in decreased energy for neuronal functioning since less acetyl-Co A is formed and its metabolism via the Tricarboxylic Acid Cycle (TCA) is therefore reduced. Also, there might be decreased production of such important neurotransmitters as acetylcholine, glutamate, and γ-aminobutyric acid (GABA) All of these factors could contribute to the impaired mental function seen in psychiatric disorders PDHC deficiency in humans has been documented and treated with some success with a high fat or ketogenic diet, thiamine, dichloroacetate, cholinergic agonists, and acetazolamide (Blass, 1979).

Preliminary studies (Sacks et al , 1988) have suggested that A + T may be useful as an ancillary therapy for chronic mental illness. The present article describes the results of our continued, and more extensive, investigation into the effects of A + T

Methods

The clinical trial was conducted with a two-period, double-blind crossover design with the patients receiving 2 g of acetazolamide and 1 5 g of thiamine daily throughout the active phase, and matched placebos during the control interval In the active phase, the medications were administered as acetazolamide in 250-mg tablets, three in the morning, three at noon, and two in the evening (after meals to avoid gastric irritation) Thiamine was given in the form of two 250-mg tablets at the same times As a precautionary measure, acetazolamide and thiamine (or matching placebos) were increased gradually during the first week of the active period so that the total dosage was reached on day 7 These dosages were determined in earlier studies (Sacks et al , 1988) to be the most effective, as well as free of side effects and consistent with amounts used to treat other disorders Both the active and the control intervals were of 8 weeks' duration with an intervening washout period of 4 weeks, and an initial baseline period of 4 weeks Twenty-four male patients participated in sequential clinical trials of 24 weeks as described above (i e , 4 weeks Baseline, then 8 weeks first active period with A + T or placebo, then 4 weeks Washout, then 8 weeks second active period with placebo or A + T) Since acetazolamide is a diuretic, patients were given 8 ounces of orange juice daily to help maintain electrolyte balance All patients' psychotropic medications were kept constant for the period of the study

The study patients had been suffering from chronic schizophrenic disorders for a minimum of 4 years and had proved resistant to therapy

Patients were selected randomly to start with either active treatment or placebos Two forms of assessment were used the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) Patients are listed in Table 1 according to descending order of improvement The assessments were performed weekly by at least two investigators who did not know whether the patient was taking the active medication or placebo The means of each kind of assessment were obtained for each trial period The change with (A + T) was expressed as (average Baseline scores - average A + T Therapy scores) - (average Washout scores - average Placebo scores) (Table 2) Significances of the differences were estimated using paired *t* tests (two-tailed)

Blood samples were drawn weekly for determinations of electrolytes, carbon dioxide, CBC, and platelets

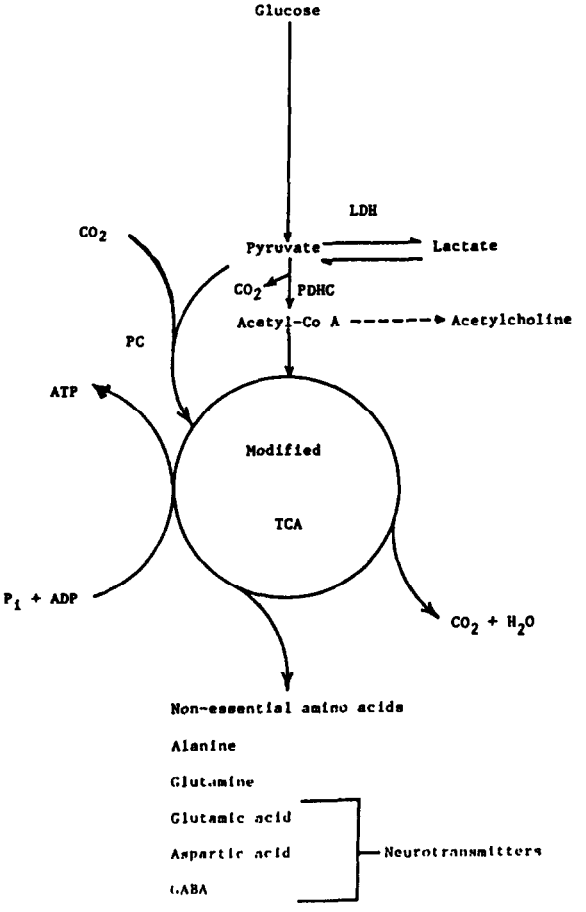
Results

The overall results are summarized in Table 2. Thirteen patients received A + T therapy in the first 8-week active interval (Group A), and 11 patients received placebo

in that first 8-week interval following the 4-week baseline period (Group B) With the total SAPS scores, there was a significant average change of 1.4633 ($p < 0.02$) With the SANS scores, there was an average change of 0.9388 ($p < 0.05$); as can be seen from the individual SANS scores, however, negative symptoms were not very prevalent in our patients.

Overall, 50% of the patients showed improvement on all assessment scales. Only 12% (3 out of 24) failed to show any improvement at all In the great majority of the remaining patients, the assessed positive changes were greater than any negative changes.

Fig. 1. Role of pyruvate dehydrogenase complex (PDHC) in human cerebral glucose metabolism



LDH = lactate dehydrogenase PC = pyruvate carboxylase TCA = tricarboxylic acid cycle (modified, see Sacks, 1983) P = inorganic phosphate ADP = adenosine diphosphate ATP = adenosine triphosphate GABA = γ-aminobutyric acid (*Note* In human brain in vivo, half of glucose carbon is metabolized to carbon dioxide and half becomes incorporated into amino acids)

Table 1. Patient information

Patient No.	Age	Years ill	Age at onset	Other medication	Group
1	32	4	28	T	A
2	32	16	16	Tı	A
3	62	22	40	C, Cl	B
4	48	25	23	F	B
5	41	6	35	H, I	A
6	22	9	13	P, C	A
7	36	20	16	H	B
8	47	31	16	F	B
9	45	14	31	H, B	B
10	45	NK	NK	Tı	B
11	25	5	20	N	B
12	33	17	16	Tı	B
13	31	15	16	Tı	A
14	34	16	18	F	B
15	37	13	24	F	A
16	49	28	21	Tr	A
17	38	8	30	N	A
18	36	26	11	F	A
19	31	9	22	Cl	A
20	53	35	18	H	B
21	55	NK	NK	Tı	B
22	36	25	11	F	A
23	44	24	20	T	A
24	27	9	18	F	A
Mean	39 1	17 1	21 0		

Note All patients were males Group A acetazolamide + thiamine therapy first Group B placebo first H = haloperidol P = perphenazine C = carbamazepine F = fluphenazine T = thiothixine I = imipramine Tı = thioridazine Tr = trifluoperazine Cl = chlorpromazine B = buspirone N = nil NK = not known

When the individual categories of each assessment scale were analyzed, the following significant average changes in SAPS scores emerged (Table 2): 0.4679 in *hallucinations* ($p < 0.05$), an improvement of 16.9% over the Baseline value, 0.4875 in *delusions* ($p < 0.05$), a 14.4% improvement, 0 3221 in *bizarre behavior* ($p < 0.02$), a 25.2% improvement; and 0 5388 in *positive formal thought disorder* ($p < 0$ 01), a 16.2% improvement. As for scores on the individual sections of the SANS, Table 2 reveals that for most of our patients the scores in all categories were quite low, i e , negative symptoms were not very prevalent in these patients. Thus, the divisions called *affective flattening or blunting, alogia, avolition-apathy,* and *attention* had average changes in scores of 0.1713, 0.21921, 0.1863, and 0.1971, respectively Although only the *alogia* change was significant ($p < 0.05$), representing an improvement of 38.3%, the others indicated improvements of 12.3% (*affective flattening or blunting*), 30.7% (*avolition-apathy*), and 18.2% (*attention*), and the combined data indicated a significant change ($p < 0$ 05) in total SANS scores (see Table 2).

Blood chemistry determinations reflected the expected minor changes associated with acetazolamide administration (i e , mild acidosis), but none of the changes were

Table 2. Results of acetazolamide plus thiamine ancillary treatment

Total SAPS

Group A (n=13)		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		11 0677	9 5169	10 5170	10 5560
SD		3 8589	5 0569	5 0821	5 0996
Group B (n=11)		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		10 2855	8 8782	10 1409	7 3536
SD		2 9136	4 0662	3 0469	3 0653
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**[1]
Mean	10 6425	8 5254	10 3957	9 6771	1 4633
SD	3 4676	4 3174	3 9851	4 5505	2 8189
Significance					t = 2 5432
					p < 0 02

Total SANS

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		4 1308	3 3977	3 5770	3 5990
SD		2 3065	1 5267	1 8833	1 3803
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		2 7082	2 3118	3 0355	1 7255
SD		1 8872	0 9871	2 0588	1 3915
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	3 6288	2 6313	3 1205	2 9248	0 9388
SD	2 2202	1 6681	1 8914	1 3336	1 8796
Significance					t = 2 4467
					p < 0 05

SAPS hallucinations

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		2 8508	2 5908	2 8580	2 9020
SD		1 5006	1 6222	1 5948	1 3703
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		2 5773	2 15191	2 6573	1 5655
SD		1 0673	1 3744	1 0142	1 2043
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	2 7621	2 1208	2 7110	2 5129	0 4679
SD	1 2774	1 5086	1 3171	1 3907	0 9398
Significance					t = 2 4391
					p < 0 05

SAPS delusions

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		3 6369	3 0869	3 4410	3 4770
SD		1 1414	1 5724	1 4634	1 4561
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		3 1982	3 0655	3 1091	2 5809
SD		1 6398	1 5071	1 2671	1 3442
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	3 3950	2 8877	3 3186	3 2614	0 4875
SD	1 2042	1 4232	1 5276	1 4609	1 0181
Significance					t = 2 3457
					p < 0 05

Table 2. Results of acetazolamide plus thiamine ancillary treatment— *Continued*

SAPS bizarre behavior

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		1 3369	1 0738	1 1720	1 2600
SD		1 0584	1 0139	1 1147	1 1330
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		1 2627	0 9336	1 2136	0 7110
SD		0 8186	0 5788	0 9746	0 6623
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	1 2804	0 9071	1 2195	1 0890	0 3221
SD	1 0007	0 8726	0 9467	0 8793	0 6294
Significance					$t = 2\ 5069$ $p < 0\ 02$

SANS positive formal thought disorder

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		3 4654	2 8708	3 0800	3 0890
SD		1 0076	1 5019	1 3989	1 4990
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		3 0855	2 8709	3 1555	2 5618
SD		1 2835	1 2802	1 0776	1 1713
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	3 3233	2 7292	3 0829	2 9748	0 5388
SD	1 0293	1 3409	1 3055	1 3576	0 9071
Significance					$t = 2\ 9095$ $p < 0\ 01$

SANS affective flattening or blunting

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		1 6723	1 3636	1 3230	1 5210
SD		0 7933	0 6236	0 9124	0 6651
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		1 1536	0 7191	1 0755	0 7264
SD		0 7199	0 5125	0 6408	0 6381
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	1 3988	1 3638	1 2343	1 1010	0 1713
SD	0 7740	0 6236	0 8008	0 7062	0 7808
Significance					$t = 1\ 0744$ $p = NS$

SANS alogia

Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		0 7669	0 4815	0 5020	0 5940
SD		0 7969	0 5726	0 5878	0 4886
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		0 3910	0 2855	0 3409	0 1580
SD		0 4849	0 2830	0 4513	0 2061
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	0 5717	0 3321	0 4252	0 4324	0 2192
SD	0 6833	0 4640	0 5233	0 4152	0 5261
Significance					$t = 2\ 0407$ $p < 0\ 05$

Table 2. Results of acetazolamide plus thiamine ancillary treatment— *Continued*

SANS avolition-apathy					
Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		0 7008	0 4862	0 4160	0 3550
SD		0 5578	0 2902	0 4831	0 2621
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		0 3673	0 3418	0 4982	0 2191
SD		0 4179	0 2784	0 6077	0 2234
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	0 6079	0 3638	0 3905	0 3481	0 1863
SD	0 5775	0 2900	0 4393	0 2640	0 5643
Significance					t = 1 6170
					p = NS
SANS attention					
Group A		**Baseline**	**A+T therapy**	**Washout**	**Placebo**
Mean		1 0515	1 0485	1 1490	0 97 30
SD		0 6482	0 7834	0 7408	0 7618
Group B		**Washout**	**Placebo**	**Baseline**	**A+T therapy**
Mean		0 8109	0 9945	1 1227	0 7200
SD		0 7862	0 6241	0 8692	0 8110
Groups A & B	**Baseline**	**A+T therapy**	**Washout**	**Placebo**	**Change on A+T**
Mean	1 0842	0 8979	0 9719	0 9843	0 1971
SD	0 7410	0 7963	0 7655	0 6753	0 7009
Significance					t = 1 3775
					p = NS

Note Significance determined using paired t tests (2-tailed) A + T = acetazolamide and thiamine SAPS = Scale for the Assessment of Positive Symptoms SANS = Scale for the Assessment of Negative Symptoms

1 (Average Baseline Scores - Average A + T Scores) - (Average Washout Scores - Average Placebo Scores)

of clinical significance. Surprisingly, except for some increased urination reported by a few patients, there were few if any side effects with the addition of A + T

Discussion

The study design called for 26 patients, but we can only report completed data on 24 patients. Two patients, who were among the most improved on A + T, are not included in this report. Their parents had given permission for the study with the understanding that if their sons showed improvement that disappeared during the 4-week washout period, we would break the code and return them to A + T treatment (if that was in fact what they had been given). These patients were then placed in our Open Label Project, which provides for continuing A + T treatment (see below).

The data indicate that half of the chronic treatment-resistant patients had a significant improvement in their psychiatric symptoms when acetazolamide and thiamine (A + T) were added to their usual medications. If we are indeed improving cerebal metabolism by enzyme activation of the pyruvate dehydrogenase complex (PDHC), it is quite possible that A + T therapy activates only a part of the PDHC. Since PDHC

consists of three enzymes (i.e., pyruvate dehydrogenase, lipoate acetyltransferase, and lipoamide dehydrogenase) and a number of coenzymes (i.e., thiamine pyrophosphate, adenosine triphosphate, nicotinamide adenine dinucleotide, and flavin adenine dinucleotide), and requires trace metals such as magnesium for activation (Blass, 1979), it is obvious that numerous deficiencies within the PDHC could exist Possibly those patients who exhibited the most notable improvement had specific brain regions that were deficient in pyruvate dehydrogenase since that enzyme requires thiamine pyrophosphate as coenzyme, which would be supplied by the thiamine in the A + T therapy Perhaps patients who did not respond favorably to A + T therapy could be helped by supplying one or more other PDHC activating factors (e g., riboflavin, niacin, lipoic acid, magnesium) with the acetazolamide.

The role of acetazolamide in stimulating PDHC is not known Since it inhibits carbonic anhydrase, it may increase PDHC activity by changing the *p*H of brain tissue. However, because of the many diverse physiological effects due to carbonic anhydrase inhibition by acetazolamide (e.g., it reduces cerebrospinal fluid formation and increases cerebral blood flow) (Maren, 1967), its effectiveness in A + T therapy may possibly result from an effect not directly related to PDHC.

Some consideration should be given to the possibility that the effectiveness of A + T derives from its alteration of the blood levels and/or metabolism of the antipsychotic drugs. The following reasons suggest, however, that this may not be the case (1) Five patients in previous studies (Sacks et al., 1988) and two in this study were drug free, and the results with A + T therapy were similar to those of treated patients in that approximately half improved markedly in the 8 weeks of treatment with A + T ancillary therapy. (2) As we described previously (Cowen et al., 1987, Sacks et al., 1988) and as we again observed in this investigation, there was a decrease in preexisting parkinsonian and chorioathetotic symptoms during A + T administration. If A + T effectively increased blood levels of the neuroleptics, we would expect to see some exacerbation of these neurological symptoms; instead, they were noticeably reduced in the majority of patients. (3) With several patients given long-term A + T (Open Label Study), continued clinical improvement followed the gradual reduction of their antipsychotic medications

The question of whether thiamine alone or acetazolamide alone could produce the same clinical improvement seen with A + T has not been addressed directly While conducting the earlier clinical trials (Sacks et al., 1988), we became aware of a report by a group of investigators in Japan showing that acetazolamide alone was beneficial to patients with "atypical" psychoses (Inoue et al., 1984). However, in our own experience, treatment of a male patient for 1 year with only acetazolamide resulted in little benefit, whereas with A + T significant clinical improvement was observed within 2 weeks in the same patient. To date, one patient who has been treated with the addition of thiamine only (because of his allergy to sulfa drugs) has exhibited only very slight clinical improvement Thus, we currently believe that the combination of acetazolamide and thiamine is responsible for the results obtained. A number of experiences have further confirmed the efficacy of A + T therapy. In an earlier clinical trial, nine schizophrenic patients had A + T therapy terminated Reports of progressive and severe psychiatric deterioration led to requests from both families and staff for us to institute an Open Label Study. As the study protocol stated, we were

continuing treatment with acetazolamide (an approved drug for nonapproved usage) and thiamine for humanitarian reasons

Since all patients who participated in our double-blind crossover study were permitted to be in our Open Label Project, and most of them elected to do so, we have had the opportunity to evaluate the long-term efficacy of the A + T therapy. At this time, there are 29 patients (24 from this study and 5 from previous investigations) receiving A + T therapy. Some who participated in earlier investigations (Sacks et al., 1988) have received this treatment for nearly 3 years. In most cases, gradual alleviation of psychiatric symptoms continued with no adverse reactions. It is of interest that some patients (i.e , #17 and #20) who had improved only slightly or not at all during the active period of our double-blind study showed very noticeable clinical improvement after several months of continuous A + T therapy (Open Label Project). Thus, it seems that 8 weeks of A + T treatment may not be sufficient to determine the full efficacy of A + T therapy with all patients. This is not surprising if one considers that a deteriorated cerebral metabolism of many years' duration could reasonably require more than 2 months' stimulation to show improvement

To date, we can find no relationship between the concurrent medications of the patients (Table 1) and the degree of clinical improvement. A report of the inhibition of PDHC in vitro by most of the neuroleptics commonly used in mental illness (Miernyk et al., 1987) suggests that if we are really dealing with a brain PDHC deficiency, use of the usual psychopharmaceuticals might impede the effectiveness of A + T therapy. As stated above, two patients in this study and five in our previous investigations were neuroleptic free both before and during the study; and with those patients, the improvement in psychiatric rating scales was similar to that of the medicated patients Patient #17, while on our Open Label Project, improved impressively and rapidly on termination of all neuroleptics and administration of A + T alone.

The results of the present investigation would seem to warrant serious consideration of A + T in the treatment of mental illness Besides apparently being quite safe and free of adverse reactions, A + T therapy should not produce neurological side effects, and seems to be effective in ameliorating these when they exist. Most important, A + T therapy represents a basic approach to treatment of mental illness conceived as a disease due to a specific brain enzyme deficiency It is medication aimed at activating an enzyme system (PDHC) whose deficiency is believed to cause psychiatric symptoms.

Further investigations will be undertaken to determine such factors as optimal dosage, best mode of administration, use of A + T as a sole treatment for acute as well as chronic schizophrenic patients, and, for those patients who do not respond to A + T therapy, addition of other pharmaceuticals that influence PDHC.

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References

Andreasen, N C Negative versus positive schizophrenia Definition and validation *Archives of General Psychiatry,* 39 789-794, 1982

Blass, J P Pyruvate dehydrogenase deficiences In Burman, D , Holton, J B , and Pennock, C A , eds *Inherited Disorder of Carbohydrate Metabolism* Baltimore University Park Press, 1979 pp 239-268

Cowen, M A , Sacks, W , Green, M R , Esser, A H , Talarico, P , and Feitel, B A new treatment for extrapyramidal disorders *Abstracts of the 140th Meeting of the American Psychiatric Association,* Chicago, May 9-14, 1987 p 79

Inoue, H , Hazama, H , Hamazoe, K , Ichikawa, M , Omura, F , Fukuma, E , Inoue, K , and Umezawa, Y Antipsychotic and prophylactic effects of acetazolamide (Diamox) on atypical psychosis *Folia Psychiatrica et Neurologica Japonica,* 38 425-436, 1984

Maren, T M Carbonic anhydrase Chemistry, physiology, and inhibition *Physiological Reviews,* 47 595-781, 1967

Miernyk, J A , Fang, T K , and Randall, D D Calmodulin antagonists inhibit the mitochondrial pyruvate dehydrogenase complex *Journal of Biological Chemistry,* 262 15338-15340, 1987

Pitts, F N , and McClure, J N Lactate metabolism in anxiety neurosis *New England Journal of Medicine,* 277 1329-1336, 1967

Sacks, W Cerebral metabolism of isotopic glucose in chronic mental disease *Journal of Applied Physiology,* 14 849-854, 1959

Sacks, W Cerebral metabolism in vivo In Lajtha, A , ed *Handbook of Neurochemistry* Vol 1 New York: Plenum Press, 1969 pp 301-324

Sacks, W Disorders of glucose in brain dysfunction In Gaull, G , ed *Biology of Brain Dysfunction* New York Plenum Press, 1973 pp 143-189

Sacks, W Human brain metabolism in vivo In Himwich, H , ed *Brain Metabolism and Cerebral Disorders* 2nd ed Flushing, NY Spectrum Publications, 1976 pp 89-127

Sacks, W. Cerebral metabolism in vivo In Lajtha, A , ed *Handbook of Neurochemistry* 2nd ed Vol 3 New York Plenum Press, York, 1983 pp 321-351

Sacks, W , Cowen, M A , Green, M R , Esser, A H , Talarico, P , and Cankosyan, G Acetazolamide and thiamine A preliminary report of an ancillary therapy for chronic mental illness *Journal of Clinical Psychopharmacology,* 8 70, 1988

Sacks, W , Schechter, D C ; and Sacks, S A difference in the in vivo cerebral production of [1-C-14]lactate from D-[3-C14]glucose in chronic mental patients *Journal of Neuroscience Research,* 6 225-236, 1981