ing subjects 1½ hours of ICSS is to reduce REM rebound by at least 50 percent in each subject. This effect was significant at least at the .01 level (one-way analysis of variance). Amounts of slow-wave sleep were almost identical in conditions A and B.

In these two experiments, we maintain that we have demonstrated that a waking behavior can reduce REM rebound patterns, and the corollary, that depriving an organism of REM sleep can affect a waking behavior. Explicitly, an organism deprived of REM sleep will be more sensitive to and select more ICSS. More specifically, we have demonstrated a reciprocal relation between REM sleep and ICSS. It is our view that the ICSS neural network is part of the neural network activated during REM sleep. From this we hypothesized that nuclei in the hindbrain that are involved in initiating aspects of REM sleep are ICSS sites. Ellman *et al.* (*12*) confirmed this hypothesis.

Our results can be explained on at least one other level. Dement and his colleagues (*9*) have maintained that REM sleep is triggered by, and in turn dissipates, a neurohumoral substance. When subjects are deprived of REM, this hypothetical substance is thought to accumulate. Jouvet has proposed (*13*) that norepinephrine is one of the biogenic amines involved in triggering and maintaining REM sleep. Stein (*14*), on the other hand, has implicated norepinephrine as an agent involved in mediating ICSS. One may explain the changes in ICSS as being potentiated by the release of norepinephrine as a result of REM deprivation. In a similar way, one could explain the reduction in REM rebound by ICSS as a partial depletion of norepinephrine. This explanation is extremely tentative, because it is not absolutely clear how norepinephrine is involved in either REM sleep or ICSS.

SOLOMON S. STEINER
STEVEN J. ELLMAN

Department of Psychology, City College, City University of New York, New York 10031

References and Notes

1. E. Evarts, *J. Neurophysiol.* **25**, 812 (1962); W. C. Dement, *New Direct. Psychol.* **2**, 165 (1965).
2. W. C. Dement, *Amer. J. Psychiat.* **122**, 404 (1965); J. H. Dewson III, W. C. Dement, T. Wagener, K. Nobel, *Science* **156**, 403 (1967).
3. H. B. Cohen and W. C. Dement, *Science* **150**, 1318 (1965); *ibid.* **154**, 396 (1966); H. B. Cohen, R. F. Duncan, W. C. Dement, *ibid.* **157**, 1646 (1967).
4. Various mammalian species find electric stimulation to certain areas of the brain positively reinforcing and will work to obtain it.
5. J. Olds, *J. Comp. Physiol. Psychol.* **51**, 320 (1958); *Physiol. Rev.* **42**, 554 (1962); E. S. Valenstein, V. C. Cox, J. W. Kakolewski, *Science* **159**, 1119 (1968); J. Olds, *ibid.* **127**, 315 (1958); D. R. Justensen, J. C. Sharp, P. B. Porter, *J. Comp. Physiol. Psychol.* **56**, 371 (1963); W. Hodos and E. S. Valenstein, *ibid.* **53**, 503 (1960); *ibid.* **55**, 80 (1962); L. Stein, *ibid.*, p. 405.
6. In ICSS experiments, the subject is placed in a chamber, and electrical stimulation is delivered whenever the animal presses the lever. The subject is tested over a range of different intensities of stimulation, and rates of lever pressing are recorded for each intensity (rate-intensity function). In this situation, one can determine a threshold for electrical self-stimulation as well as a rate-intensity function.
7. Deprivation of REM was accomplished by placing the subject on a circular platform situated in the center of a vessel filled with water. The REM deprivation platform was 7 cm in diameter and protruded less than 1 cm above the level of the water. Loss of tonus from the neck muscles, which occurs at the onset of REM sleep, causes loss of balance, immersion in water, and consequent awakening. This procedure effectively deprives the subject of almost all REM sleep. Electroencephalographic recordings confirmed that this procedure prevented the subject from going into REM sleep, while allowing 65 percent of baseline slow-wave sleep to occur.
8. Two controls were run, because the results of our experiment might be due to the nonspecific stressful effects of being placed on the circular platform. Control subjects in both groups were placed on a 13-cm platform. Recordings demonstrated that animals on the large platform were not deprived of REM. Yoked control subjects were tested simultaneously with animals from a REM deprivation group, and every time a subject deprived of REM fell into the water, the corresponding yoked control subject was simultaneously dunked into the water (by tipping over its platform). Animals in the nonyoked control group were simply placed on a 13-cm platform. All subjects showed about a 35 percent reduction in slow-wave sleep.
9. W. Dement, P. Henny, H. Cohen, J. Ferguson, in *Sleep and Altered States of Consciousness*, E. Evarts and H. Williams, Eds. (Williams & Wilkins, Baltimore, 1967), p. 456; W. C. Dement, *Science* **131**, 1705 (1960); B. Morden, G. Mitchell, W. Dement, *Brain Res.* **5**, 339 (1967).
10. If there was any evidence of convulsion, even signs such as teeth grinding, standing in a fixed glazed position, and so forth, then the intensity of stimulation that produced this behavior was judged too high for use during the experiment. Subjects were tested as described (*6*) until an intensity was found which produced reliable subject response for stimulation and which was at least 20 mv below the intensity that produced even partial signs of convulsive behavior.
11. R. Fishman and H. P. Roffwarg, *Exp. Neurol.*, in press.
12. S. Ellman, R. Ackerman, J. Farber, L. Mattiace, S. Steiner, in preparation; J. Farber, S. Steiner, S. Ellman, paper presented at the meeting of the Eastern Psychological Association, New York, April 1971.
13. M. Jouvet, *Science* **163**, 32 (1969).
14. L. Stein, paper presented at the International Symposium on Antidepressant Drugs, Milan, April 1966.
15. Supported in part by NIMH grant 18908.

26 April 1972

Behavioral Changes of Chronic Schizophrenic Patients Given L-5-Hydroxytryptophan

Abstract. *Oral administration of the serotonin precursor* L-*5-hydroxytryptophan with a peripheral decarboxylase inhibitor produced mild to moderate improvement in six of seven chronic undifferentiated schizophrenic patients who were resistant to phenothiazine treatment, as compared to an oral administration of a placebo. Two of four chronic paranoid schizophrenic patients who were resistant to phenothiazine treatment became worse with 5-hydroxytryptophan, one improved. It is presumed that these psychological changes were directly or indirectly produced from increases in brain serotonin. Indirect data from animals and humans indicate that there may be an abnormality in serotonin metabolism in some schizophrenics. While our data are consistent with this hypothesis, other explanations for our data must be entertained.*

There are three lines of investigation supporting the hypothesis that some schizophrenic patients have an abnormality in serotonin metabolism (*1*). Two of these, sleep and psychotomimetic drug research, approach the problem indirectly. Animal and human sleep data indicate that serotonergic neurons may exert their influence by suppressing phasic events such as rapid eye movements (REM's) and pontine geniculate occipital spiking during nonrapid eye movement (NREM) sleep and perhaps during waking. These phasic events are thus normally forced to appear during REM or dreaming sleep (*2*). Some schizophrenic patients seem to have an abnormal frequency of REM's during NREM sleep (as defined by the electroencephalogram and the electromyogram), few during REM sleep, and, as opposed to most normal subjects, do not have REM compensation after REM deprivation (*1*). Cats given *p*-chlorophenylalanine, a drug that inhibits the synthesis of serotonin, have features of sleep and behavior similar to those of schizophrenic patients (*2*). This also appears to be true of the sleep of humans given *p*-chlorophenylalanine for medical purposes. In addition, a small number of such patients have had psychotic episodes while on this drug (*3*).

A possible endogenous substance that might produce these changes is the hallucinogen dimethyltryptamine. An enzyme capable of synthesizing di-

methyltryptamine has recently been shown to be present in the human brain (*4*). It is of considerable interest that dimethyltryptamine slows the firing of raphe neurons of the rat and that cells in these nuclei are the source for most brain serotonin (*5*). Based on a molecular model, Smythies has proposed that hallucinogens might act by intercalation at the putative serotonin receptor sites while Freedman has demonstrated that indoleamine hallucinogens alter brain serotonin metabolism (*6*). Furthermore, substances that increase brain serotonin in both animals and humans have generally been shown to counter the effects of both dimethyltryptamine and LSD (lysergic acid diethylamide), while those which reduce brain serotonin generally enhance the hallucinogenic effect.

Finally, more direct studies measuring either serotonin or the principal metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), have shown them to be low in the blood, urine, and spinal fluid of schizophrenic patients (*1*). On the other hand, 5-HIAA has just as frequently been shown to be normal or elevated, and low 5-HIAA concentrations seem to be common to many diseases of central nervous system origin.

Attempts to elevate brain serotonin have generally, although not exclusively, failed to produce ameliorative effects in schizophrenics. This may be due to the fact that the drugs used (monoamine oxidase inhibitors or tryptophan) increase substances in addition to serotonin. 5-Hydroxytryptophan, the immediate precursor of serotonin, has probably not been given in dosages that would greatly affect brain serotonin.

In this study, we gave L-5-hydroxytryptophan (5-HTP) with the peripheral decarboxylase inhibitor L-α-hydrazino-α-methyldopa (MK-486). The decarboxylase inhibitor prevents the peripheral utilization of 5-HTP and, since it does not cross the blood brain barrier, makes more 5-HTP available for conversion to serotonin within the brain parenchyma (*7*). In addition, it was thought that the peripheral decarboxylase inhibitor would decrease the gastrointestinal irritation produced by serotonin. In six of seven chronic, undifferentiated schizophrenic patients, 5-HTP produced ameliorative effects. Two of four chronic paranoid schizophrenics became worse with 5-HTP treatment, one improved.

Eleven chronic, male schizophrenic patients (Table 1) between the ages of 21 and 36, and averaging over 8 years of hospitalization, were studied. The diagnosis of schizophrenia was made by three psychiatrists, as well as a referring psychiatrist, according to American Psychiatric Association criteria. When free from drugs, the patients exhibited hallucinations, delusions, thought disorders, unusual mannerisms, desocialization, and nighttime insomnia. Patients were diagnosed as paranoid when there was considerable suspiciousness present. Subgroup diagnoses were made during the first placebo period. While the behavior of the patients had been modified with phenothiazine and butyrophenones, none had been able to leave the hospital for prolonged periods or were expected to be able to do so within 6 months. Although the experimental design was modified because of unforeseen circumstances, as noted below, the original plan was to have the patients on placebo medication 30 days, 5-HTP and MK-486 for 30 days, and placebo again for 30 days. The drug period was lengthened to a maximum of 3 months because the initial two patients appeared to have measurable improvement during the last 10 days of the 30-day trial. For patient 2, the drug trial had to be terminated because of severe vomiting. Patient 5 withdrew from the study. The drug trial for patients 6 and 7 was terminated because the drug made them worse.

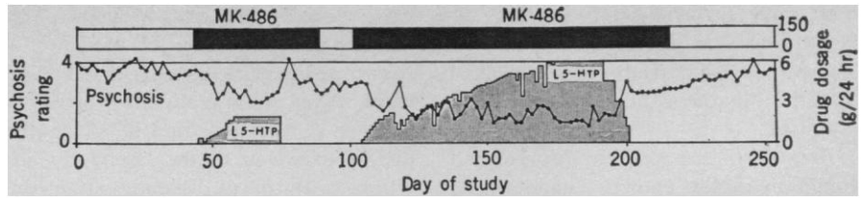

Fig. 1. Dosage of the peripherial decarboxylase inhibitor MK-486 and L-5-hydroxytryptophan (5-HTP) in a chronic schizophrenic patient (patient 1). The degree of psychosis was measured by the nursing staff daily; but points here are 2-day means.

The drugs were given in capsular form in constant numbers throughout the study by means of a code known only to the prescribing physician. During the drug period, the patients were given 150 mg of MK-486 per 24 hours and up to 6 g of 5-HTP per 24 hours. When it was possible to increase the 5-HTP slowly over a 60-day period, the gastrointestinal side effects could be completely avoided. The beginning of treatment for each patient was staggered by at least 2 weeks to prevent group effects from greatly influencing individual ones. In addition, while it was expected that the "blindness" of the experiment would be somewhat diminished because of drug side effects,

Table 1. Effect of administration of L-5-hydroxytryptophan (5-HTP) on a rating of psychosis of chronic schizophrenic patients. The psychosis rating was the mean for the last 7 days for each period. The ratings were done by a team of four nurses each day of hospitalization of the patients. The rating consisted of the nonweighted means of subscales designed to measure hallucinatory, delusional, paranoid, and bizarre behaviors in addition to thought disorders. Patient 2 did not get a full therapeutic trial because he was a difficult management problem combined with our inability to raise the 5-HTP dosage fast enough to make his behavior tolerable. Patients 6 and 7 became decidedly worse and the active drug period was discontinued. Patient 5 withdrew from the study before a clear change in behavior was demonstrated. Abbreviation: U, undifferentiated; P, paranoid; and max, maximum.

Patient (No.)	Age (years)	Hospital stay (years)	Subgroup	Maximum 5-HTP (mg/24 hr)	Psychosis ratings			
					First placebo	5-HTP (max)	Second placebo	5-HTP change*
1	33	14	U	6000	3.6	1.0	3.6	Improved
2	21	7	U	1500	4.1	3.3	4.5	Improved
3	22	7	U	6000	5.0	2.8	4.8	Improved
4	36	15	U	4000	2.9	2.4	3.5	Improved
5	33	9	P	800	2.8	2.3	2.3	None
6	33	10	P	2700	2.8	3.9	2.9	Worse
7	30	10	P	2400	3.7	5.0	4.5	Worse
8	25	2	P	6000	2.3	1.3	2.4	Improved
9	19	2	U	6000	2.5	1.0	0.5	None
10	33	3	U	6000	2.2	1.4	2.6	Improved
11	34	9	U	6000	3.0	2.5	3.7	Improved

* For there to be a change, a two-tailed *t*-test had to be significant ($P < .05$) for both placebo and 5-HTP comparisons.

there were a sufficient number of identifying side effects and behavioral changes opposite from those expected that the blindness did not seem compromised.

Because of the severely disorganized condition of the patients, standardized ratings that require an interview could not be carried out. Instead ratings based on inference after several hours of observation were made. The patients were rated by two nurses on the day shift and two nurses on the evening shift on an eight-point (0 to 7) behavior and mood scale shown to have good interrater reliability (*8*). For the purpose of this study, the mean psychosis scale for the last week on 5-HTP was compared to the last week of the placebo periods both prior to and after the 5-HTP treatment. For the effect to be considered either positive or negative, the ratings during the drug period had to be higher or lower (two-tailed *t*-test, $P < .05$) than both placebo periods. The psychosis scores of patients 5 and 9 during 5-HTP treatment fell between those of the two placebo periods and therefore no statement can be made about the effectiveness of the drug with them. No attempt was made to compare 5-HTP treatment with conventional drugs.

Six of seven chronic undifferentiated schizophrenic patients had positive effects while for one no determination could be made (Table 1). Two of the four paranoid patients became worse, one improved, and for one no change could be determined. Owing to episodes of unpredictable violence combined with our inability to quickly increase the drug dosage because of vomiting, patient 2 did not get a full dosage of 5-HTP. The dosage of patient 4 was not raised to 6 g because he did not appear to be getting progressively better with the dosage increases as did the other patients. The two patients who became worse had their drug dose discontinued when this became clinically evident. The daily psychosis rating and 5-HTP dosage of patient 1 is shown in Fig. 1. It appears that 5-HTP takes effect only gradually (probably because of the slow rate at which the drug dosage can be increased). In addition, with drug discontinuation the return of symptomatology was generally slow, except for what appeared to be immediate withdrawal effects.

Twenty-four-hour urine collections (*9*) were made during placebo and drug periods. Mean 5-HIAA concentrations expressed in micrograms per milligram of creatinine excreted for five patients, in whom it was thought complete urine samplings were achieved, increased from 3.7 for placebo to 330 for 5-HTP treatment (average 5-HTP dosage was 2500 mg). In two patients when serial measurements were made, the 5-HIAA excretion was linear to the 5-HTP dosage.

Interpretation of these findings must be made with considerable caution. 5-Hydroxytryptophan was not compared with any drug other than placebo, but this precursor to natural serotonin when compared to placebo led to behavioral changes in six of seven chronic undifferentiated and three of four chronic paranoid schizophrenic patients. Of those that improved, no patient at his best would have been able to return to the community for long periods of time. Further studies are necessary to determine if this drug combination has any long-term therapeutic benefit.

Although 5-HTP is probably converted to serotonin within cells that normally contain serotonin, it has been shown that other cells containing aromatic decarboxylase can also convert 5-HTP to serotonin (*10*). In the latter cells, serotonin may be acting in a nonphysiologic manner. For example, in dopaminergic cells, serotonin could be acting in place of dopamine and since both the phenothiazines and butyrophenones block dopamine receptors, its antipsychotic action could occur through this mechanism. On the other hand, none of our patients had extrapyramidal signs suggestive of an antidopaminergic effect.

We do not know the mechanism of 5-HTP action but it does appear to be capable of producing changes in at least some chronic schizophrenic patients. This finding may provide a tool for further understanding the schizophrenic syndrome and normal human behavior.

RICHARD J. WYATT
THOMAS VAUGHAN
MARC GALANTER
JONATHAN KAPLAN, RICHARD GREEN
Laboratory of Clinical Psychopharmacology, Division of Special Mental Health Research, National Institute of Mental Health, Saint Elizabeths Hospital, Washington, D.C. 20032

References and Notes

1. R. J. Wyatt, B. Termini, J. Davis, *Schizophrenia Bull.* **4**, 10 (1971).
2. W. Dement, V. Zarcone, J. Fergusen, A. Cohen, T. Pivik, J. Barchas, in *Schizophrenics —Current Concepts and Research*, D. V. Siva Santer, Ed. (PJD Publications, New York, 1969), p. 775.
3. K. Engelman, W. Lovenberg, A. Sjoerdsma, *N. Engl. J. Med.* **227**, 1103 (1967).
4. A. J. Mandell and M. Morgan, *Nature* **230**, 85 (1971); J. Savaadra and J. Axelrod, *Science* **175**, 1365 (1972).
5. G. K. Aghajanian, W. E. Foote, M. H. Sheard, *J. Pharmacol. Exp. Ther.* **171**, 178 (1970); A. Dahlström and K. Fuxe, *Acta Physiol. Scand.* **62** (Suppl. 232), 1 (1964).
6. J. R. Smythies, F. Benington, R. D. Morin, *Int. Rev. Neurobiol.* **12**, 207 (1970); D. X. Freedman, in *Psychochemical Research in Man: Methods, Strategy, and Theory*, A. J. Mandell and M. P. Mandell, Eds. (Academic Press, New York, 1969), p. 89.
7. A. Horita and A. E. Hamilton, *J. Pharm. Pharmacol.* **22**, 389 (1970); the 5-HTP was supplied by Drs. L. Freeman and J. Lubitz (Calbiochem). The MK-486 was supplied by Dr. M. Jaffe (Merck Sharp and Dohme).
8. R. J. Wyatt and D. J. Kupfer, *Psychol. Rep.* **28**, 1331 (1968).
9. C. E. Dalglieshi, in *Advances in Clinical Chemistry*, H. Sobotka and C. P. Stewart, Eds. (Academic Press, New York, 1958), vol. 1, p. 193.
10. A. B. T. Moir and D. Eccleston, *J. Neurochem.* **15**, 1093 (1968).
11. We thank our patients, nurses, and research staff for working together in what at times were extremely difficult conditions.

24 April 1972; revised 9 June 1972