Table 1. Learning ability of mice raised from birth on diets which caused serotonin deficiency.

Treatment	No. of mice	Av. score
None	90	7.5
Water, hourly	15	7.5
DL-Phenylalanine + L-tyrosine	103	6.3
Reserpine	99	6.6
Chlorpromazine	32	6.5

onstrated that the results of this maze test were reproducible within a standard deviation of $\pm$ 0.2 in the score.

Excess phenylalanine (by way of phenylpyruvic acid) causes deficiency of serotonin and of catechol amines, probably by the inhibition of the decarboxylase which forms these hormones, and possibly also by other related inhibitions (*1*). Two other independent means of bringing about the deficiencies were also studied. One was to feed reserpine (10 mg/kg of ration) to the mothers, starting 2 days before parturition, and then to the young (5 mg/kg) until they were mature. This is known to cause a lack of the hormones by combination of the drug with some of the hormonal receptors (particularly those in the storage vesicles), with consequent displacement of the hormones from the tissues. The other was to feed chlorpromazine (500 mg/kg of diet) in the same way. Although chlorpromazine does not displace serotonin from tissues, it does block the receptors for serotonin and for catechol amines in such a way that the tissues will no longer respond to these hormones (*1*). The end result is a *functional* lack of the hormones.

The data in the table show that mice that had been reared from birth under these various conditions which caused deficiencies of these hormones had a subnormal learning ability as measured in the maze test. This was true regardless of the way in which the deficiency was induced (*11*). The fact that the animals fed phenylalanine and tyrosine actually were excreting phenylpyruvic acid was established by chromatography and the ferric chloride test of the urine. The fact that they were deficient in serotonin has been demonstrated earlier (*9*) by analysis of the tissues of animals similarly treated.

The importance of beginning the treatments at birth was demonstrated. When any one of the treatments was not started until weaning, and the mice were then tested when they were mature, no deficit in learning ability was found. Thus, mice fed phenylalanine plus tyrosine from weaning until maturity gave an average score of 7.3. The need for establishment of the disease early in infancy in mice thus corresponded with the findings in the human disease.

The phenylketonuric mice were physically quite normal when they were mature just as is the case with phenylketonuric human beings. They tended to be somewhat less active and perhaps more quarrelsome than normal mice, but it is difficult to be sure of such differences. Sometimes the infant mortality was high but with adequate technique in the dosing procedure, this could be eliminated. The animals raised on reserpine showed a variable and sometimes high infant mortality and a slight retardation of development as indicated by lateness in the opening of the eyes. When higher doses of reserpine were used, the learning deficit was considerably greater, but the infant mortality was so high and so variable from litter to litter that it was not feasible to use these higher doses.

Proof was found that the mental defect was the result of serotonin deficiency and not the result of other changes. Hourly administration of serotonin derivatives (melatonin or hydroxytryptophan) to phenylketonuric mice did not correct the excretion of phenylpyruvic acid, but did produce animals with normal scores for learning ability.

D. W. Woolley
Th. van der Hoeven
Rockefeller Institute, New York

References and Notes

1. D. W. Woolley, *The Biochemical Bases of Psychoses* (Wiley, New York, 1962).
2. C. M. B. Pare, M. Sandler, R. S. Stacey, *Lancet* **1**, 551 (1957); I. Huang, S. Tannenbaum, L. Blume, D. Y. Hsia, *Proc. Soc. Exptl. Biol. Med.* **106**, 533 (1961).
3. H. Weil-Malherbe, *J. Mental Sci.* **101**, 733 (1955); D. E. Boggs, R. Rosenberg, H. A. Waisman, *Proc. Soc. Exptl. Biol. Med.* **114**, 356 (1963).
4. J. H. Fellman, *Proc. Soc. Exptl. Biol. Med.* **93**, 413 (1956).
5. A. N. Davison and M. Sandler, *Nature* **181**, 186 (1958).
6. V. H. Auerbach, H. A. Waisman, L. B. Wyckoff, *ibid.* **182**, 871 (1958).
7. A. Yuwiler and R. T. Louttit, *Science* **134**, 831 (1961).
8. V. J. Polidora, D. E. Boggs, H. A. Waisman, *Proc. Soc. Exptl. Biol. Med.* **113**, 817 (1963).
9. D. W. Woolley and Th. van der Hoeven, *Science* **139**, 610 (1963).
10. D. W. Woolley, *ibid.* **136**, 330 (1962).
11. J. Werboff and R. Kesner [*Nature* **197**, 106 (1963)] have tested rats for learning ability after treatment during intrauterine life with reserpine or chlorpromazine. They found no significant decrease in learning ability, but their animals were not treated with the drugs during infancy as ours were.
12. Abstracts of portions of this work have appeared in *Federation Proc.* **23**, 146 (1964) and in *Proc. Second International Pharmacology Meeting* (1963). Support of U.S. Public Health Service grant A3386 is gratefully acknowledged.

17 March 1964

Markovian Model of Time Patterns of Speech

Abstract. *The time pattern of speech is describable as a first-order Markov process when presence or absence is sampled at a rate of 200 times per minute. Two types of monolog were generated under different conditions of environmental constraint. Although both fit the model, estimates of their mean range of statistical dependency differed significantly.*

The temporal patterns of speech may be described in terms of the frequency distributions of (i) the durations of sound bursts, and (ii) the intervening durations of silence. Both of these distributions have been found to be approximately exponential, with frequency inversely related to duration (*1*). Mosteller (see *1*) has proposed a stochastic model of such vocal time patterns based upon alternate random drawings from the sound and silence distributions respectively. Using this model he was able to hand-simulate a reasonable approximation to actually observed data.

We are exploring such probabilistic hypotheses by sampling the presence or absence of the speech signal. The sampling time unit, which is initiated at a rate of 200 times per minute, is 30 msec in duration. Each successive unit is either a state of sound or silence, depending upon the presence or absence of a signal above threshold at some time during the sampling interval. Our initial attempts to generate observed frequency distributions were

$$\begin{array}{ccc} & & \text{State } s \text{ at Time } t{+}1 \\ & & \begin{array}{cc} 0 & 1 \end{array} \\ P = \text{State } s \text{ at time } t & \begin{array}{c} 0 \\ 1 \end{array} & \begin{array}{|c|c|} \hline p(0/0) & p(1/0) \\ \hline p(0/1) & p(1/1) \\ \hline \end{array} \end{array}$$

Fig. 1. First-order transition matrix for monolog.

based on the assumption that successive samples were statistically independent, and yielded very poor approximations. Continuation of sound or silence from one unit to the next is more frequent than would be predicted from absolute probabilities of the two states. This indicates that prior events in the sequence exert some degree of constraint upon subsequent ones. As suggested by Miller (*2*), a Markov chain with two alternatives was therefore adopted as the simplest model of dependent probabilities for examination of these sequences. A first order Markov process has the property that the state occupied at time $t+1$ is dependent upon the state at time t, but is independent of events prior to t.

Let a voice relay actuated by a single speaker be in either of two states s at any instant of sampling t, ($s = 0, 1$, corresponding to silence and sound, respectively). The transition matrix P in Fig. 1 gives the probabilities of being in each of the two states at time $t+1$ depending upon the state occupied at time t.

It is required that:

$$\begin{aligned} p\,(0) \quad + p\,(1) \quad &= 1, \\ p\,(0/0) + p\,(1/0) &= 1, \\ p\,(0/1) + p\,(1/1) &= 1. \end{aligned}$$

In the case of dialog, the two voice relays of the separate speakers, sampled simultaneously, can assume any of four different states. These are the four possible configurations of two binary digits, yielding a 16-cell transition matrix. This will be reported elsewhere (*3*).

P is then a stochastic matrix, and the entries $p_{ij}^{(1)}$ are the first-order transition probabilities, that is, of going from s_i at time t to s_j at time $t+1$. Similarly, the probabilities of going from s_i at time t to s_j at time $t+2$ are given by a second-order transition matrix with entries $p_{ij}^{(2)}$. The entry $p_{ij}^{(n)}$ is the probability of reaching s_j from s_i in n steps. If the process under investigation is to be described as a first-order Markov chain, then the higher order transition probabilities of the data should be predicted by matrix multiplication of P with itself. The actually observed entries $p_{ij}^{(n)}$ should not differ significantly from comparable entries of the powers P^n of the first-order transition matrix.

In order to test the hypothesis, two 5-minute monologs were obtained from each of 25 subjects. In condition A the instructions were to tell a story about a picture while observing it. In condition B the subjects were instructed to speak spontaneously about themselves, and were relatively unconstrained by interaction with the environment. All subjects were applicants to an outpatient psychotherapy clinic, were free of speech disorders, and were cooperative in the testing. The sequence of the two conditions was randomized. High-fidelity tape recordings of the monologs were processed by a special analogue to digital converter which records the sound-silence pattern automatically on punch cards (*4*). The sampling rate of 200 time units per minute yielded 1000 observations for each monolog. Actual transition probabilities up to the sixth order and, as a prediction, the second through the sixth powers of the first-order matrix were computed on the I.B.M. 7090.

The assumption that the transitional probabilities are stationary or independent of time, was not tested. The mean frequencies for the predicted and obtained matrices in conditions A and B are shown in Tables 1 and 2, respectively. Chi-squared tests for first- versus second-order chains were performed on the obtained matrices as proposed by Anderson and Goodman (*5*). These were not significant at the .05 level, thus confirming the hypothesis that the chain is describable as first order.

To determine the accuracy with which the model predicts the obtained data we calculated root mean squares of the discrepancies for each condition within each order (Tables 1 and 2). The root mean squares, which indicate the range of error which might be expected for an individual subject, vary from 1.13 percent to 5.77 percent of the total frequencies of their associated matrix rows. We were also curious about the possibility that monologs elicited in different ways would be differently approximated by the model. Analysis of variance of the discrepancies for conditions A and B provided no evidence in support of this possibility.

In order to estimate the range of statistical constraint, successive powers of the first-order matrix were computed until the fixed point vector was reached. With the criterion that both rows of the matrix be identical to the second (uncorrected) decimal place, the mean power on convergence was 13.6 for condition B and 16.8 for condition A (4 to 5 seconds). That is to say, if we sampled every 17th time unit we would find that successive samples were statistically independent of each other. Although there was wide individual variation on this measure (2 to 11 seconds) the point biserial correlation between the number of steps required to reach a "steady state" for conditions A and B was .55, significant beyond the .01 level. The difference between the mean number of steps for the two groups was also significant at the .01 level, using a test of the difference between correlated means ($t = 3.231$).

The conclusion reached is that a first-order Markov process adequately describes the time patterns of monologs elicited by the conditions of this experiment. Thus, although Markovian structures are inadequate for description of grammars (*6*), they seem to describe simple time patterns of speech. Estimation of the range of sequential dependency, in terms of the number of steps (at 200 time units per minute) until the matrix achieves a "steady state," indicates a mean value of the order of 4 to 5 seconds. The correlation between individuals' scores on this meas-

Table 1. Comparisons of obtained and predicted mean cell frequencies of higher order transition matrices and the root mean squares (R.M.S.) of their differences for condition A.

Obtained		Predicted		R.M.S.	Power*
420	72				1
72	438				1
365	127	371	121	7.39	2
126	384	121	389	7.27	2
325	167	337	155	14.86	3
166	344	155	356	14.66	3
300	192	314	178	18.47	4
191	319	178	332	18.26	4
285	207	297	195	18.40	5
206	304	194	316	18.19	5
277	215	286	206	15.38	6
214	297	206	305	14.91	6

* Powers refer to the predicted matrix.

Table 2. Comparisons of obtained and predicted mean cell frequencies of higher order transition matrices and the root mean squares (R.M.S.) of their differences for condition B.

Obtained		Predicted		R.M.S.	Power*
279	70				1
70	582				1
230	119	234	115	7.75	2
118	534	114	537	7.40	2
199	150	204	145	13.97	3
149	503	144	507	13.65	3
179	171	184	165	18.23	4
169	483	164	488	17.76	4
166	183	171	179	20.14	5
180	471	177	474	19.41	5
160	190	162	188	19.87	6
187	465	186	465	19.36	6

* Powers refer to the predicted matrix.

ure under the two conditions suggests that relatively stable individual characteristics may be inherent in these patterns. The difference between the means suggests that the range of statistical dependency in the temporal patterns is sensitive to the instructions under which the speech is generated. One may speculate that the 4- to 5-second range reflects some syntactical unit in the lexical pattern of speech or perhaps the respiratory cycle, but this cannot be ascertained from the present data.

JOSEPH JAFFE
Department of Psychiatry,
College of Physicians and Surgeons,
Columbia University, New York
LOUIS CASSOTTA
STANLEY FELDSTEIN
Research Department, William
Alanson White Institute, New York

References and Notes

1. A. C. Norwine and O. J. Murphy, *Bell System Tech. J.* **17**, 281 (1938); E. D. Chapple, *Proc. Natl. Acad. Sci. U.S.* **26**, 10 (1940); F. Mosteller, unpublished manuscript; M. Verzeano, *J. Speech Hearing Dis.* **15**, 197 (1950); F. Goldman-Eisler, *Brit. J. Psychol.* **42**, 335 (1951); W. A. Hargreaves, *Lang. and Speech* **3**, 164 (1960); J. D. Matarazzo, H. F. Hess, G. Saslow, *J. Clin. Psychol.* **18**, 416 (1962).
2. G. A. Miller, *Psychometrika* **17**, 149 (1952).
3. J. Jaffe, S. Feldstein, L. Cassotta, in K. Enslein (Ed.), *Proceedings of the 1963 Rochester Conference on Data Acquisition and Processing in Biology and Medicine* (Pergamon, New York, in press).
4. L. Cassotta, S. Feldstein, J. Jaffe, *J. Exptl. Anal. Behav.* **7**, 99 (1964); J. Jaffe, S. Feldstein, L. Cassotta, *Behav. Sci.*, in press (abstract).
5. T. W. Anderson and L. A. Goodman, *Ann. Math. Statist.* **28**, 89 (1975).
6. N. Chomsky, and G. A. Miller, *Inform. and Control* **1**, 91 (1958).
7. Supported by grant MH-04571-03 to the William Alanson White Institute and a general research support grant to the College of Physicians and Surgeons, Columbia University, both from the National Institute of Mental Health. We thank George A. Miller, Alfred H. Conrad, Alex Heller, David McK. Rioch, and Jacob Cohen for their helpful suggestions.

28 February 1964

Psychological Changes Associated with Induced Hyperammonemia

Abstract. *Normal volunteers infused with ammonium acetate for 3 hours developed a characteristic behavior pattern resembling that of prehepatic coma. They demonstrated certain specific defects in motor performance and recognition as well as significant lowering of critical flicker fusion. These findings are correlated with the concentration of ammonia in arterial blood.*

Attempts to prove ammonia intoxication as the necessary and sufficient cause for hepatic coma have thus far been unsuccessful. Some investigators feel that hyperammonemia is only incidental to the coma state, while others consider it crucial either alone or in combination with another substance (*1*). It has been reported that patients without liver disease who were accidentally infused with large amounts of ammonium chloride over several hours developed a state resembling hepatic coma (*2*).

The data presented in this report bear on the role of hyperammonemia in altering behavior with special reference to the coma of hepatic disease. A method for obtaining an altered behavioral state with ammonia is also described.

Twelve prisoner volunteers free of liver and central nervous system disease were infused intravenously for 3 hours at two periods: in one period 0.75 meq/kg per hour of ammonium acetate in 2½ percent of glucose in water was infused; in the other, 2½ percent of glucose in water, considered as a placebo, was given. The infusion periods were separated by at least 24 hours. Six volunteers received the ammonia first and six were given the placebo first. The subjects were unaware of which substance was being infused. On a day prior to infusion, the 12 prisoner volunteers were given practice sessions with the critical flicker-fusion apparatus (*3*, *4*) and with the repetitive psychometric measures (*5*, *6*).

In a separate procedure, five other prisoner subjects were given the ammonium infusion alone and arterial blood samples were drawn at 0 time (5 to 10 minutes before infusion was begun) and at half-hour intervals thereafter for 3 hours. Ammonia determinations were done within 10 minutes by a modification of Seligson's method (*7*). For technical reasons, only two arterial samples were obtained for the 3-hour measurement.

The mean concentrations of ammonia in arterial blood obtained from the group of five subjects and the corresponding characteristic behavior patterns noted at each stage in the group of 12 subjects are combined in Fig. 1. These behavioral observations were found in 10 out of 12 subjects during ammonia infusion. The disturbances that occurred disappeared within 1 to 1½ hours after the infusion was stopped. Seven of the 12 subjects vomited at some time during ammonia infusion. The behavioral observations were made by the experimenter alone and were of a direct clinical type. Alterations were found only during ammonia infusion.

In Table 1 are depicted the mean ammonia, mean placebo, and the mean and standard deviation of the mean of the placebo versus ammonia performance differences plus the *t*-tests of these differences on the repetitive psychometric measures and critical flicker-fusion tests (*3*, *6*). Analysis of variance of the psychometric measures showed no significant amount of variation due to the order of infusion, or between subjects under placebo infusion, or between subjects that did and did not vomit [except with the aiming test (*5*)]. For the critical flicker-fusion tests, at the 15-minute test period only, the subjects receiving ammonia first and placebo second showed significantly greater lowering of the critical flicker-fusion value than those receiving placebo first. In this respect then, with the flicker-fusion tests at 15 minutes, there was a statis-

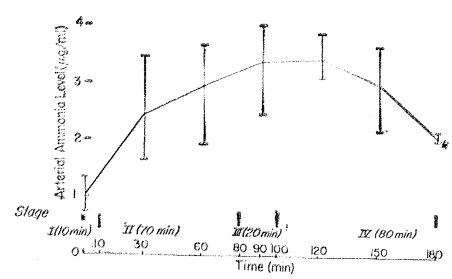

Fig. 1. Mean and range of arterial ammonia concentrations correlated with the characteristic behavior pattern during 3-hour infusion of ammonium acetate (0.75 meq/kg per hour). $N = 5$ for ammonia concentrations; $N = 12$ for the behavioral observations; $^{*}N = 2$. Behavioral observations: stage I, giddy, blurred vision, and apprehension; stage II, increased verbal activity, more alertness, and greater interpersonal interaction; stage III, generalized uncomfortable feeling (7 out of 12 subjects felt very jittery, nervous, or jumpy); stage IV, progressive decrease in speech, flaccid muscles, less alertness, decreased interpersonal interaction, and tremor appearing toward end of infusion.