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 U.S.* **26**, 10 (1940); F. Mosteller, unpublished manuscript; M. Verzeano, *J. Speech Hearing Dis.* **15**, 197 (1950); F. Goldman-Eisler, *Brit.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-

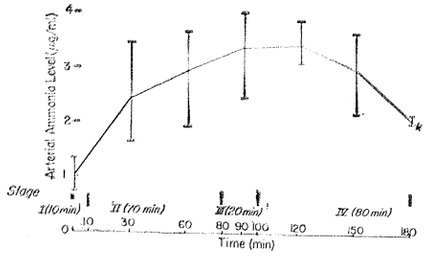

Fig. 1. Mean and range of arterial ammonia concentrations correlated with the characteristic behavior pattern during 3-hour infusion of ammonium acetate (0.75 meq/kg per hour). $N = 5$ for ammonia concentrations; $N = 12$ for the behavioral observations; $*N = 2$. Behavioral observations: stage I, giddy, 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.

tically significant variance due to order of infusion ($p < .05$).

The range of concentrations of ammonia in the blood achieved by this infusion procedure (Fig. 1) is the same as that found in clinical states of hepatic precoma and coma, between 2 to 5 μg/ml (*8*). At the end of the infusion, the observed state of these subjects (flaccid facial muscle tone, decreased speech, decreased interaction with the examiner, and tremor) is similar to the picture of hepatic precoma. Figure 1 shows that the peak concentration of ammonia in the blood corresponds to stage III of the characteristic behavior pattern which was marked by generalized discomfort and in most subjects by anxiety. In studies with animals, it has been demonstrated that appreciable amounts of ammonia appear in the brain tissue only after this peak concentration of ammonia in the blood is reached (*9*). If this is also true for the human being then one might reason that the findings in stage IV are associated with elevated concentrations of ammonia in the brain tissue. The fall in arterial ammonia concentration may be understood in terms of a clearing mechanism which becomes operative when the concentration reaches a certain peak. Evidence for such a mechanism located in both brain and muscle has been brought forth in both animal and human studies (*9*, *10*).

With the repetitive psychometric measures, it is considered that the decrement on the aiming test at 180 minutes reflects disturbances in eye-hand coordination. This may be related to the tremor found in hepatic coma. The defect on the speed of closure test (*5*) at 180 minutes was ascribed to disturbance in recognition which might be the analog of the disorientation in the clinical hepatic precoma state. The initial stimulatory effect on this test is reflected in the *t*-value at 15 minutes, which shows significantly improved performance. This stimulatory effect corresponds to the hyperactivity of stage II (see Fig. 1) noted in the characteristic behavior pattern. Such an initial stimulatory effect is reminiscent of the action of other drugs such as alcohol and anesthetics which, when administered over longer periods, have a depressing effect.

The significant *t*-tests at the 90-minute period on both the number facility test and the visualization test (*5*) may relate to the effects of anxiety on performance rather than reflect psychological impairment with impending hepatic coma. If this is so, the subsequent improvement of performance on these tests at 180 minutes demonstrates that the abilities required for their performance are not sensitive to prolonged hyperammonemia. The lowering of the critical flicker-fusion value is considered to be an indicator of organic perceptual disturbances and is consistent with what might be expected in prehepatic coma. Such lowering is found both with chlorpromazine and with reserpine (*11*).

The data suggest that an altered behavioral state is associated with a 3-hour period of hyperammonemia. This altered state resembles prehepatic coma in the detachment, disturbance in recognition (speed of closure test), tremor, and impaired eye-hand coordination (aiming test) that were found. The effects do not appear to be due to the infusion procedure itself since they were not observed during the placebo infusion period. Work with ammonium chloride has been challenged because of the question of whether the changes in *p*H that occur would alter the permeability of the blood-brain barrier (*12*). Ammonium acetate was used in this study in order to avoid this possibility.

It might be reasoned that these findings of altered behavior are not specific for hepatic precoma but would occur in other precoma states as well. In both the clinical hepatic state and the experimentally induced state, however, the arterial ammonia levels are in the range of 2 to 4 μg/ml. The fact that in some clinical cases of hepatic coma elevated ammonia levels are not found presents a problem which remains to

Table 1. The mean scores for performance on repetitive psychometric measures tests; and critical flicker-fusion test, during infusion with ammonium acetate (¾ meq/kg per hour) and placebo (2½ percent glucose in water); plus the mean differences plus or minus standard deviation, and the *t*-test of these mean differences. The values for the psychometric measures tests are the number of units done correctly per time limit for each test [see (*5*) for further explanation]. The critical flicker-fusion test value is number of flashes per second [see (*3*) for further explanation].

Tests	*N*	Mean scores		Mean difference	*t*
		Ammonia acetate	Placebo		
		At 15 minutes			
Aiming test	12	− 8.1	− 3.4	−4.7± 9.0	−1.51
Speed of closure test	12	7.2	3.1	4.1± 2.5	2.67*
Number facility test	12	0.1	0.8	−0.7± 5.1	−0.54
Perceptual speed test	12	1.9	2.0	−0.1±10.0	0.03
Visualization test	12	− 1.5	1.3	−2.8± 7.7	−1.14
Critical flicker fusion	10	40.2	40.7	−0.5± 1.5	−1.15
		At 90 minutes			
Aiming test	12	− 9.5	− 3.8	−5.7± 8.4	−2.18†
Speed of closure test	12	5.1	7.0	−1.9± 3.3	−1.85†
Number facility test	12	− 2.4	2.0	−4.4± 6.8	−2.19†
Perceptual speed test	12	1.2	5.2	−4.0± 9.9	−1.70
Visualization test	12	− 2.9	2.5	−5.4± 9.8	−1.80†
Critical flicker fusion	10	39.5	40.2	−0.7± 1.3	−1.60
		At 180 minutes			
Aiming test	12	− 8.9	− 0.3	−8.6±11.0	−2.47‡
Speed of closure test	12	4.0	6.4	−2.4± 3.5	−2.37‡
Number facility test	12	0.3	1.6	−1.3± 5.1	−0.81
Perceptual speed test	12	2.0	4.0	−2.0± 6.7	−0.95
Visualization test	12	− 0.8	1.8	−2.6± 7.7	−1.15
Critical flicker fusion	10	39.5	40.3	−0.8± 1.2	−2.00†

* Significant at $p < .025$ (one tailed) in opposite direction to that predicted. † $p < .05$ (one tailed). ‡ $p < .025$ (one tailed).

be clarified. Nevertheless, from this study it is submitted that prolonged hyperammonemia produces an altered behavioral state analogous to the early stages of hepatic coma.

MYRON EICHLER
Psychiatric Institute, University of Maryland, Baltimore

References and Notes

1. S. Sherlock, *Ann. Rev. Med.* **11**, 47 (1960); S. P. Bessman, *Ann. Internal Med.* **44**, 1037 (1956); K. S. Warren and S. Schenker, *Am. J. Physiol.* **199**, 1105 (1960); W. V. McDermott, D. H. Henneman, C. Laumont, *J. Surg. Res.* **1**, 307 (1961).
2. A. S. Relman, P. F. Shelburne, A. Tallman, *New Engl. J. Med.* **264**, 848 (1961).
3. The critical flicker-fusion data were obtained in the following manner. For each test period, the subject reported flicker fusion five times approached from flicker and five times approached from fusion. These were averaged separately and then their means were averaged to obtain the critical flicker fusion (*4*). The differences in critical flicker fusion between placebo and ammonia were then averaged and a parametric *t*-test of these differences was carried out.
4. E. Simonson and J. Brozek, *Physiol. Rev.* **32**, 349 (1952).
5. L. J. Moran and R. B. Mefferd, *Psychol. Rep.* **5**, 269 (1959). In the aiming test, dots must be placed with a pencil in circles measuring 0.15 cm in diameter. In the speed of closure test, four-letter words embedded in a series of letters must be encircled. The number facility test requires addition of rows of numbers. In the perceptual speed test, the subject crosses out a given number in a series of numbers which is designated at the beginning of each row. In the visualization test, tangled lines must be traced with eyes alone from a numbered box on the left to the correct box on the right. Each test has a given time limit.
6. With the repetitive psychometric measures, in order to control for individual differences in innate ability, the values used were derived by subtracting the raw score on the psychometric measures test from the subject's median practice score. A parametric *t*-test was then done on the mean of the differences between placebo and ammonia performance. This follows the concept of ipsatization of behavioral performance data. D. M. Broverman, *Psychol. Rev.* **69**, 295 (1962).
7. D. Seligson and H. Seligson, *J. Lab. Clin. Med.* **38**, 324 (1951).
8. J. Egense, *Acta Med. Scand.* **173**, 8 (1963).
9. F. Navazio, T. Gerritsen, G. J. Wright, *J. Neurochem.* **8**, 146 (1961).
10. S. P. Bessman and A. N. Bessman, *J. Clin. Invest.* **34**, 622 (1955).
11. D. C. Watt and G. Crookes in *Neuropsychopharmacology*, E. Rothlin, Ed. (Elsevier, New York, 1961), vol. 2, pp. 410–413.
12. K. S. Warren, F. L. Iber, W. Dölle, S. Sherlock, *J. Lab. Clin. Med.* **56**, 687 (1960).
13. This study was supported by the career investigator training grant (MH 4867) from the National Institute of Mental Health, U.S. Public Health Service. Parts of these data were presented in a talk entitled, "Psychopathology associated with induced hyperammonemia" at the annual meeting of the American Psychiatric Association in 1963. I thank Mrs. Eilver Diggs for performing the ammonia determinations.

2 January 1964

Induction of a Stereoscopic Depth Effect

Abstract. *Two pairs of horizontal lines of equal length, with different configurations of dots above and below, are presented stereoscopically. Upon fusion, the two lines are perceived as tilting in space in directions opposite to the depth effects of the dots.*

It is generally assumed that an object will look flat if its image on one retina is an exact copy of the image on the other retina. If a pair of horizontal lines of equal length is presented stereoscopically, one line to each eye, the fused lines should not have any depth. And this is what happens if the lines are presented in isolation. I considered the possibility that the context in which the lines are perceived may induce a depth effect in the stereoscopically combined lines.

In my experiment I assumed that a depth effect in the context induces an opposite depth effect of points in its immediate neighborhood. Figure 1 may be considered to be a test of this assumption. The dots above and below the lines form the context. The horizontal distances between pairs of dots on the left side of the figure are unequal to those of the corresponding pairs of dots on the right side of the figure. Of course, the image of the dots on one retina is not an exact copy of the image on the other retina. All horizontal lines are equal in length. Upon stereoscopic fusion the dots either recede or move forward. For example, with respect to the upper half of the figure, the right-hand dots recede and the left-hand dots move forward. In accordance with the assumption, the right-hand end of the fused line should move forward and the left-hand end should recede. Thus, the line should appear slanted in space. The lower line, on the other hand, should appear slanted in the opposite direction (*1*). A preliminary experiment confirmed this particular test of the assumption.

There was the possibility that in setting the type for Fig. 1 slight differences in the lengths of a pair of corresponding lines emerged that might have been responsible for the depth effects. This would mean that the left

Fig. 1. The figure is viewed stereoscopically. The length of a line, 13 mm, provides the scale for all other measurements. Reduction 22 : 13½.

upper line and the right lower line should be slightly longer than their paired lines. As a control for this possibility a new figure, in which only the positions of the dots were shifted, was composed from the same type as that used for Fig. 1. Essentially, the upper and lower halves of Fig. 1 were reversed for the new figure.

Twenty subjects viewed the two figures, first one then the other, through a Keystone No. 46 Telebinocular stereoscope. Each subject was informed that a given line could appear in one of three ways with respect to his line of sight: the right end could appear closer than the left end, the left end closer than the right end, or both ends could appear equidistant. In giving his report, a subject oriented a pencil in space in order to illustrate what he saw. Sixteen of the 20 subjects perceived the predicted slantings of the lines in each of the two figures. Moreover, upon questioning, the subjects reported that they perceived a particular line as a unit slanting in space. Apparently, they did not judge either end of a given line in relation to its surrounding dots and then infer a depth effect (*2*). The remaining four subjects perceived slants only in some of the lines. Finally, possible printing errors are not responsible for the depth effects of the lines.

It may be concluded that the depth effects of the fused dots induce opposite depth effects in the horizontal lines. Further experiments, testing the generality of this effect, are in progress.

NICHOLAS PASTORE
Queens College of the City University of New York, Flushing 11367

References and Notes

1. H. Werner, *Am. J. Psychol.* **51**, 489 (1938), has reported a similar effect with a different figure and interpreted it as a "binocular contrast effect." However, K. N. Ogle, *ibid.* **59**, 111 (1946), has questioned Werner's interpretation.
2. Crossing the eyes as a substitute for presentation of figures with a stereoscope leads to similar results; of course, reverse depth effects are obtained. Subjects find it difficult to cross their eyes or they are reluctant to do so. Consequently, this observation is based on myself and another person.

2 March 1964