creatinine excretion as much as 30 percent (*14*). We have observed in the present study that during the period of reduced protein intake the excretion of creatinine was diminished. The chief ingredient for diminishing or increasing the creatinine output is meat, which of course is formed of muscle and contains large amounts of preformed creatine.

Our clinical observations suggest that the variations of the three tryptophan derivatives in the urine are associated with changes of appetite; in general our patients ate less for 3 or 4 days before the exacerbations of behavior, with resulting loss of weight in some instances, whereas with improvement in behavior, appetite and weight were restored. Additional evidence for the effects of an impaired appetite is the negative nitrogen balance in the first observation of E.S. for the period of 7 days including those immediately preceding the peak behavioral disturbance. In all instances of behavioral worsening, moreover, motor restlessness occurred. The latter increased the caloric demands at a time when food intake was diminished. In any event, a possible mechanism for activation of the psychotic symptoms consists of a change of muscle metabolism as indicated by the greater elimination of creatinine, a process involving a shift of caloric supplies from exogenous to endogenous sources. The body consumes its own substance as a source of calories, and amino acids—including tryptophan and methionine—are released from muscle protein.

As a working hypothesis, the chain of events shown in Fig. 1 could be considered to occur. First comes the initiating cause, of unknown origin, which evoked the behavioral worsening, and an early sign of the increased behavioral disturbance is the loss of appetite. When the initiating cause ceases operation, both appetite and behavior are restored to their usual states. For the second step we propose an endogenous metabolic factor, the release of tryptophan and perhaps methionine. The concomitant increase of creatinine suggests changes in muscle metabolism with muscle protein as a source of amino acids as the food intake decreases and the body must utilize its own substance to supply caloric demands. The two amino acids tryptophan and methionine act like a positive feedback to intensify the behavioral disturbance evoked by the initiating factor. The effect of experimental administration of tryptophan or methionine (*1*) may be regarded as introducing into the body an exogenous metabolic factor which, however, requires the presence of monoamine-oxidase to activate the psychotic symptoms. In regard to this difference induced by drugs, Brune and Himwich (*4*) reported both similarities and dissimilarities in the symptoms occurring spontaneously in schizophrenic patients and those provoked by the administration of a monoamine oxidase inhibitor and methionine to such patients. Third is the production of a psychotogenic indole which is enhanced by the materials furnished by the metabolic factors, whether endogenous or exogenous. In view of the experiments of Pollin, Cardon, and Kety (*1*) showing that amino acids other than tryptophan and methionine fail to call forth behavioral changes, it seemed to Brune and Himwich (*2*) that tryptophan and methionine may together be involved in a common mechanism in which increases of indoles derived from tryptophan and an elevated concentration of methyl groups donated by methionine might facilitate the formation of methylated indole amines with psychotogenic properties. Such a possibility may apply not only to the exogenous but also to the endogenous metabolic factor. Though we do not know the nature of the psychotogenic substance, we suggest a methylated indole such as *N,N*-dimethyltryptamine (*15*). The final link in this hypothetical chain is the action of a psychotogenic indole to cause behavioral exacerbations in psychotic patients (*16*).

H. H. Berlet, C. Bull
H. E. Himwich, H. Kohl
K. Matsumoto, G. R. Pscheidt
J. Spaide, T. T. Tourlentes
J. M. Valverde
Galesburg State Research Hospital, Galesburg, Illinois

References and Notes

1. W. Pollin, P. V. Cardon, Jr., S. S. Kety, *Science* **133**, 104 (1961).
2. G. G. Brune and H. E. Himwich, *J. Nervous Mental Dis.* **134A**, 447 (1962).
3. H. Sprince, C. Parker, D. Jameson, F. Alexander, *ibid.* **137**, 246 (1963).
4. G. Brune and H. E. Himwich, "Acta of the International Meeting on the Techniques for the Study of Psychotropic Drugs," Bologna, 26–27 June 1960.
5. ———, *Arch. Gen. Psychiat.* **6B**, 324 (1962); *Recent Advan. Biol. Psychiat.* **5**, 144 (1963).
6. A. Sjoerdsma, J. A. Oates, P. Zaltzman, S. Udenfriend, *J. Pharmacol. Exptl. Therap.* **126**, 217 (1959).
7. H. Weissbach, W. King, A. Sjoerdsma, S. Udenfriend, *J. Biol. Chem.* **234**, 81 (1959).
8. S. Udenfriend, E. Titus, H. Weissbach, *ibid.* **216**, 499 (1955).
9. Method of Jaffe in *Practical Physiological Chemistry*, P. B. Hawk, B. L. Oser, W. H. Summerson, Eds. (Blakiston, Philadelphia, 1949), p. 840.
10. F. M. Scales and A. P. Harrison, *J. Ind. Eng. Chem.* **12**, 359 (1920).
11. W. C. Rose, *Federation Proc.* **8**, 546 (1949); ———, G. F. Lambert, M. F. Coon, *J. Biol. Chem.* **211**, 815 (1954).
12. J. P. Peters and D. D. Van Slyke, *Quantitative Clinical Chemistry Interpretations* (Williams and Wilkins, Baltimore, ed. 2, 1946), vol. 1, p. 908.
13. C. F. Consolazio, R. E. Johnson, L. J. Pecora, *Physiological Measurements of Metabolic Function in Man* (McGraw-Hill, New York, 1963), p. 262.
14. R. E. Bleiler and H. P. Schedl, *J. Lab. Clin. Med.* **59**, 945 (1962).
15. S. Szara, *Experientia* **12**, 441 (1956).
16. The complete results of this study will be presented in a series of papers; one paper will be contained in the proceedings of the meeting of the American Psychopathological Association held in New York in 1964, "Psychopathology of schizophrenia."

17 February 1964

Habituation of Responses to Novel Stimuli in Monkeys with Selective Frontal Lesions

Abstract. *Monkeys with surgically produced lesions of the orbital frontal cortex, monkeys with lesions of the lateral frontal cortex, and normal controls were tested for the effects of repeated presentation of novel stimuli on lever-pressing for food rewards. The results support the conclusion that the habituation of responses to novel stimuli was more impaired in monkeys with orbital frontal lesions than in monkeys with lateral frontal lesions.*

The withholding of responses in a successive discrimination task (*1*) and in extinction (*2*) is more impaired in monkeys with surgically produced lesions of the orbital frontal cortex than in monkeys with lesions of the lateral frontal cortex. These findings suggest that orbital frontal lesions may disturb the suppression of strong response tendencies to a greater extent than lateral frontal lesions do (*3*). If this view is correct, then one might expect the suppression of responses other than those usually measured in instrumental learning situations to be more impaired in monkeys with orbital frontal lesions than in those with lateral frontal lesions. More specifically, it was predicted that monkeys with orbital frontal lesions would show slower habituation of responses to repeatedly presented novel stimuli than monkeys with lateral frontal lesions would.

The subjects of our study were 11 monkeys (*Macaca mulatta*); three had surgically produced bilateral lesions of the orbital frontal cortex, four had bilateral lesions of the lateral frontal cortex, and four were unoperated con-

trols. The surgical procedures are described elsewhere (*2*). The intended sites of the lesions are shown in Fig. 1. All the animals had had prior experience in operant conditioning and extinction, both before and after surgery. Surgery had been performed approximately 1 year prior to the experiment described.

The animals were trained and tested in a sound-shielded enclosure containing a lever which they could press to obtain food pellets. An automatic food dispenser delivered the pellets to a receptacle located beneath the lever. A white light bulb mounted in the ceiling illuminated the enclosure, and a speaker on one wall produced white masking noise (60 decibels above threshold). A red light bulb and a green one were also mounted on one wall of the enclosure. The presentation of rewards and stimuli was automatically programmed, and lever-pressing responses were recorded on electrical counters.

The strength of responses to novel stimuli was determined by the amount of interference which these stimuli produced in lever pressing. In order to reliably determine the effects of novel stimuli on lever pressing, a stable base line of responding was first established, by the following procedure. The monkeys were trained daily for 30 minutes to press the lever for food rewards, which were presented intermittently, on a variable-interval schedule with a mean inter-reinforcement interval of 50 seconds. In addition, lever pressing was rewarded only within a limited period after a reward was programmed (this period is called the "limited hold"). Initially the limited hold was maintained at 10 seconds, until the animals met the criterion of response stability by obtaining at least 30 rewards in each of three consecutive sessions. The limited hold was then reduced in 2-second steps to 4 seconds; reduction of the limited hold occurred only when the criterion of response stability was achieved. One unoperated animal failed to meet this criterion and was not tested further.

After the completion of training the animals were tested for the effects of novel stimuli on lever pressing. In daily test sessions lever pressing was rewarded as in the last stage of training;

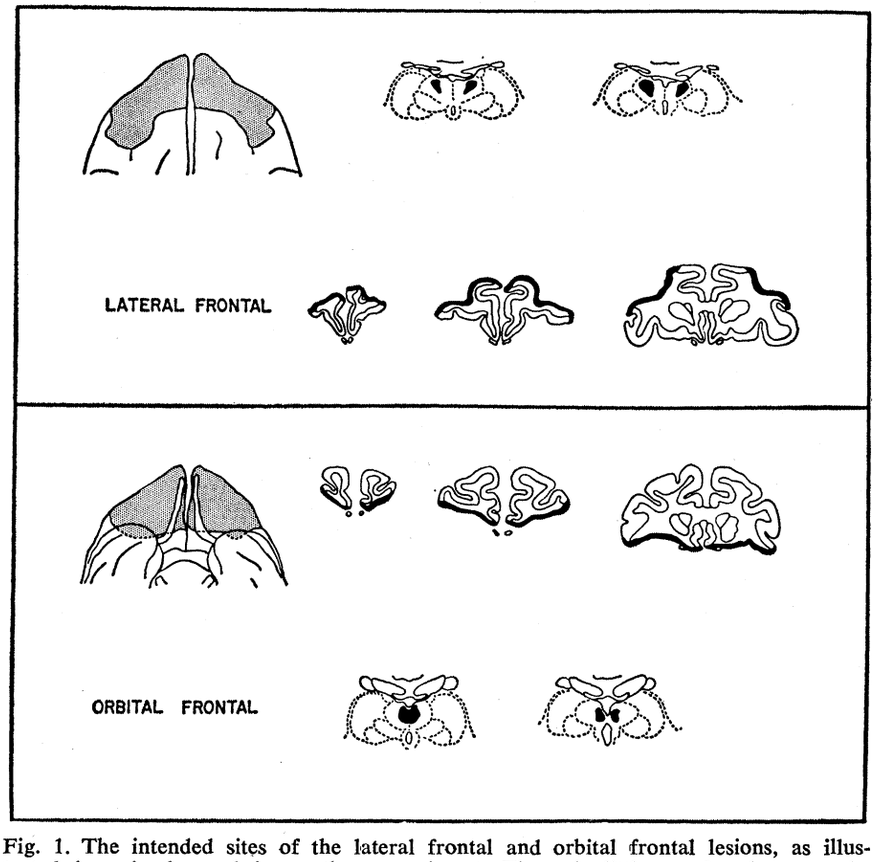

Fig. 1. The intended sites of the lateral frontal and orbital frontal lesions, as illustrated in animals used in another experiment. There is little overlap between the two lesions or between the loci of retrograde degeneration in the thalamus. The orbital lesion extends under, but does not invade, the temporal lobes.

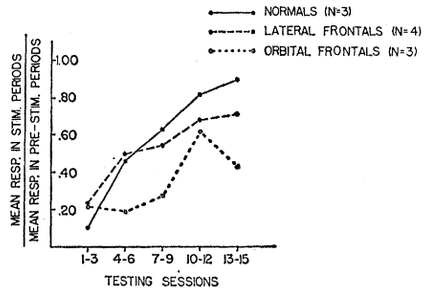

Fig. 2. Mean ratios of number of lever presses in 20-second stimulus periods to number of lever presses in the immediately preceding 20-second periods for the three groups of animals. Each mean ratio was computed from values for individual subjects summed over stimulus periods in 3-day blocks.

however, at predetermined intervals the white noise and the overhead light in the enclosure were discontinued and novel auditory and visual stimuli were presented for 20 seconds. The novel auditory stimuli consisted of a tape recording of repetitive drum beats (70 decibels above threshold) presented over the speaker in the enclosure. The novel visual stimuli were provided by illumination of the red and green light bulbs, not previously illuminated, which were flashed on and off at 0.5-second intervals. At the end of each presentation of the novel stimuli, the white noise and the overhead light were turned on. The novel stimuli were presented four times in each 30-minute test session, once in each of four 7¼-minute intervals. Within each of these intervals the stimuli were presented at randomly selected times. Testing was conducted in this manner for 15 consecutive days.

There were no reliable group differences in total number of lever presses in the training and the test sessions. Furthermore, all the animals showed marked decrements in rate of lever pressing during stimulus periods in the first three test sessions (see Fig. 2).

During stimulus periods in subsequent sessions, however, the operated monkeys, especially those with orbital frontal lesions, showed abnormally slow recovery in rate of lever pressing. This result is reflected in an analysis of variance as a highly significant group x-session interaction ($p < .001$). Furthermore, an orthogonal contrast of the data (*4*) reveals that the animals with orbital frontal lesions, in comparison to the others, showed a significantly smaller increment in rate

of lever pressing from the first three test sessions to the last three ($p < .005$). In addition, the animals with lateral frontal lesions showed reliably smaller increases in rate of lever pressing than did the normal animals ($p < .0005$). The effect of repeated presentation of the stimuli within test sessions was not significant. Furthermore, there were no reliable group differences in the number of lever presses in pre-stimulus periods.

The finding that the animals with frontal lesions were abnormally slow in increasing their rates of lever pressing, over successive stimulus periods, suggests that their ability to habituate responses to the novel stimuli was impaired. Furthermore, it appears that in the monkeys with orbital frontal lesions habituation occurred more slowly than it did in those with lateral frontal lesions. This interpretation is consistent with the view that orbital frontal ablation disturbs the animal's ability to suppress strong response tendencies more than lateral frontal ablation does.

On the other hand, these results appear to be equally consistent with the view that the animals with orbital frontal lesions had *less* difficulty than the other animals in suppressing another strong response tendency—the tendency to press the lever for food rewards. This view, however, is not supported by the finding that monkeys with orbital frontal ablations, trained to press a lever for food, show perseveration of these responses in extinction (*2*).

Indeed, on the basis of that finding one might have expected the monkeys with orbital frontal lesions not to suppress lever pressing when the novel stimuli were presented. It may be possible to resolve the apparent contradiction between these results and the present findings in the following manner. While monkeys with orbital frontal lesions show perseveration of food-rewarded responses in extinction, the responses of such monkeys to the initial presentation of the novel stimuli used in this study were strong enough to interfere with lever pressing and become dominant. This assumption that responses to the novel stimuli were initially dominant is supported by the finding that the lever-pressing rates of all animals dropped almost to zero when these stimuli were presented for the first time. According to the view that frontal lesions impair the ability to suppress the dominant response (*3*), one might expect perseveration of responses to novel stimuli in these animals. In order to determine whether this analysis is valid, responses to novel stimuli as well as responses rewarded with food would have to be directly measured in monkeys with frontal lesions.

Although responses to the novel stimuli were not directly measured, it should be noted that orienting responses typically shown by monkeys in novel situations were observed in the animals during stimulus periods. However, one cannot rule out the possibility that the novel stimuli produced other kinds of responses, such as fear, which might have interrupted lever pressing.

Finally, it should be noted that lesions of the amygdala produce alterations in behavior which resemble those found in monkeys with orbital frontal lesions. Thus, amygdalectomized monkeys show enhancement of food-rewarded responses in extinction (*5*) and abnormally slow habituation of locomotor activity in the presence of novel stimuli (*6*). Moreover, since a portion of the orbital frontal cortex and the amygdala are closely related anatomically (*7*), it appears that a direct comparison of the effects of lesions in these two areas on extinction and habituation would be fruitful.

CHARLES M. BUTTER
Department of Psychology, University of Michigan, Ann Arbor

References and Notes

1. S. Brutkowski, M. Mishkin, H. E. Rosvold, in *Proceedings of the Conference on Central and Peripheral Mechanisms of Motor Functions*, E. Gutman and P. Hník, Eds. (Czechoslovak Academy of Sciences, Prague, 1963), p. 133.
2. C. M. Butter, M. Mishkin, H. E. Rosvold, *Exptl. Neurol.* **7**, 65 (1963).
3. M. Mishkin, E. S. Prockop, H. E. Rosvold, *J. Comp. Physiol. Psychol.* **55**, 178 (1962).
4. W. G. Cochran and G. M. Cox, *Experimental Designs* (Wiley, New York, 1950).
5. L. Weiskrantz, *J. Comp. Physiol. Psychol.* **49**, 381 (1956).
6. J. S. Schwartzbaum, W. A. Wilson, Jr., J. R. Morrisette, *ibid.* **54**, 334 (1961).
7. W. J. H. Nauta, *Brain* **85**, 505 (1962).
8. This experiment was performed during the tenure of a U.S. Public Health Service postdoctoral fellowship, MF-9588-C1, at the National Institute of Mental Health in the Section on Neuropsychology. I thank Drs. H. Enger Rosvold and Mortimer Mishkin for providing the facilities for performing this experiment, Morris Waxler for testing the animals, and Nathaniel Ehrlich for performing the statistical analyses.

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Newborn Attention as Affected by Medication during Labor

Abstract. *Babies, 2- to 4-days old, whose mothers received heavy medication during labor were less attentive than those babies whose mothers received light medication.*

Moya and Thorndike (*1*) have recently presented a comprehensive review of the effects of drugs used in labor on the fetus and newborn. The accumulation of data from experimental animal studies and human clinical investigations indicates that "The newborn shows marked susceptibility to the depressant effects of drugs used in labor. This heightened sensitivity is related in part to increased permeability of the blood-brain barrier, inefficient metabolism, and asphyxia and physical trauma associated with the delivery process." One of the important limitations of the human studies cited is that the evaluation of the neonate has been limited to what can be observed in the delivery room.

While there is good reason to expect that for the newborn the effect will persist beyond the immediate delivery, and will indeed persist beyond the normal adult period of pharmacological effectiveness (*2*), clearcut demonstration has been lacking largely because of the difficulty of finding sufficiently sensitive techniques for evaluating the functioning of a baby who is a few days old. Standard neurological techniques are gross, and discriminate only marked pathology.

By means of a stimulus presentation technique similar to that of Fantz (*3*), a visual fixation on a series of three different stimuli has been used here to test the effect of medication during labor on visual attentiveness in the neonate.

Twenty full term babies from 2 to 4 days old, from normal deliveries and with no gross pathology constituted the study sample. Earlier than 2 days, eyelid swelling from silver nitrate administered at delivery impairs testing of vision. Three stimuli were presented in random order, each for a duration of 1 minute. Each experimental session contained three replications of the stimulus presentation, each with a new random ordering. Thus, there was a total of 9 minutes of stimulus exposure for each baby. All subjects were quietly awake at the start of a session. Three