linked recessive lethal gene (*6, 8*). The only kind of affected animals available are the hemizygous males, *jpY*. The tremor is very similar in jimpy and quaking mice, and appears at about the same age. Jimpy mice have a more severe disease. Some have weak hind limbs by weaning age, and a few develop complete paralysis of hind limbs. Most jimpy mice respond to sound and swim well. By the 4th week of life they have generalized tonic-clonic seizures without focal onset. The head is arched back, while the extremities are extended and abducted at the distal joints. Most seizures last less than 1 minute, and are followed by total cessation of activity and then by resumption of prior behavior. The animals usually die by 30 days of age, commonly after a seizure.

Brains of jimpy mice have been examined at 12 to 39 days of age. As with quaking, far less myelin was found in any given region of the central nervous system at any age than in the littermate controls. Again the peripheral nervous system was myelinated. The general architecture of gray and white matter was normal. Cell bodies and axons were normal or were affected to a slight degree compared with the myelin sheaths.

The pathology differs in jimpy and quaking in one major respect. In jimpy, cells of certain white matter tracts, particularly the basis pedunculi, optic tract, and white matter of cerebellum and spinal cord, contained nonpolar lipids in the form of strongly sudanophilic cytoplasmic droplets of various sizes. Most of these cells appear to be fatty macrophages. Some were present in the 12-day-old brain, when myelination in the controls was still at an early stage, and later the number of sudanophilic cells in the white matter increased.

Initial chemical analyses (*9*) confirmed the histological findings. Brains of adult quaking and jimpy mice were homogenized in chloroform-methanol. After washing, the lower phase was partitioned by differential elution from a Florisil column and each fraction was analyzed further by thin-layer chromatography. The brains of the mutant mice contained markedly reduced amounts of cerebroside and sulfatide, which are lipid constituents of myelin. Several phospholipid fractions were qualitatively normal. No cholesterol ester was found in the controls or in quaking; jimpy brains had traces of cholesterol ester, less than 1 percent of the total cholesterol.

These two mutants have several advantages for further study of myelin formation and its disorders. Both mutants can be propagated readily in numbers suitable for experimentation. The uniform distribution of the failure to form myelin throughout the central nervous system reduces the sampling problem which so often limits neurochemical studies. The apparent disparity between the relatively good neurological function, especially in quaking mice, and the paucity of myelin merits further attention.

The disease in quaking mice seems different from known human diseases and appears to be expressed almost purely as a severe (though not complete) failure of myelination in the central nervous system. Jimpy mice have a more complex disease, involving both impaired myelination and destruction of myelin. In terms of the onset early in life and the presence of sudanophilic breakdown products of myelin, the disease in jimpy mice resembles some of the human inherited sudanophilic leucodystrophies, and is the first readily available experimental model.

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9. R. Hayes, H. Moser, R. L. Sidman, unpublished data.
10. Supported in part by research grant No. NB 03262-03 from the National Institute of Neurological Diseases and Blindness, and carried out in part while R.L.S. and S.H.A. were visiting investigators at the Jackson Laboratory. The work of M.M.D. was supported in part by research grant CA 00362-15 from the National Cancer Institute and in part by U.S. Atomic Energy Commission contract AT(30-1)-3249.

3 February 1964.

Endogenous Metabolic Factor in Schizophrenic Behavior

Abstract. *Exacerbations of schizophrenic behavior are associated with elevations of urinary tryptophan metabolites. Free tryptophan and methionine possibly arising from the breakdown of muscle protein may act like an endogenous metabolic factor which enhances behavioral worsening. Some of the apparently spontaneous activations of psychotic symptoms may be intensified by the endogenous liberation of these two compounds.*

Pollin, Cardon, and Kety (*1*) have shown that the administration of either one of two essential amino acids, tryptophan and methionine, in the presence of a monoamine-oxidase inhibitor drug, evoked activations of psychotic behavior in some schizophrenic patients; these observations have been confirmed (*2, 3*). Unlike these studies on the effects of increased amounts of amino acids, ours was undertaken to determine whether or not reductions of the amino acids tryptophan and methionine in the diet could improve behavior and ameliorate psychotic symptoms. Other work from our laboratory (*4, 5*), based on an entirely different viewpoint, was concerned with urinary indole metabolism both during periods of spontaneous worsening of behavior and during the administration of drugs. In those studies the average outputs of urinary indole metabolites in patients with schizophrenia did not differ significantly from normal values when all data were considered. But a striking correlation was observed in some patients between increases in the urinary excretions of tryptophan derivatives, particularly tryptamine, and the exacerbations of schizophrenic activity in terms of aggravations of hallucinatory and delusional experiences as well as aggressiveness and hostility. This report concerns only those results from the current investigation which are directly applicable to a further analysis of the relationship between increases of urinary indoles and worsening of behavior.

Our observations were made under strictly controlled conditions including those of diet, nitrogen equilibrium, and intake of tryptophan and methionine.

Urine (24-hour and 5-day collections) was examined for three tryptophan derivatives—tryptamine (*6*), total 3-indoleacetic acid (*7*), 5-hydroxyindoleacetic acid (*8*)—as well as for creati-

nine (*9*). Total nitrogen content was determined (*10*) on portions of urine, food, and feces, all of which were collected for 7-day periods.

Observations on behavior were made by a team of four physicians on nine chronic schizophrenic male patients ranging in age from 39 to 59 years (mean 53) and having hospitalization periods from 6 to 28 years (mean 19). These patients had active symptoms such as hallucinations or delusions which they discussed. They were managed without tranquilizing drugs for a period commencing 2 to 4 months before the studies and continuing throughout the period of the present observations. The patients were interviewed weekly and rated for attitude during the interview, motor behavior, affectivity, thought content, stream of thought, sensorium, and ward adjustment. In addition, daily observations were made by the medical staff and the trained psychiatric aides of the wards in which these patients lived.

The study started with a control period of 6 weeks during which the daily diet offered contained between 80 to 85 g of protein, 1.0 to 1.5 g of tryptophan, and 4.5 to 5.0 g of methionine. In the second phase, tryptophan was reduced to 0.25 to 0.30 g/day, the minimal daily requirement for the maintenance of nitrogen equilibrium (*11*). Methionine was similarly diminished to the minimal requirement of 1.1 to 1.2 g/day for the first 4 weeks and for the last 8 weeks to 0.35 to 0.40 g/day. In order to accomplish these reductions the protein content of the diet was lowered to 35 g/day. Nonprotein nitrogen

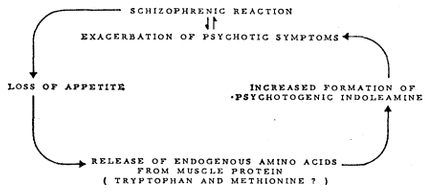

Fig. 1. A hypothetical chain of events in behavioral exacerbations of schizophrenic patients.

in the form of glycine was added so that the total nitrogen content of the diet offered was 4 g/day. Finally came a second control period of 8 weeks when the original control dietary conditions were restored. All food ingredients known to contain preformed indoles were excluded from the diet.

We were not able to establish a clear-cut relationship between the intensity of the psychotic symptoms and the type of diet. However two of our nine patients exhibited marked behavioral activations, thus permitting correlations between behavioral and biochemical changes as indicated by urinary analyses. Table 1 reveals rises of the three tryptophan metabolites in most instances, that of tryptamine being the most marked in 24-hour urinary samples during four episodic outbursts of increased schizophrenic activity in patients J. F. and E.S. This confirmation of our previous observations (*4*, *5*) is especially significant because the increases occurred on an actual tryptophan intake which was practically constant. In addition, for each of these patients the episode with the higher elevation of tryptamine was accompanied by the greater creatininuria. The first of these behavioral exacerbations in E.S. was by far the most severe of any for either patient and occurred during the first control dietary period. We see that the largest rises of the three indole compounds occurred in this instance. This patient also exhibited a mean daily nitrogen balance of −1.0 g for this 7-day period. This value may be compared with a positive balance of +2.1 g in a previous 7-day period while the patient was also on a control diet, but did not show any intensification of the psychotic symptoms. On two other occasions, however, one for each of the patients, during which there were relatively mild behavioral changes, the total nitrogen balance remained positive.

The increases of the three tryptophan derivatives in the urine probably reflect similar elevations of their concentration in the blood. It would seem probable, therefore, that these increases were the result of release of free tryptophan in the body. Because the increases occurred only during behavioral worsening, it would seem that tryptophan acts like an endogenous metabolic factor in intensifying the psychotic symptoms. In the first episode of E.S. (Table 1), the peak excretions of the three tryptophan derivatives occurred before the day of most severe behavioral worsening and receded before improvement began. In another instance, however, the rises of the urinary constituents accompanied rather than preceded the behavioral worsening. Brune and Himwich (*4*) and Sprince *et al.* (*3*) have reported similar urinary increases before the activation of the psychotic symptoms; but in those studies, unlike the present ones, the patients were receiving various medications.

In seeking an explanation for the increased amounts of tryptophan metabolites in the urine during spontaneous behavioral worsening, we may turn to the observation that the urinary excretion of creatinine is related closely to the active muscle mass of the body (*12*). In fact, the urinary creatinine output is constant over long periods and under the most varied circumstances including exercise and large variations of urinary volumes. On the other hand, it is also true that in addition to muscle mass, other factors, known and unknown, produce changes in creatinine excretion (*13*). It is known, for example, that the ingestion of a diet devoid of creatine and creatinine but adequate in protein lowers

Table 1. Urinary indole and creatinine excretion in correlation with tryptophan intake by schizophrenic patients on a normal diet during two episodes of worsening behavior. Values are given in percentage deviation from the values during usual behavior and are computed as averages of several 5-day urinary excretions obtained during periods of usual behavior and with controlled tryptophan intake. The usual range is defined as the highest and lowest deviations in single observations from the control. The dietary tryptophan intake presents the range within which the daily intake varied during a particular collection period, and it was calculated on the basis of the nitrogen content of the actual food intake. The behavioral worsening with increased psychotic and motor activity is marked by a scale ranging from 0 to −4; when a range is given, it denotes day-to-day variations within an observation period.

Item	Tryptophan intake (g/day)	Tryptamine (%)	3-IAA (%)	5-HIAA (%)	Creatinine (%)	Variations of behavioral exacerbations
			Patient J.F.			
Usual range*	1.0–1.5	+5 to −4	+21 to −14	+35 to −33	+5 to −4	
Period I (daily)	0.90–0.97	+98	+34	+43	+35	−2 to −4
Period II (daily)	0.53–0.69	+192	+43	−2	+40	−4
			Patient E.S.			
Usual range*	1.0–1.5	+3 to −2	+20 to −17	+21 to −23	+1 to −1	
Period I (daily)	0.83–0.92	+261	+169	+79	+92	−2 to −4
Period II (5 days)	0.80–1.03	+111	−7	+37	+12	−2 to −3

* The range during usual behavior.

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*).

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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-