optical isomers of α-monodeuterotyramine (I, R_1 = H; R_2 = D; and I, R_1 = D; R_2 = H) may be responsible for the isotope effect observed with the bisdeutero amine. Both optical isomers of α-deuterotyramine were prepared enzymically from tyrosine (*9*) and assayed as above. The results are shown in Fig. 1 (*2C* and *4B*) (*10*) and clearly establish that the isotope effect is completely stereospecific in accordance with a three-point contact between tyramine and monoamine oxidase. The absolute dependence on configuration of the isotope effect on the nictitating membrane response fully agrees with our deductions based on in vitro studies with liver monoamine oxidase (*9*).

Conclusions. From these observations, the following conclusions emerge: (i) The enzyme monoamine oxidase must be intimately associated with adrenergic effector cells and must be an important factor in the limitation of the action of tyramine and tryptamine. (ii) The monoamine oxidase involved in adrenergic mechanisms displays an absolute stereospecificity which is identical to that of liver monoamine oxidase, thus making it probable that these two enzymes are very similar in properties and mechanism of action. (iii) Norepinephrine is not a substrate for the enzyme at the adrenergic effector cell level. This excludes an oxidative deamination of transmitter as part of the sequence of events leading to a response or to inactivation of the substrate. (iv) The role of the enzyme in adrenergic mechanisms can best be pictured as a protective device for the rapid disposition of circulating or endogenous nontransmitter material.

So far as we are aware, this is the first report on the use of kinetic isotope effects in the field of pharmacology (*11*) and constitutes a novel approach that should prove a powerful tool in mechanism studies at the receptor level. A full description of this and related work in progress will be published elsewhere (*12*).

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10. The unusual blood pressure effect of the enzymically prepared tyramine (Fig. 1, 2C) has been traced to the presence of a minute amount of a phenolic impurity which is formed when oxygen is not excluded from the incubation mixture. A purely synthetic sample of optically active α-D-tyramine produced a typical blood pressure response (Fig. 1, 3B).
11. It should be mentioned, however, that G. R. Clemo and G. A. Swan, [*J. Chem. Soc.* **1953**, 395 (1953)] have described the synthesis of completely deuterated epinephrine but could observe no difference in blood pressure response when compared with epinephrine.
12. This work was supported in part by the National Research Council of Canada.

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Effects of Amino Acid Feedings in Schizophrenic Patients Treated with Iproniazid

Abstract. Large oral doses of individual amino acids were given three or four times daily for periods of 1 week to schizophrenic patients, some of whom were maintained on iproniazid. Marked alterations in behavior in some patients were associated with the administration of *l*-methionine and of *l*-tryptophan.

Recent reports have indicated that certain amino acids or their endogenous derivatives may affect mental state and behavior, and have led to hypotheses of their involvement in the pathogenesis of some forms of schizophrenia (*1*). Evidence for such hypotheses has been sought in the psychotomimetic properties of certain amines or their congeners (*2*), and in qualitative or quantitative abnormalities among the amino acid products excreted in the urine of schizophrenic patients (*3*).

This report describes a study of the effects of large quantities of certain amino acids given to a group of 12 chronic schizophrenic patients, previously described (*4*), nine of whom were also given iproniazid throughout the study in an effort to increase tissue concentrations of endogenous amines. None had received somatic therapies within the previous 18 months.

The study is summarized in Table 1. There were three time blocks (periods A, B, and D) during which, in a Latin square design, every patient received in rotation each of the tabulated amino acids (or amino acid combinations) for approximately 1 week. During periods C, E, and F the Latin square design was not used. Instead, certain individuals received only one of the substances tabulated, selection depending primarily on their having previously responded to the same, or a related substance. Except as noted in Table 1, the *l* forms of amino acids were given, suspended in chocolate milk, three times daily. The appearance, consistency, and taste of the suspensions were made as similar as possible by adding barium sulfate or flavoring agents as needed.

Behavioral observations were made continuously by nursing personnel. Each patient was evaluated daily by one or more of three psychiatrists. Three additional physicians together examined the patients at weekly intervals and were the only participants aware of the drug and amino acid regimens. All patients were observed for signs of hepatic disturbance, and serum transaminase was measured each week. No hepatic dysfunction was detected. Electroencephalographic, psychometric, and biochemical studies, which complemented the behavioral and psychiatric evaluations, are in preparation.

Marked behavioral changes occurred with *l*-methionine loading in four of the nine patients receiving iproniazid—in two patients on each of three trials, in one on two of three trials, and in one on one of two trials. The major clinical features in these patients were an increasing flood of associations often reaching "word salad," increasing anxiety approaching or reaching panic, increasing tension and motor activity, depression accompanying a brief period of sharply increased insight, an upsurge of hallucinatory activity, and brief intermittent periods of disorientation at the height of agitation.

One such patient, essentially mute for many years, manifested a flood of speech and ideas that was uncontrollable for hours. Another patient, paranoid but usually coherent and in good contact, described a flood of ideas, had a sudden depressed insight into the effects of his psychosis on himself and those about him, was flooded with associations, reached the stage of "word salad," and finally repeated isolated letters continuously.

Most changes disappeared abruptly upon withdrawal of methionine, but concurrently each marked reactor was thought to show some unexpected clinical improvement which persisted for weeks or months. The dose level of iproniazid did not seem to influence the intensity of methionine effects.

The changes cannot be attributed to the metabolic acidosis or persistent gas-

Table 1. Behavioral change in chronic schizophrenic patients maintained on iproniazid and loaded with amino acids or related substances.

Weeks of study	Load period	Loading substance and amt. (g/70 kg daily)	Incidence of change*	
			Iproniazid† 50 mg/70 kg daily (9 patients)	Iproniazid placebo† (3 patients)
1–3		Glycine, 25	0/9	0/3
4–6	A	Phenylalanine, 20, and methionine, 20	3/9	0/3
		Glutamine, 40, and histidine, 20	0/9	0/3
		Trytophan, 15	?/9	0/3
9		Glycine, 25	0/9	0/3
10–12	B	Methionine, 20	3/9	0/3
		Phenylalanine, 20	0/9	0/3
		Tyrosine, 20	0/9	0/3
19	C	*dl*-Methionine‡, 15,	0/5	0/0
		or placebo	0/4	0/3
25			Iproniazid increased 150 mg/70 kg daily	
29–30	D	Tryptophan, 7 or 15§	7/9	0/3
		Phenylalanine, 20	0/9	0/3
31–32	E	Methionine, 20‡,	3/3	0/1
		or 5-HTP ‖	0/3	0/1
		or DOPA ‖	0/3	0/1
37	F	NH_4Cl, 15¶,	0/4	0/0
		or placebo§	0/0	0/3

* Number of patients showing behavioral change/number of patients given loading substance. † Started at beginning of 2nd week and maintained throughout study. ‡ Given in gelatin capsules in four divided daily doses for 1 week. § In the 1st week six patients received the lower dose; in the 2nd week the remaining six patients received the higher dose. ‖ 5-HTP (*dl*-5-hydroxytryptophan) and DOPA (*l*-dihydroxyphenylalanine) were given intravenously once daily starting with 6 mg and increasing in daily steps of 6 mg to 60 mg, then in steps of 12 mg, to 108 mg on the final day, except for two patients in whom injections were discontinued after 96 mg of DOPA and 24 mg of 5-HTP because of side effects. ¶ Enteric tablets in four divided daily doses for 1 week.

tric distress which usually accompanied methionine administration, since changes occurred when the amino acid was subsequently administered in capsules, which prevented the distress, and did not occur with administration of ammonium chloride, which produced both gastric distress and acidosis of greater severity.

The extent to which these clinical changes represent a biochemically induced acute flare-up of a chronic schizophrenic process on the one hand, or a toxic delirium superimposed upon chronic schizophrenia on the other, is, as yet, uncertain and is being further investigated (*5*).

Equivocal changes were noted in a few patients during the first tryptophan load in association with the lower dosage of iproniazid. During the higher dose of iproniazid, tryptophan administration was accompanied by mild to marked changes characterized primarily by mood elevation, increased involvement and extroversion, an early and transitory phase of somnolence, and more active deep tendon reflexes (*6*).

One guarded paranoid patient became euphoric and freely expressed delusions and amorous feelings. A withdrawn, almost mute patient became verbal, intelligible, freely responsive to questions, and talked freely, though psychotically, about his activities and feelings. Five of the remaining seven patients showed similar but less marked changes, which were most evident in some by a sudden increase of hostility and depression when tryptophan was stopped. There was no overlap between marked methionine and tryptophan reactors.

Some of the patients, while receiving the higher dose of iproniazid, were given 5-hydroxytryptophan or *l*-dihydroxyphenylalanine in gradually increasing daily intravenous dosage up to 108 mg. Nausea, abdominal discomfort, or vomiting occurred in association with the higher doses of 5-hydroxytryptophan, and transitory hypertension, brachycardia, and ventricular extrasystoles with *l*-dihydroxyphenylalanine. Neither of these substances nor the other amino acids administered altered behavior in a manner detectable clinically.

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Serum Glutamic Oxalacetic Transaminase Content in Hypothermia

Abstract. When the body temperature of pentobarbitalized dogs was lowered, by surface-immersion technique, to 27°–26°C, elevations in serum glutamic oxalacetic transaminase were found only after a period of prolonged hypothermia (12 hours). When the animals were rewarmed, serum levels returned to normal. Histologic study of organs rich in glutamic oxalacetic transaminase revealed no necrosis. The cause for the elevations is not known, although increased membrane permeability secondary to prolonged cold may be a factor.

Injury to tissue rich in glutamic oxalacetic transaminase results in elevated levels of this enzyme in serum (*1*). It has been felt that actual necrosis must occur for liberation of the enzyme from the cell into the serum. Recent evidence, however, suggests that, while ischemia is an important factor, necrosis per se is not required (*2*). It has been demonstrated that during hypothermia oxygen availability, transport, and use are adequate and no tissue damage develops (*3*). Physiological function essentially returns to normal. Histological studies of hypothermic animals have revealed necrosis, reportedly due to hypoxia (*4*). Another investigation differed, for no cellular damage was found (*5*).

The heart and the liver are particularly rich in glutamic oxalacetic transaminase cellular enzyme (*6*). Myocardial function is considered adequate during short-term hypothermia, with some question of adequacy after 6 hours of cold (*7*). Upon resuscitation of the animal, the hypothermic liver regains