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

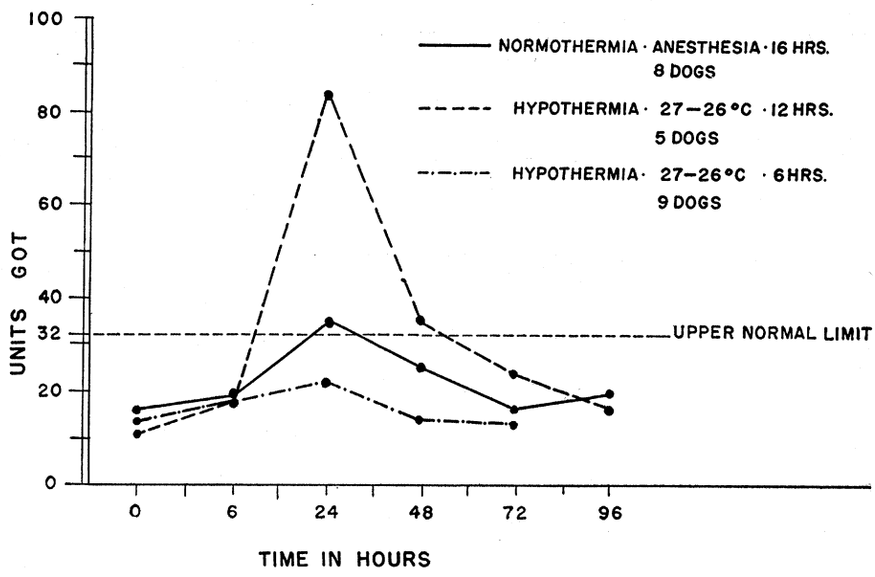

Fig. 1. Levels of glutamic oxalacetic transaminase (GOT) in prolonged hypothermia. Peak elevations occurred within 24 hours after arousal, with return to baseline levels within 72 hours. There was a tendency for serum glutamic oxalacetic transaminase to rise in the normothermia control animals.

its activity except for a lag in cellular oxidation (*8*).

Since a high level glutamic oxalacetic transaminase in the serum suggests tissue derangement, possibly due to necrosis, the present study was undertaken to determine serum levels of the enzyme in the pentobarbitalized dog cooled to 27°–26°C by the surface-immersion technique. Normothermic anesthesia controls were run for times approximately as long as those of the experiments involving prolonged hypothermia. Some of the animals breathed spontaneously, while others were given intermittent positive-pressure breathing with tank oxygen. Hypothermia was maintained for 6 and 12 hours in two separate groups, after which the dogs were rewarmed. Samples of arterial or venous blood, or both (the level of glutamic oxalacetic transaminase was the same in both), were drawn before the animals were cooled and 6, 24, 48, 72, and 96 hours after they were rewarmed. Sections of the following organs were taken after the last blood sample: ventricle, liver, kidney, adrenal gland, and skeletal muscle. The amount of the enzyme was determined by the method of Karmen (*9*). The upper limit of normal for this laboratory was established at 32 units.

All of the animals survived but were sacrificed for the tissue examinations. Spontaneously breathing and respiratory-supported animals demonstrated similar trends. Averages of the data are shown in Fig. 1. The control dogs showed tendency toward a rise in serum glutamic oxalacetic transaminase with the peak at 24 hours after the periods of anesthesia (8 and 16 hours) and return to normal in another 24 hours. In the treated animals there were no elevations until after 12 hours of cooling. Within 72 hours serum levels of the enzyme were normal, with one exception, which returned to normal in the next 24 hours. Histological examination revealed no necrosis in the tissue studied and no unusual morphological differences between the control and the treated groups.

The reason for the elevations in serum glutamic oxalacetic transaminase, both in the anesthetized and the hypothermic groups, is not clear, especially in the absence of cellular necrosis. Tissue oxygenation does not appear to be a factor, since no differences were found between the respiratory supported and the unsupported animals. The intracellular content of the enzyme is high, and a large gradient exists between the cell and the serum. It may be speculated that membrane permeability to the enzyme was altered sufficiently to permit escape of the enzyme into the serum, under the conditions of this study. Increased membrane permeability with increased flux of ions during hypothermia has been demonstrated (*10*). Cold may affect the rate of transamination.

The effect observed in this study, whatever its cause, is transient, and apparently the normal gradient is reestablished within 72 hours after recovery from hypothermia. Evaluation of physiological function during hypothermia has been limited to short-term observations, and, generally, function (certainly oxygenation) appears to be adequate. Effects from prolonged exposure to cold may prove serious. If elevation of serum glutamic oxalacetic transaminase may be used as a yardstick of functional integrity, then one might predict that prolonged hypothermia might result in physiological disturbances.

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Radiotelemetry of Physiological Responses in the Laboratory Animal

The measurement of physiological reactions in laboratory animals has long presented problems. Recording is usually accomplished under conditions varying from complete restraint to the partial restraint of extended wires. The animal may never grow entirely accustomed to the attachments, and this factor may constitute a source of stress. Restraint is reported in the literature as being extensively used as a stressor, the work of Selye on this topic being widely known. It is apparent, therefore, that measurement of physiological variables under conditions of even minimal restraint may yield a distorted picture of such responses. In addition, the cues inherently present in attachments of any kind, as well as the transfer of an animal to the study environment, are major—if not, at times, fatal—methodologic obstacles to classical conditioning. The development of the transistor offers new possibilities for classical conditioning.

With this in mind we set out to develop a system of radio telemetry for use as an adjunct to studies in classical conditioning. This methodological ad-