glycine infusions may be used as a means to produce ammonia intoxication for experimental purposes. This method may be more physiological than the use of inorganic compounds of ammonia.

Summary. 1. Glycine, alanine or an acid hydrolysate of casein were intravenously infused in dogs over a 2-hour period, and the concentrations of ammonia, urea and amino acid nitrogen in the blood were determined at 30-minute intervals. 2. At rates of infusion of glycine above 1 mg amino N/kg/min. significant increases in blood ammonia occurred, which were directly related to amounts of glycine infused. At the maximum infusion rate used (7 mg amino N/kg/min.) the dog expired in respiratory failure at the end of the 2-hour infusion. The results of these experiments indicate that the toxicity attributed to rapid rates of infusion of glycine may actually be due to ammonia intoxication. 3. After administration of a casein hydrolysate increases in blood ammonia were less and those of urea were greater than predicted from administration of glycine at comparable rates. This suggests that certain amino acids in the mixture decrease blood ammonia levels by enhancing urea production.

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Received June 15, 1956. P.S.E.B.M., 1956, v92.

Comparative Effect of Arginine and Monosodium Glutamate on Blood Ammonia.* (22544)

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In a previous study(1) on the effect of intravenously administered amino acids on ammonia levels in the blood it was noted that after the administration of a mixture of amino acids (casein hydrolysate) increases in blood ammonia were less and those of urea were greater than predicted from the infusion of a single amino acid (glycine) at a comparable rate. These findings suggested that certain amino acids in the mixture effected a decrease in blood ammonia levels by enhancing urea production. The effect of a single amino acid infused together with glycine was therefore studied in order to investigate this hypothesis. For this purpose, arginine was selected because of its role in the urea cycle.

The use of monosodium glutamate has been advocated as a means to reduce high blood ammonia levels in human patients by Walshe (2) and by McDermott(3). The reduction is presumably effected through amidation of L-glutamic acid to form glutamine. It was therefore of interest to compare the effect on blood ammonia of glutamic acid with that of arginine. This would serve to indicate relative efficiency for detoxification of ammonia of amidation of glutamic acid as compared to urea production.

Procedure. Ammonia toxicity was induced in adult male mongrel dogs by intravenous administration of glycine as described by Harper *et al.*(1). Blood samples were drawn before the infusion and at 30-minute intervals thereafter, for a 2-hour period. Heparin was used as the anticoagulant. The blood samples were analyzed for ammonia, urea, and amino acid nitrogen. Ammonia nitrogen was determined by the microdiffusion method of Conway(4), urea nitrogen by the method of Van Slyke and Kugel(5) and amino acid

* Supported by the Christine Breon Fund for Medical Research.

TABLE I. Ammonia, Urea and Amino Nitrogen in Blood after Intravenous Infusions of Various Amino Acid Combinations in Dogs.

	Interval (min.) 0	30	60	90	120
	Glycine (3.5 mg N/kg/min.)				
Ammonia N*	.4	6.62	11.1	15.32	18.73
Urea N†	17.6	20.6 (3.)	24.3 (6.7)	25.4 (7.8)	27.8 (10.2)
Amino N‡	3.3	21.2	25.3	32.7	38.6
	Glycine (3.5 mg N/kg/min.) and arginine (1.75 mg amino N/kg/min.)				
Ammonia N*	.1	.99	.99	1.7	1.7
Urea N†	20.	28.2 (8.2)	38.5 (18.5)	52.5 (32.5)	63. (43.)
Amino N‡	3.7	45.9	55.3	66.1	71.5
	Glycine (3.5 mg N/kg/min.) and monosodium glutamate (1.75 mg N/kg/min.)				
Ammonia N*	.24	1.75	5.36	9.49	13.94
Urea N†	17.4	21.7 (4.3)	21.7 (4.3)	25.4 (8.0)	28.5 (11.1)
Amino N‡	4.6	32.3	57.8	56.6	57.1
	Glycine (3.5 mg N/kg/min.) and monosodium glutamate, 50 g during 2nd hr				
Ammonia N*	.69	6.58	11.72	19.23	24.75
Urea N†	16.9	21.9 (5.)	23.1 (6.2)	25. (8.1)	29.9 (13.)
Amino N‡	4.1	22.2	28.6	65.2	77.9
	Glycine (3.5 mg N/kg/min.) and arginine, 50 g during 2nd hr				
Ammonia N*	.55	3.59	8.81	1.29	.67
Urea N†	18.8	21.2 (2.4)	22.4 (3.6)	39.8 (21.0)	48.5 (29.7)
Amino N‡	4.2	23.3	27.6	49.4	50.3
	Glycine (3.5 mg N/kg/min.) and arginine, 25 g during 2nd hr				
Ammonia N*	.39	2.85	9.17	2.39	1.08
Urea N†	15.5	18.6 (3.1)	19.8 (4.3)	28.5 (13.)	23.5 (8.)
Amino N‡	4.6	22.8	26.5	33.3	44.6

* μg/ml.
† mg/100 ml. Increase over fasting level shown in parentheses.
‡ mg/100 ml (plasma).

nitrogen by the method of Hamilton and Van Slyke(6).

In the first series of experiments glycine was infused (1) alone, at a rate of 3.5 mg amino N/kg/min.; (2) together with 1.75 mg amino N/kg/min. of L-arginine hydrochloride or (3) with 1.75 mg amino N/kg/min. of L-monosodium glutamate. In a second series of experiments the blood ammonia was raised by the continuous infusion of glycine at 3.5 mg amino N/kg/min. for 1 hour. At this time the glycine infusion was continued at the same rate but 50 g of arginine or of monosodium glutamate were added to the glycine infusion and this mixture was administered during the second hour. A similar experiment was also conducted using glycine with 25 g of arginine added at the second hour.

Results. The concentrations in blood or plasma of ammonia, urea and amino acid nitrogen after the infusion of various amino acid combinations are shown in Table I. The data were derived from individual experiments under the conditions described. The blood ammonia levels were markedly lower when arginine and glycine were infused together as compared to those observed when only glycine was infused at a comparable rate. In fact, at the termination of the infusion of arginine together with glycine the reduction in blood ammonia was 10-fold. A striking elevation in blood urea accompanied the marked lowering of blood ammonia that was observed with arginine. On the other hand, the concomitant administration of monosodium glutamate with glycine effected only a moderate decrease in blood ammonia and the rise in urea was no greater than that expected from the amount of glycine infused. The contrast in the effects of the 2 amino acids was even more striking when the experi-

ment was conducted by attempting to lower blood ammonia after it had been allowed to increase rather than by preventing the rise through concomitant administration of the 2 amino acids. Under these conditions arginine was immediately effective in lowering the levels of ammonia in the blood whereas monosodium glutamate proved to be completely ineffective.

Discussion. The relationship between hepatic encephalopathies and elevated blood ammonia levels was first suggested by Hahn (7) in Pavlov's laboratory and later confirmed by Burchi(8) and by Van Caulaert (9). This syndrome has been actively studied in recent years because of its association with hepatic coma and its occasional occurrence as a consequence of the surgical production of vascular shunts to ameliorate portal hypertension. As a means to decrease or to prevent a rise in blood ammonia several procedures have been advocated. These include a reduction in dietary intake of protein in an effort to limit the amounts of that substrate which is the major source of ammonia produced within the intestine; oral administration of neomycin to inhibit bacterial production of ammonia within the intestine(10); and oral or intravenous administration of glutamic acid to aid in detoxification of ammonia by formation of glutamine (2,3).

Ammonia is metabolized *in vivo* by 3 routes. It may be excreted as ammonium salts, or used in transamination (*e.g.* of glutamic acid to glutamine) but it is mainly utilized in the formation of urea. Thus enhancement of urea production should be the most effective method to reduce blood ammonia. The results of these experiments indicate that arginine administration exerts an effect on production of urea as evidenced by the extensive rise in blood urea which follows its administration in the presence of excess ammonia. The effectiveness of this method to remove ammonia from the blood was demonstrated by the rapid fall which occurred in blood ammonia in as short a period as one-half hour and after an infusion of only 25 g of arginine.

duRuisseau *et al.*(11) have reported that the prior or concomitant intraperitoneal administration into rats of arginine with an $LD_{99.9}$ dose of ammonium acetate exerted marked protection against the lethal effects of ammonia intoxication. They also concluded from their studies on the levels of ammonia and urea in the blood that the ability of arginine to protect these animals was attributable to its role in production of urea.

We have applied our studies to the treatment of several patients with ammonia intoxication associated with portacaval anastomoses or with acute or chronic liver disease, with encouraging results. A report of this clinical experience is in preparation.

Summary. 1. Elevated levels of ammonia in the blood were induced in dogs by intravenous administration of glycine. 2. The effects on levels of ammonia in the blood of simultaneous or delayed administration with glycine of L-arginine hydrochloride or L-monosodium glutamate were then studied. 3. Arginine given concomitantly with glycine prevented any significant rise in blood ammonia. When administered one hour after the commencement of glycine infusion, it effected a prompt reduction of levels of ammonia in the blood. On the other hand, monosodium glutamate was only slightly effective under the former experimental conditions and completely ineffective under the latter. 4. The rise in blood urea which accompanied the marked fall in blood ammonia when arginine was given indicated that this amino acid exerted its effect on the blood ammonia by an influence on the production of urea.

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Received June 15, 1956. P.S.E.B.M., 1956, v92.

Pharmacology of the Psychotherapeutic Drug Benactyzine (β-Diethylaminoethyl Benzilate Hydrochloride). (22545)

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Several clinical studies in the European medical literature have indicated that benactyzine* (β-diethylaminoethyl benzilate hydrochloride) may be of value in symptomatic treatment of anxiety and other manifestations of psychoneurosis and psychosomatic disease (3,4,10,13,14). Jacobsen and his associates showed that the drug eliminated experimentally-induced conflict behavior in cats(7) and rats(5,8). Human beings exposed to emotion-provoking stress showed less intense autonomic responses after benactyzine(9).

Benactyzine was first prepared in 1936 (16), but studies of the pharmacological activity of the compound have been limited. *In vitro* anticholinergic and antihistaminic activity were demonstrated by Burtner and Cusic (2) using rabbit intestinal muscle. Lands *et al.*(11) showed that benactyzine has a weaker effect on salivary secretion and on dilation of the pupil than does atropine. The present study describes further pharmacological properties of the compound, and compares it with other psychotherapeutic agents.

Acute toxicity. In mice, benactyzine caused hyperexcitability and convulsions. After intraperitoneal administration of about one-half of an LD_{50} the animals became hypersensitive to sound and touch and had extended S-shaped tails (Straub reaction). Most animals also had clonic convulsions which alternated with periods of exhaustion. Doses higher than 90 mg/kg produced clonic convulsions of great violence. The LD_{50} was 155 ± 9 mg/kg and the mean convulsant dose (CD_{50}) was 86 ± 6 mg/kg. *Effect on behavior.* In adult Rhesus monkeys (*Macaca mulatta*) doses ranging from 1 to 6 mg/kg intravenously caused only minor changes in behavior. After 1 mg/kg there was mydriasis and some decrease in locomotion. Although the animal exhibited less withdrawal from the experimenter there was no real taming effect. At 2 mg/kg the animals became ataxic and occasional convulsive jerks occurred. Six mg/kg put one monkey into frank convulsions. These were clonic, lasting 1 to 5 seconds, and recurred at intervals of 5 to 15 seconds. This stage was present for about 10 minutes and was followed by post-ictal depression lasting over one hour. After intravenous administration, effects were seen within one minute and there was usually some evidence of recovery in one hour. Pupillary dilation was the most persistent effect, sometimes lasting as long as 20 hours.

Potentiation of hexobarbital anesthesia. Groups of mice were given hexobarbital sodium 100 mg/kg and benactyzine hydrochloride simultaneously by the intraperitoneal route and the duration of hexobarbital anesthesia was measured(17). The antihistaminic diphenhydramine (Benadryl), which causes marked prolongation of hexobarbital anesthesia was used for comparison. The results

* Benactyzine is the generic name for β-diethylaminoethyl benzilate hydrochloride accepted by the Scandinavian Pharmacopoeia Commission. The drug is sold in Europe under the trade names Suavitil, Nutinal and Parasan.