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Glutamic Acid and Vomiting in Dogs: Its Administration into the Portal System and Extremity Veins.*

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The intravenous administration of solutions containing glutamic acid has been shown to produce vomiting both in dogs[1] and in man.[2] Price, Waelsch and Putnam,[3] on the other hand, have given as much as 20 g of glutamic acid orally to epileptic patients per day in divided doses and did not record any incidence of vomiting. The increased tolerance to orally administered glutamic acid may be due either to slow absorption from the digestive tract, or to the fact that products which are absorbed from the gastro-intestinal tract by way of the blood are first conveyed to the liver. In this organ many reactions occur which could destroy free glutamic acid, such as deamination, transamination, or peptide formation. In order to study the detoxifying action of the liver on glutamic acid two methods of administration were used whereby the infusions would enter the portal system before reaching the general circulation. This was accomplished by infusing the solutions containing glutamic acid either directly into the spleen or the portal vein. Using these procedures an attempt was made to determine whether the animals could tolerate glutamic acid better by the intraportal than by the peripheral intravenous route. Studies were also made in an attempt to relate the amino acid nitrogen and urea nitrogen content of the blood with the route of administration, and the production of vomiting.

Methods. Six adult male mongrel dogs were used in this study. Under intravenous nembutal anesthesia the abdomen was entered through a left rectus incision. After freeing the integument over the left half of the abdomen the left external and internal oblique muscles were resected. A rent was made in the transverse muscle and peritoneum through which the spleen was delivered. The hilus of the spleen was sutured to the margin of the peritoneum to prevent herniation of an abdominal viscus through it. The purpose of removing the external and internal oblique muscles was twofold: first, to allow more space for the implanted spleen; secondly, to prevent obstruction of the splenic circulation, either by scar tissue or by spasm of these muscles during an intrasplenic infusion. The abdomen was closed with interrupted cotton sutures.

In 3 animals, at the same time the spleen was transplanted, a small plastic tube† was sutured on the portal vein and brought to the outside through a small incision. The free end of the plastic tube was covered with sterile gauze and taped to the animal's side. This tube served the same purpose as the metal catheters used by London[4] in his angiostomy technic. Thus, by running a needle down this tube it was possible to infuse the glutamic acid solution into the portal vein in the unanesthetized animal without difficulty.

The glutamic acid solution used for all the infusions was prepared by adding 7 g of l +

* A preliminary report of this work was given before the American Federation for Clinical Research, Chicago, October 30, 1947.

1 Madden, S. C., Woods, R. R., Shull, F. W., Remintong, J. H., and Whipple, G. H., *J. Exp. Med.*, 1945, **81**, 439.

2 Smyth, C. J., Levey, S., and Lasichak, A. G., *Am. J. Med. Sci.*, 1947, **214**, 281.

3 Price, J. C., Waelsch, H., and Putnam, T. J., *J. Am. Med. Assn.*, 1943, **122**, 1153.

† The plastic tubing used was that supplied by the Baxter Company for their disposable infusion sets.

4 London, E. S., Harvey Lectures, 1927-28, p. 208, Williams & Wilkins Co.

TABLE I.
Effect of Route of Administration of Glutamic Acid Solutions on the Production of Vomiting in Dogs.

Dog No.	Wt, kg	Glutamic acid admin. Route	Vol. received, ml	Rate, ml/min	Reaction
1	11.8	I.V.*	150	10.0	Vomited
		I.S.†	200	8.0	0
		I.V.	145	7.2	Vomited
		I.S.	275	11.2	0
		I.V.	145	8.0	Vomited
		I.S.	285	9.5	0
		I.V.	150	8.8	Vomited
2	16.6	I.V.	80	7.5	Vomited
		I.S.	125	8.9	”
		I.V.	58	8.3	”
		I.S.	150	12.5	0
		I.S.	160	10.0	Vomited
		Intestinal vein	135	10.3	Vomited
3	15.4	I.V.	100	11.0	”
		I.S.	175	8.0	”
		I.V.	150	10.8	”
4	12.2	I.V.	150	10.0	”
		I.S.	315	10.5	”
		I.V.	110	9.0	”
		P.‡	200	10.1	”
5	11.8	I.V.	95	9.5	”
		I.S.	155	10.3	”
		I.V.	100	12.2	”
		I.V.	100	9.5	”
		I.S.	160	8.0	”
		P.	300	8.4	” after infusion stopped
6	11.4	I.V.	95	5.0	Vomited
		I.S.	175	5.0	”
		P.	165	4.5	”

* Intravenous.
† Intrasplenic.
‡ Injection into the portal vein by the angiostomy technic.

glutamic acid (Merck)‡ and 2 g of sodium bicarbonate to 500 ml of pyrogen-free saline. The solutions were sterilized by autoclaving.

Approximately 3 weeks after the transplantation of the spleen, the animals received the first intravenous infusion of glutamic acid. The solution was allowed to run into a leg vein at a uniform rate until the animal vomited. At this point the volume infused and the rate of infusion were recorded. Several days subsequent to the intravenous infusion the animal received an intrasplenic injection of glutamic acid. Since the transplanted spleen permitted the palpation of the gland, the needle could be easily directed into this organ. In addition, the intrasplenic position of the needle was confirmed by the aspiration of blood fluid. The solution was allowed to flow into the substance of the spleen at a uniform rate until the animal vomited. In some cases when approximately two times the intravenous dose was given into the spleen and the animal did not vomit, the intrasplenic infusion was discontinued because of danger of overhydration. After a few days

‡ We wish to thank Merck and Co., Inc., Rahway, N. J., for supplying the glutamic acid used in this study.

3 of the animals received a third infusion directly into the portal vein by the angiostomy technic, and the volume of fluid necessary to make the animal vomit was recorded. Some of the animals received more than one test involving a single method of infusion.

Results and discussion. A comparison of the tolerance of animals to glutamic acid administered either intravenously or directly into the portal system is presented in Table I. More glutamic acid could be administered into the portal system without the animals vomiting than could be given into the peripheral venous circulation. In a single case (Dog 2) the glutamic acid solution was injected into an intestinal vein isolated under local anesthesia and a greater tolerance was found for the amino acid when given in this manner than when administered into one of the leg veins.

Since there was no constant difference in either the blood amino acid nitrogen or the urea plus ammonia nitrogen dependent on the route of administration these data will not be presented. Also there was no level of blood amino acid nitrogen following the glutamic acid infusion which was uniformly associated with vomiting.

This work was initiated on the assumption that free glutamic acid could be partially destroyed or removed by passage through the liver. Thus if an infusion of this amino acid were permitted to pass first into the liver it should be better tolerated than if it were given into a peripheral vein. The present study supports this view. The vomiting which followed the intraportal infusions may signify that the capacity of the liver to remove this substance is exceeded. Friedberg and Greenberg[5] have reported the partition of amino acid nitrogen among the various tissues of the rat 15 minutes after the intravenous administration of glutamic acid. They found that the amino acid is slowly cleared from the plasma and at the same time the concentration of the amino acid nitrogen in the liver approached a control value. This could be interpreted as showing that free glutamic acid is rapidly being destroyed or conjugated in the liver.

Summary and conclusions. A method is presented by which the spleen may be readily transplanted subcutaneously in dogs and used for intraportal infusions.

Dogs could tolerate more glutamic acid solution without vomiting when it was given either intrasplenically or directly into the portal vein by using the angiostomy technic, as compared to the peripheral venous administration.

The increased tolerance to glutamic acid solution when given intraportally is attributed to the direct passage of these amino acids to the liver where they may be removed from the circulation.

[5] Friedberg, F., and Greenberg, D. M., *J. Biol. Chem.*, 1947, **168**, 411.

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Effect of Atmospheric Carbon Dioxide on Adrenal Cortical Hyperplasia and Associated Changes Due to Stress.

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By submitting animals to anoxia, under a high carbon dioxide partial pressure, Langley,[1] Hailman,[2] and their co-workers succeeded in preventing the activation of the adrenal

* This work was done during the tenure of a Life Insurance Medical Research Fellowship.

[1] Langley, L. L., Nims, L. F., Harvey, T. S., and Clarke, R. W., National Res. Counc. Div. Med. Sc., 1943, Rep. 108.

[2] Hailman, H. F., *Endocrinology*, 1944, **34**, 187.