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Studies of the Intestinal Absorption of Tyramine

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STUDIES ON THE INTESTINAL ABSORPTION OF TYRAMINE

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VITA

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Studies on the intestinal Absorption of Tyramine

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Introduction

Hanke and Koessler[1] found that bacteria from the intestines of normal individuals can produce toxic amines. If these amines are produced in the intestine, it would be valuable to know something about their absorption. Koessler and Hanke[2] studied the absorption of one of these amines, histamine. Mammoser, Albi, and Boyd[3] have also studied the absorption of histamine as influenced by certain chemical agents. Another toxic amine is tyramine. It is also known as ergotamine and parahydroxyphenylethylamine. Hanke and Koessler[1] found that eleven out of eighteen stools from normal individuals contained microorganisms that converted tyrosine into tyramine. They do not state specifically that tyramine is ever present in the large intestine, but they give good evidence for that supposition. If it were present, might it not be absorbed and give rise to high blood pressure and headaches? By injecting large doses intramuscularly in man Findlay[4] obtained a marked rise in blood pressure foll owed by a fall and accompanied by a severe headache. The exact manner in which tyramine acts is still open to question. Burn[5] gave a review of the literature on the subject and

added his extensive research. He compared the action of tyramine to adrenalin first on the intact animal and then upon the isolated parts. He found that the heart action was augmented and the visceral arteries were constricted by tyramine. The peripheral arteries were slightly constricted a nd then dilated, the latter action being moreprominent. The blood pressure effect is a rise. In the following experime nts this effect is used as an index or criterion of absorption of tyramine from the intestine.

I. Absorption from the colon of the dog The procedure was, briefly, as follows: The dog was allowed to fast for one or two days. It was then anesthetized with ether and kept under anesthesia until it was killed at the end of the experiment. Injections were made by means of a rubber catheter, which was tied in place in the ascending colon. The carotid artery was cannulated with a cannula that was connected to a mercury mannometer which rwcorded the blood pressure upo n a kymograph. The respiratory movements were also recorded by means of tambours.

The drug was in the form of tyramine hydrochloride (Eastman), a white, crystalline compound. All of the doses given in this paper are in terms of weights of the dry compound. Each dose was weighed out separately and was not dissolved until a few minutes before its injection. It was dissolved in five to ten cubic centimeters of nine tenths

percent salt solution and washed with another five or ten cubic centimeters, so that the maximum amount of fluid injected was twenty cubic centimeters. The solutions were warmed by holding them under warm tap water just before injection.

These experiments are based upon the assumption that if tyramine can be absorbed from the intestine without being changed chemically, and if it is absorbed at a sufficiently rapid rate and in sufficient quantity, and if it is not destroyed or detoxified by the liver or stored there and gradually liberated into the blood over a long period of time, it will cause a rise in blood pressure shortly after its injection into the intestine. A rise in blood pressure after the injection and following a period of fairly constant pressure can be taken as positive evidence of absorption. The simplest interpretation of the failure of the blood pressure to rise after an injection is that the tyramine was not absorbed in a sufficient amount to produce that effect, but other interpretations are possible. The results (table one) show one positive result out of three injections of two milligrams per kilo of body weight. Of ten injections of three milligrams per kilo five were positive. Two injections of four milligrams per kilo both gave negative results. Three out of five injections of five milligrams per kilo were positive. Injections of larger doses all gave positive results. The positive results show undoubtedly that tyramine can be readily absorbed from the colons of dogs under anes-

thesia, but the negative results do not necessarily show non-absorption. Ewins and Laidlaw[6] found that indolethylamine was converted by the perfused liver into indolacetic acid. This finding suggested that perhaps some of the tyramine that was absorbed from the colon was detoxified by the liver. Meakins and Harrington[7] found that the liver exercises a protective function against large doses of histamine, probably by delaying the entrance of the histamine into the general circulation, due to the enormous capillary bed which it must traverse before reaching the inferior vena cava. This finding suggested that the absorption of tyramine from the intestine might be faster than was indicated by the general and prolonged rise in blood pressure which was obtained (figure two). Accordingly, injections were made into the splenic vein, the femoral vein, the femoral artery, and the ascending colon for comparison. The rised in blood pressure in direct order of their height and steepness for equal doses of tyramine were femoral vein, femoral artery, splenic vein, and ascending colon. The rationality of comparing the effects of injecting the same dose in different places depends upon the assurance that the same dose injected twice in the same place will produce the same effect. Chen and Meek[8] repeatedly injected tyramine inteavenously into a dog and obtained repeated rises in blood pressure, each successive rise being only slightly lower than the preceding rise. In my experiments repeated injection of the

same dose into the ascending colon of the same dog did not produce the same effect. Hence, nothing definite can be concluded as far as the colon is concerned . Dr. Boyd suggested another possible reason for the negative results, namely, that there might be a physical adsorption between the tyramine and some constituent of the feces, such as small bits of bone. Fasting for one or two days did not cause evacuation in any case, and before the fast bones were available for the dogs to chew on. It did not seem advisable to employ enemas or cathartics because Mammoser, Albi, and Boyd found that injury to the intestinal mucosa rendered it more permeable to histamine, andthe same might be true in the case of tyramine. No attempt was made to regulate the diet. Another possible explanation of the negative results is that there was little or no epinephrine in the circulation of the animals that did not respond to tyramine. Burn[5] found that tyramine has two actions upon the peripheral arteries, a slight constriction followed by a dilatation. He discovered that the constrictor action occurred only in the presence of epinephrine. He does not say that epinephrine is necessary to the action of tyramine on the heart. Chen and Meek[8] say that tyramine shows a synergysm with epinephrine both in intensity and duration. While all of the above explanations are possible and worth considering, until they are investigated and proved, it is logical tentitively to assume that the negative results mean that the tyramine was not absorbed.

If that be so, the absorptive power of the colon of the dog varies in the different individuals.

II. Absorption from the colon and the duodenum of the cat. The procedure was the same as was used in the experiments on the dog except that sodium barbital was used instead of ether for anesthesia and when injections were made into the duodenum they were made by means of a catheter tied in the pyloric sphincter. The results (table three) show that doses of ten, fifteen, twenty, twenty five, and forty milligrams per kilo (figure six) when injected into the ascending colon failed to produce any rise in blood pressure, but a rise was obtained after injection of fifty milligrams per kilo (figure seven). Doses of thirty and forty milligrams per kilo injected into the duodenum (table four) produced a rise (figure eight). Absorption is, therefore, faster from the duodenum than from the colon. Meakins and Harrington[7] found this to be true in regard to histamine. But histamine is not absorbed from the colons of dogs at all under normal conditions, whereas tyramine is readily absorbed. In cats, on the other hand, histamine is more easily absorbed than tyramine. The difference in the dose of tyramine required to produce a rise in blood pressure is probably due to a difference in absorption from the colons of the dog and the cat, but one must not overlook the possibility that the drug does not have the same pharmacological effect upon the two animals. Intravenous injections were made to

determine this point. The results (table five) that in one out of six cats there was no rise in blood pressure; in the other five there was a rise. The possible reasons advanced for negative results in the dog experiments might apply here, also. In addition, the tyramine might be detoxified by the mucosa of the colon while being absorbed. Koessler and Hanke[2] present evidence that this may be true in the case of histamine. However, until any other explanation of the negative results is definitely proved, it is logical to interpret them as meaning that the tyramine is not absorbed.

CONCLUSIONS

1. Tyramine, in amounts as small as two or three milligrams per kilo of body weight can be absorbed from the colon of the dog under ether anesthesia.

2. Tyramine is not absorbed from the colons of the cat under barbital anesthesia unless it is present in very large amounts.

3. Absorption of tyramine in the cat is faster from the duodenum than from the colon.

4. When a rise in blood pressure occurs after tyramine has been put into the intestine of the dog or the cat, it is gradual and moderate.

BIBLIOGRAPHY

1. Hanke, M. T.,and Koessler, K. K., "On the faculty of normal intestinal bacteria to form toxic amines", J. Biol. Chem., 1924, lix, 835
2. Koessler, K. K., and Hanke, M. T., "The intestinal absorption and detoxication of histamine in the mammalian organism", J. Biol. Chem., 1924, lix, 889
3. Mammoser, L. F., R. W. Albi, and T. E. Boyd, "Studies on the absorption of histamine from the intestine", Amer. Jour. Physiol., 1929, xc, no. 2
4. Findlay, L., "The systolic pressure at different points of the circulation in the child and the adult", Quart. Jour. Med., 1911, iv, 489
5. Burn, J. H., "The cardio-vascular action of tyramine", Quart. J. Pharm. and Pharmacol., iii, 1930, 187
6. Ewins, A. J. and P. P. Laidlaw, "The fate of indolethylamine in the organism", Biochem. Jour. 1913, vii, 18
7. Meakins, J., and C. R. Harrington, "The relation of histamine to intestinal intoxication", J. Pharmacol. and Exper. Ther., xx, 45
8. Chen, K. K., and W. J. Meek, "A comparative study of ephedrine, tyramine, and epinephrine with special reference to the circulation", J. Pharmacol., 1926, xxviii, 59

TABLE 1.

Tyramine injected into the ascending colon of the dog under ether anesthesia. Sex and pregnancy: not recorded because no pregnant females were used. Weights of dogs: not recorded because doses are given in mgms. per kilo. Previous injections: not recorded because they do not appreciably lessen the action of tyramine.

Dose in mgm. per kilo.	Date	Result	Extent of rise	Duration of rise	Other information
2	3/16/31		10 mm.	28 min.	Doubtful because of respiratory changes.
2	3/16/31	—			
2	2/5/31	+	6 mm.	24½ min.	Vagus cut
3	1/27/31	—			Vagus cut
3	1/30/31	—			Vagus cut
3	1/31/31	+	13 mm.	35 min.	Vagus cut
3	2/17/31	+	6 mm.	22 min.	
3	2/26/31	+	6 mm.	more than 18 min.	
3	3/14/31	—			
3	3/17/31	+	7 mm.	more than 25 min.	
3	3/17/31	+	9 mm.	more than 48 min.	Vagus cut
3	3/19/31	—			
3	3/19/31		105 mm.	more than 13 min.	Vagus cut Doubtful because of respiratory changes.

Table 1 (continued)

Dose in mgm. per kilo	Date	Result	Extent of rise	Duration of rise	Other information
4	3/3/31	—			
4	3/3/31	—			
5	1/21/31		32 mm.	44 min.	Vagus cut Doubtful
5	2/27/31	+	48 mm.	more than 110 min.	
5	3/5/31	+	6 mm.	14 min.	
5	3/5/31	—			
5	3/14/31	+	18 mm.		Female in heat. Duration doubtful because of respiratory changes. Given castor oil previous day.
10	1/20/31	+	28 mm.	more than 52 min.	
15	1/15/31	+	70 mm.	25 min.	
20	1/14/31	+	33 mm.	more than 16 min.	

TABLE 2

Tyramine injected in various ways into dogs under either anesthesia for the purpose of comparison. No sick or pregnant dogs were used.

Date	Dose in mgm.	Place of injection	Result	Extent of rise	Time required for rise	Duration of rise and remarks
2/26/31	3 per kilo	splenic vein	+	11 mm.	15 min.	more than 20 min.
	3 per kilo	ascending colon	+	7 mm.	6 min.	15 min.
3/5/31	5 per kilo	splenic vein	+	56 mm.	5½ min.	more than 20 min.
	5 per kilo	ascending colon	+	6 mm.	8 min.	17 min.
	5 per kilo	ascending colon	−			
3/16/31	2 per kilo	splenic vein		6 mm.	24½ min.	28½ min.
	2 per kilo	ascending colon	−			
	2 per kilo	ascending colon		9 mm.	15 min.	39 min. Both results doubtful because of changes in respiration and depth of anesthesia.
2/20/31	2	splenic vein	+	7 mm.	3½ min.	more than 10 min. Dog weighed 5.1 kilos
	2	femoral vein	+	25 mm.	2 min.	more than 10 min.

(continued on the next page)

Table 2 (continued)

Date	Dose in mgm.	Place of injection	Result	Extent of rise	Time required for rise	Duration of rise and remarks
2/28/31	2 per kilo	femoral vein	+	87 mm.	2½ min.	14½ min.
	2 per kilo	femoral artery	+	46 mm.	3½ min.	7 min.
3/3/31	4 per kilo	ascending colon	—			
	4 per kilo	ascending colon	—			
	4 per kilo	femoral vein	+	37 mm.	2 min.	5 min.
3/19/31	3 per kilo	ascending colon	—			
	3 per kilo	ascending colon	+	6 mm.	17 min.	more than 17 min.
	3 per kilo	femoral vein	+	105 mm.	2 min.	more than 14 min.
3/14/31	5 per kilo	ascending colon	+	22 mm.	33 min.	duration doubtful because of changes in depth of anesthesia Female dog in heat
	3 per kilo	ascending colon	—			
3/17/31	3 per kilo	ascending colon	+	7 mm.	9 min.	
	3 per kilo	ascending colon	+	19 mm.	33 min.	After vagi were cut.

TABLE 3

Tyramine injected into the ascending colon of the cat under barbital anesthesia. Sex: no pregnant females were used. Previous injections: not recorded because they do not greatly lessen the action of tyramine.

Dose in mgms. per kilo	Date	Result	Extent of rise	Duration of rise
10	3/27/31	—		
10	4/7/31	—		
15	3/27/31	—		
15	4/2/31	—		
20	4/2/31	—		
25	4/7/31	—		
40	4/13/31	—		
50	4/8/31	+	15 mm.	33 min.

TABLE 4

Tyramine injected into the duodenum of the cat under barbital anesthesia. Sex: no pregnant females were used. Previous injections: not recorded because they do not greatly lessen the action of tyramine.

Dose in mgms. per kilo	Date	Result	Extent of rise	Duration of rise
10	4/14/31	−		
20	4/2/31	−		
20	4/14/31	−		
20	4/21/31	−		
25	4/21/31	−		
30	4/15/31	+	29 mm.	37 min.
30	4/21/31	−		
40	4/15/31	+	20 mm.	18 min.

TABLE 5

Tyramine injected in various ways into the cat under barbital anesthesia for the purpose of comparison. Sex: no pregnant females were used. Injections are shown in the order in which they were made.

Date	Dose in mgm.	Place of injection	Result	Extent of rise	Time required for rise	Duration of rise & other information.
4/7/31	10 per kilo	splenic vein	+	98 mm.	3 min.	10 min. Rise followed by low pressure
	10 per kilo	ascending colon	—			
	25 per kilo	ascending colon	—			
4/13/31	1	femoral vein	+	24 mm.	1 min.	duration uncertain due to changes in depth of anesthesia. 3.12 kilos, weight
	40 per kilo	ascending colon	—			
4/22/31	1	femoral vein	—			weight, 2.08 kilos
	2	femoral vein	—			
4/27/31	5	femoral vein	+	11 mm.	1½ min.	weight, 3.32 kilos
	2	femoral vein	+	14 mm.	1½ min	3½ min.
	5	femoral vein	+	23 mm.	1 min.	2½ min.
	5	femoral vein	+	20 mm.	2 min.	duration uncertain due to changes in depth of anesthesia.

Table 5 (continued)

Date	Dose in mgm.	Place of injection	Result	Extent of rise	Time required for rise	Duration of rise & other information.
5/12/31	1	femoral vein	+	24 mm.	5½ min.	8½ min. weight 1.8 kilos
	1	femoral vein	+	33 mm.	3 min.	8 min.
	2	femoral vein	+	29 mm.	2 min.	9 min.
	2	femoral vein	+	26 mm.	3 min.	6 min.
5/13/31	1	femoral vein	+	17 mm.	2 min.	more than 7½ min.
	1	femoral vein	+	14 mm.	2½ min.	more than 11 min.
	2	femoral vein	+	16 mm.	2 min.	more than 15 min.
	2	femoral vein	+	13 mm.	2 min.	more than 9 min.

Observation: In experiment 5/13/31, although the blood pressure had not quite returned to normal when the second dose of 1 mgm. of tyramine was injected, the blood pressure rose to within 1 mm. of the level recorded after the first injection of 1 mgm. The second dose of 2 mgm. produced a rise to exactly the same level as the first dose of 2 mgm., although here, also, there had been no return to normal.

GRAPHS

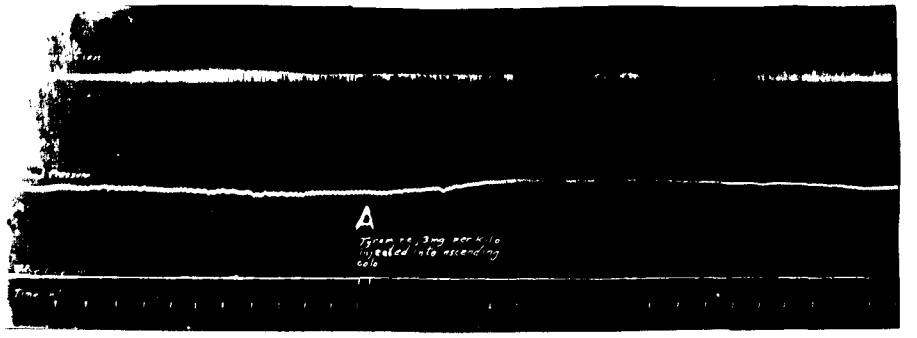

Figure 1. Dog. At "A" 3 mgms. per kilo of tyramine were injected into the ascending colon. Top line, respiration; next to top, blood pressure; next to bottom, base line for blood pressure and time of injection; bottom line, time intervals of 30 seconds. The same arrangement is followed in all of the graphs.

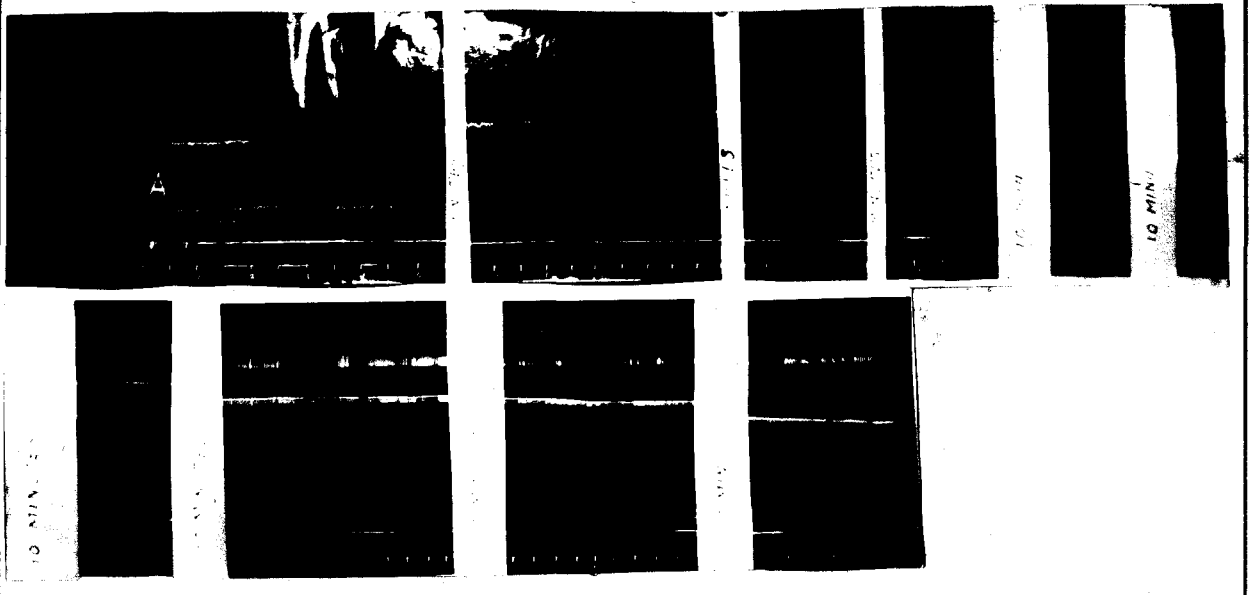

Figure 2. Dog. At "A" 5 mgms. per kilo of tyramine were injected into the ascending colon. Narrow white spaces are 5 minute intervals; wide white spaces are 10 minute intervals.

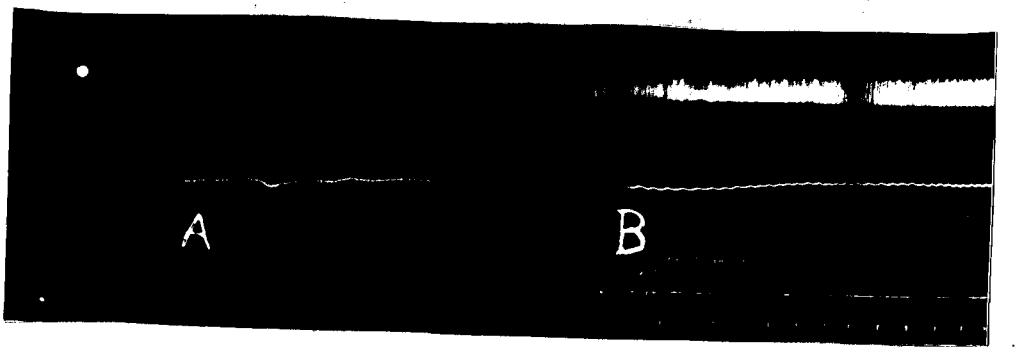

Figure 3. Dog. At "A" 3 mgms per kilo of tyramine were injected into the splenic vein; at "B" the same amount was injected into the ascending colon.

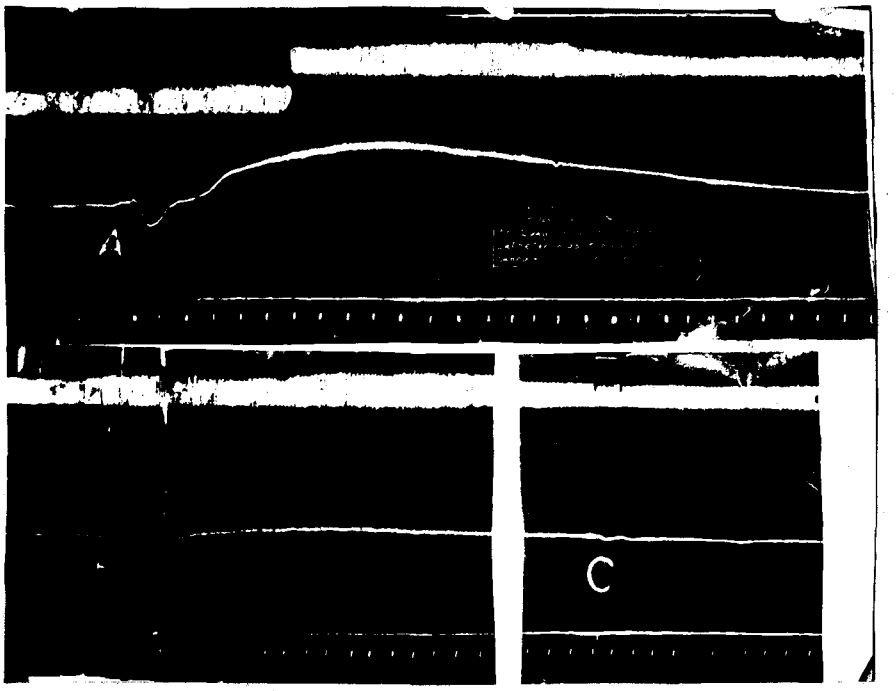

Figure 4. Dog. At "A" 5 mgms. per kilo of tyramine were injected into the splenic vein; at "B" and at "C" the same amount was injected into the ascending colon. Note the difference from figure 3. Retouched with white ink on account of faintness of the lines.

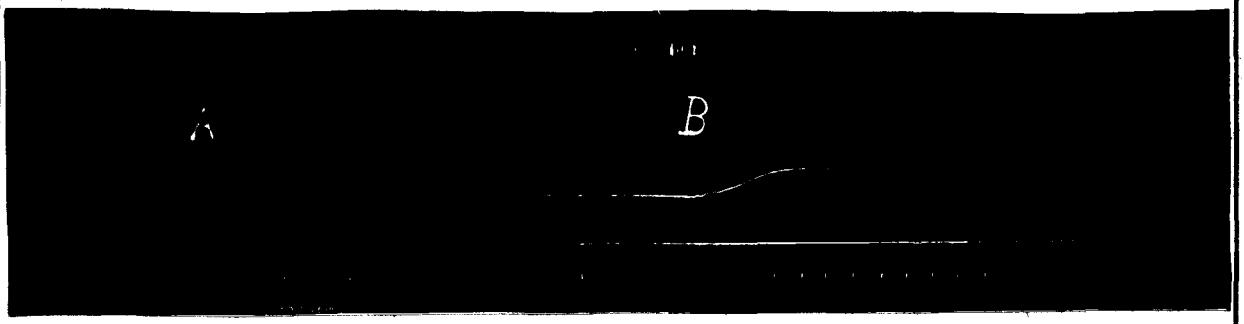

Figure 5. Dog. At "A" 2 mgms. of tyramine were injected into the splenic vein; at "B" the same amount was injected into the femoral vein.

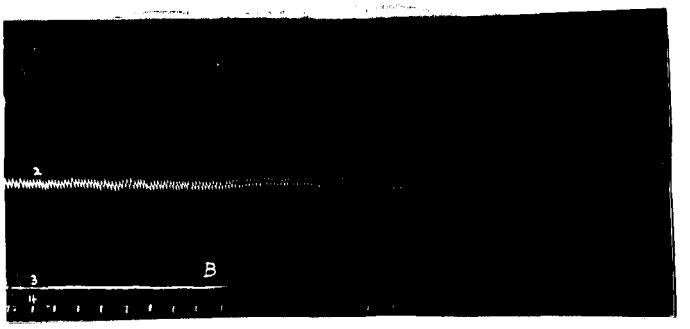

Figure 6. Cat. At "B" 40 mgms. per kilo of tyramine were injected into the ascending colon.

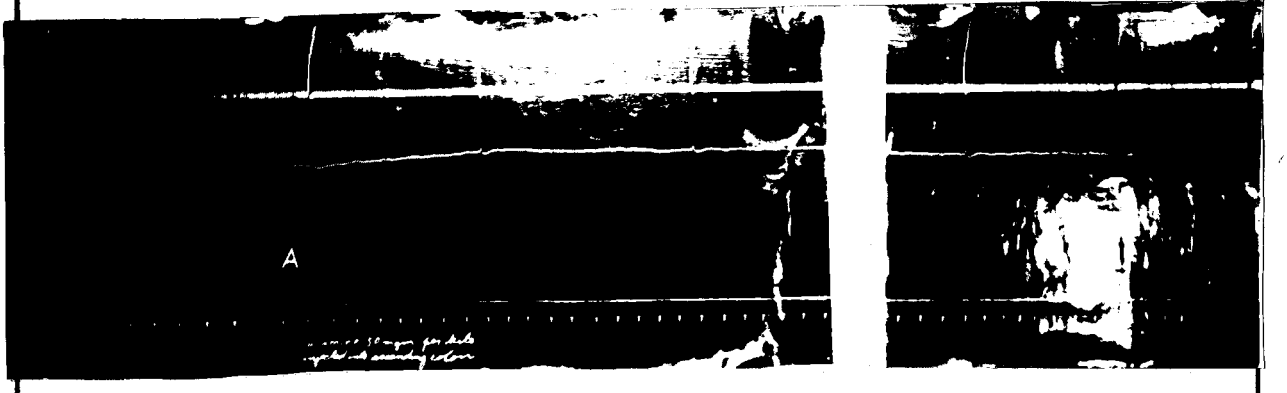

Figure 7. Cat. At "A" 50 mgms.per kilo of tyramine were injected into the ascending colon. The white space represents a ten minute interval.

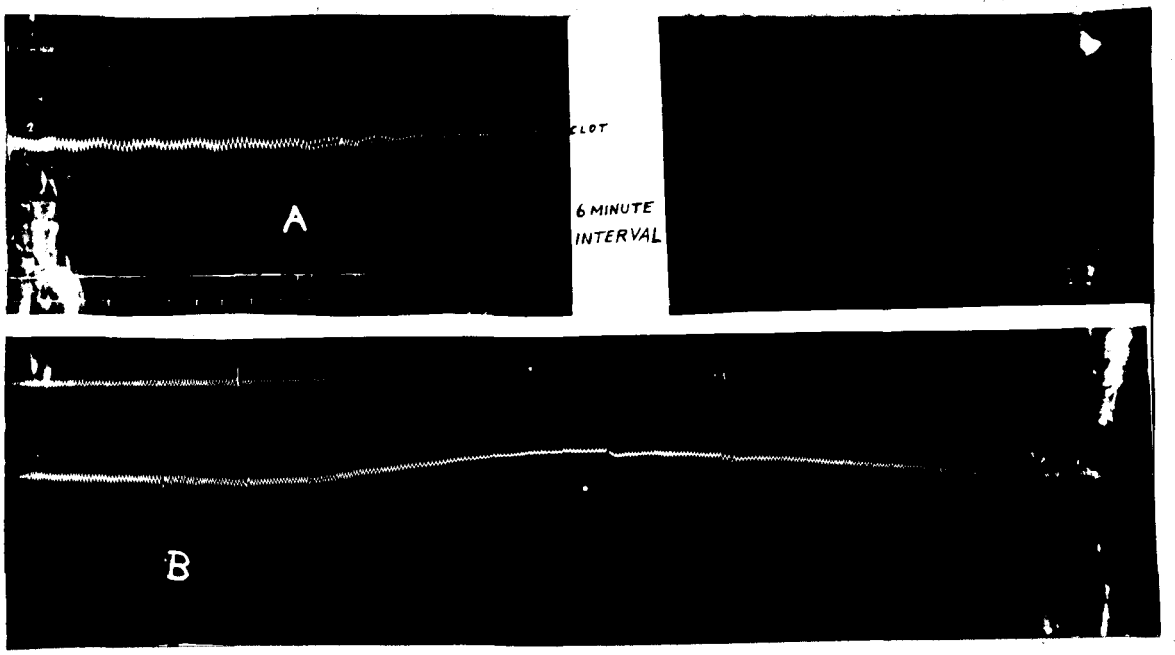

Figure 8. Cat. At "A" 30 mgms. per kilo of tyramine were injected into the duodenum; at "B" 40 mgms. per kilo were injected into the duodenum.

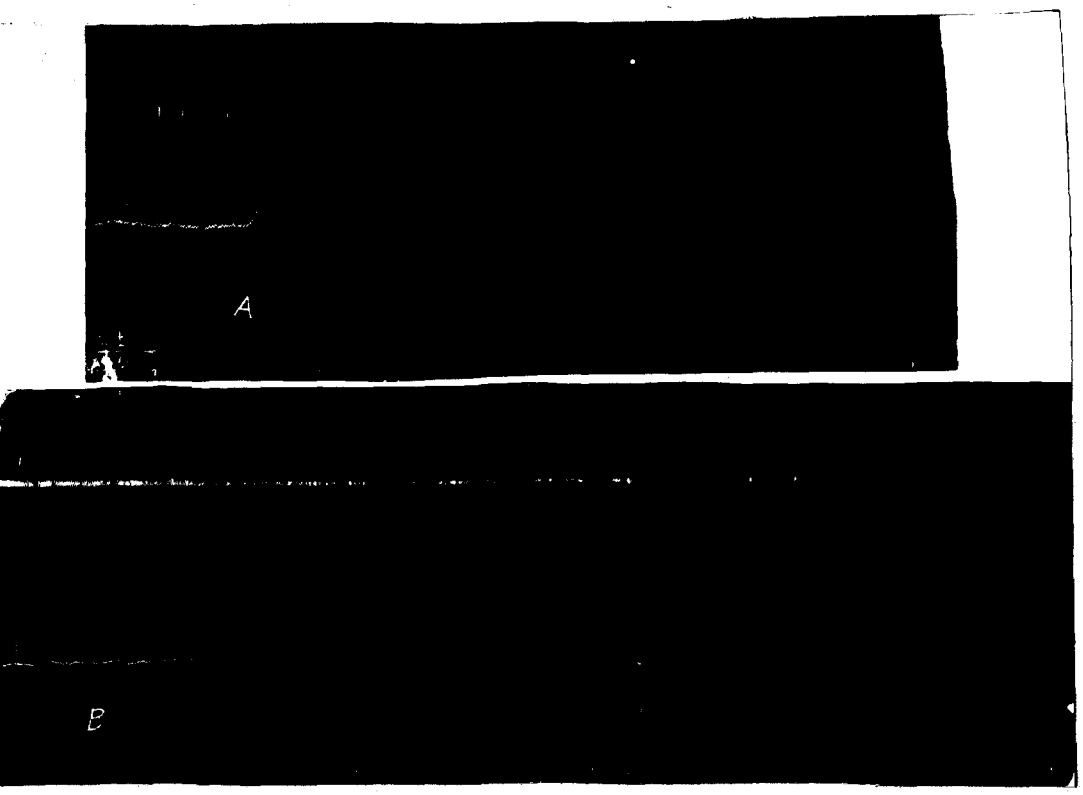

Figure 9. Cat. At "A" 10 mgms. per kilo of tyramine were
ected into the splenic vein; at "B" the same amount was in-
ted into the ascending colon; at "C" 25 mgms. per kilo were
ected into the ascending colon.