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ACTION OF PSYCHOPHARMACOLOGIC AGENTS ON INTERDIGESTIVE GASTRIC SECRETION IN THE RAT

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In studies on the effect of emotional stress on gastric secretion, we found that such stress-induced secretion could be inhibited by either a cholinergic or adrenergic blocking agent. We postulated that both a cholinergic and an adrenergic neurohumoral agent were involved in inducing this secretion.[1] By what is as yet indirect evidence, we suggested that these agents are probably supplied by the hypothalamus and produce their effect on gastric secretion through the pituitary adrenal axis.

Reserpine has been shown to increase both gastric motor and secretory activity,[2-4] and Shore *et al.*[5] have presented convincing evidence to the effect that the central action of reserpine is mediated through the free serotonin which it releases in the brain. Serotonin is found in the brain stem, especially in the hypothalamus,[6, 7] as is monoamine oxidase, the enzyme which metabolizes it.[8] Brodie and Shore[9] believe that there are provocative suggestions for the action of serotonin as a chemical mediator in the brain and that it may be the transmitter substance for the parasympathetic division of the autonomic system. They would then account for the parasympathomimetic effects of reserpine by the view that it causes a constant flow of free serotonin to stimulate parasympathetic centers. These results, coupled with our own evidence to indicate that both an adrenergic and a cholinergic neurohumoral agent are involved in the stimulation of gastric secretion following emotional stress, made it attractive to consider whether serotonin might be that cholinergic agent. Furthermore, the location of the highest concentration of norepinephrine in the brain stem was found by Vogt[10] to be in the hypothalamus. This could make norepinephrine a possible candidate for the adrenergic factor which we believe to be involved as well in the same secretory mechanism. Accordingly, the effect of serotonin, of 5-hydroxytryptophan (5-HTP), its precursor, of iproniazid (Marsilid), the inhibitor of its metabolizing enzyme monoamine oxidase, and of lysergic acid diethylamide (LSD), an antagonist of serotonin, were studied on gastric secretion in the rat. The effect of chlorpromazine was also investigated. The detailed technique for the method used for studying secretion has been described previously[11] and a preliminary result of the effect of serotonin on such secretion was reported recently.[12]

Methods and Material

Wistar strain male rats grown in our colony and weighing 120 to 200 gm. were used. In all experiments litter mates were chosen for controls and for treatment. After proper fasting, the pylorus was ligated and the stomach was lavaged with saline and emptied completely. The drug to be studied was then administered subcutaneously. Animals were inspected at frequent intervals for gross behavior and signs of toxicity. Four hours after pylorus ligation the animals were killed and their gastric contents were collected quantitatively. The gastric contents were measured and analyzed for free and total acidity and pepsin concentration when sufficient amounts were available. The rate of secretion and the total acid and pepsin output were calculated per 100 gm. of body weight for the four-hour period.

The dosage levels at which the respective drugs were administered follow. Each dose group included approximately 20 animals for the control and 20 for a drug study. All drugs were administered subcutaneously.

1. Serotonin, in doses ranging from 0.0625 to 2.0 mg. per 100 gm. of body weight.
2. 5-HTP, 1 mg. and 2 mg. per 100 gm. of body weight.
3. Iproniazid (Marsilid), 10, 20, and 40 mg. per 100 gm. of body weight, *one hour prior* to pylorus ligation.
4. *brom*-LSD, 5, 20, and 80 μg. per 100 gm. of body weight.
5. LSD, 80 and 160 μg. per 100 gm. of body weight.
6. Chlorpromazine, 0.025, 0.05, 0.1, and 0.2 mg. per 100 gm. of body weight.

Results

The tables show the data on body weight, rate of secretion, free and total acid concentration, and total acid and pepsin output of the gastric secretion per 100 gm. of body weight in control and treated animals.

Serotonin. In table 1 are presented the results obtained after six dose levels of serotonin. A dose of 0.0625 or 0.125 mg. per 100 gm. of body weight produced no significant changes in gastric secretion. As the dose of serotonin was increased to 0.25 and 0.5 mg. per 100 gm. of body weight, a significant decrease in total acid and pepsin output occurred, as well as in rate of secretion. Further increase in the dose of drug to 1 mg. per 100 gm. produced, in addition, a significant lowering in free acid concentration. The 2 mg. per 100 gm. dose produced not only a quantitative effect over the 1-mg. dose, but a significant depression of total acid concentration as well. However, at the 2-mg. dose level, the rate of secretion was so low that the reduced total acid concentration probably represents a partial neutralization of such minimal secretion.

Figure 1 shows the dose response curve of percental inhibition of the rate of secretion and total acid output. Above a dosage level of 0.25 mg. per 100 gm. of body weight, the degree of inhibition increases as the dose of serotonin is increased.

5-Hydroxytryptophan. In table 2 are given the results of gastric secretion after administration of 5-HTP. This compound in a dose of 1 mg. per 100 gm. of body weight produced a significant decrease in rate of secretion and in total acid and pepsin output. At a dose of 2 mg. per 100 gm. of body weight, 5-HTP also produced a significant depression in free and total acid concentration. The degree of suppression in total acid output corresponds to that seen after 1 mg. per 100 gm. of body weight of serotonin (fig. 2).

Marsilid. The results after Marsilid are presented in table 3. This compound produced a significant depression in rate of secretion, free and total acid concentration, and total acid and pepsin output of gastric secretion after 10, 20, or 40 mg. per 100 gm. of body weight of the drug. The percental inhibition of total acid and pepsin output increased as the dose of Marsilid was increased (fig. 2).

The log dose response of output of gastric acid and of pepsin to these three compounds is shown in figures 2 and 3.

brom- Lysergic Acid Diethylamide (brom-LSD). The results of gastric secretion after 5, 20, and 80 μg. per 100 gm. of body weight of *brom*-LSD are presented in table 4. This compound at these dosage levels and LSD at 80 or 160 μg. per 100 gm. of body weight failed to alter gastric secretion in the rat significantly.

Chlorpromazine. The effect of chlorpromazine on gastric secretion was studied in the rat preparation in order to compare its action with that of serotonin and to determine whether it produced the same results in this species as it did in man[13, 14] and in the dog.[15] This drug was tested at four dose levels given subcutaneously. The results listed in table 5 show that 0.025 mg. per 100 gm. of body weight of chlorpromazine failed to influence the rate of secretion, free acidity, total acid, or pepsin output. A dose of 0.05 mg. per 100 gm. lowered the rate of secretion and the pepsin output significantly, but failed to alter free acidity or total acid output.

At the 0.1 and 0.2 mg. per 100 gm. levels all parameters of secretion tested were depressed significantly. The effective action of chlorpromazine in depressing gastric secretion followed a log dose response (fig. 4).

TABLE 1

Effect of serotonin on interdigestive gastric secretion in the rat

	0.0625 mg.*					0.125 mg.*					0.25 mg.*				
	Control		Drug			Control		Drug			Control		Drug		
	n†	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*
Body weight (gm.)	19	121.0 15.0	20	119.0 16.9	0.391	20	134.7 12.9	20	119.4 11.1	4.017¶	19	117.0 14.2	18	123.0 14.7	1.262
Rate (ml./100 gm./4 hr.)	19	3.72 1.21	20	3.36 0.95	1.027	20	3.70 0.26	20	3.15 0.31	1.93	19	3.79 1.37	18	2.48 1.07	3.238§
Free acid concentration (mEq./L.)	19	84.6 14.96	21	85.2 11.94	0.010	20	87.6 17.94	20	84.4 13.77	0.648	19	82.1 15.75	16	84.6 17.53	0.454¶
Total acid concentration (mEq./L.)	19	108.6 13.76	21	112.4 8.05	1.08	20	114.3 11.24	20	111.35 13.03	0.767	19	110.1 12.67	16	119.2 12.61	2.119‡
Total acid output (mEq./100 gm./4 hr.)	19	0.411 0.160	20	0.384 0.122	0.589	20	0.426 0.110	20	0.356 0.130	1.838	19	0.426 0.176	16	0.322 0.105	2.072‡
Pepsin output (Mett units/100 gm./4 hr.)	19	66.3 28.1	19	67.5 31.2	0.12	20	60.7 25.9	20	56.8 21.7	0.520	19	117.0 39.8	16	90.0 31.5	2.195‡
	0.50 mg.*					1.0 mg.*					2.0 mg.*				
Body weight (gm.)	18	120.8 14.2	22	111.8 10.8	2.280‡	20	120.0 16.1	21	107.0 8.8	3.235§	19	132.7 12.7	20	128.9 10.1	1.040
Rate (ml./100 gm./4 hr.)	18	4.13 1.64	22	2.50 1.04	3.816¶	20	4.49 1.16	21	1.58 0.81	9.334¶	19	3.74 1.08	20	0.47 0.35	12.897¶
Free acid concentration (mEq./L.)	18	74.2 21.88	22	68.7 23.20	0.764	20	82.8 14.69	20	51.6 30.44	4.123¶	19	85.4 14.65	18	15.9 23.51	10.836¶
Total acid concentration (mEq./L.)	18	105.8 25.51	22	110.1 20.42	0.595	20	110.9 12.77	19	100.6 32.15	1.330	19	111.8 13.74	14	59.9 22.65	8.186¶
Total acid output (mEq./100 gm./4 hr.)	18	0.466 0.224	22	0.282 0.134	3.181§	20	0.501 0.134	19	0.185 0.105	4.628¶	19	0.422 0.138	14	0.041 0.032	9.831¶
Pepsin output (Mett units/100 gm./4 hr.)	17	114.8 44.8	20	71.0 30.4	3.527§	20	102.6 40.5	18	54.8 21.7	4.466¶	19	92.3 30.2	6	27.5 10.0	5.106¶

* Dose (milligrams per 100 gm. of body weight).
† *n*, number of observations.
‡ Significant at probability of <0.05.
§ Significant at probability of <0.01.
¶ Significant at probability of <0.001.

Discussion

Because of the established effect of reserpine in stimulating gastric secretion and the role assigned to serotonin in the central action of reserpine, coupled with the suggestion that serotonin possibly acts in the brain as the transmitter substance for the parasympathetic division of the autonomic system, we anticipated that serotonin, if it affected gastric secretion, would stimulate it. The contrary, however, occurred. When we first started our studies with serotonin we were not aware that, in ordinary dosage, it would not pass the blood-brain barrier. The suppressive effect on gastric secretion which we observed in our rats,[12] an effect which Haverback *et al.*[14] observed independently in dogs, must, therefore, have resulted from a peripheral effect of serotonin. The known vasospastic action of serotonin could explain its peripheral inhibitory effect upon gastric secretion.

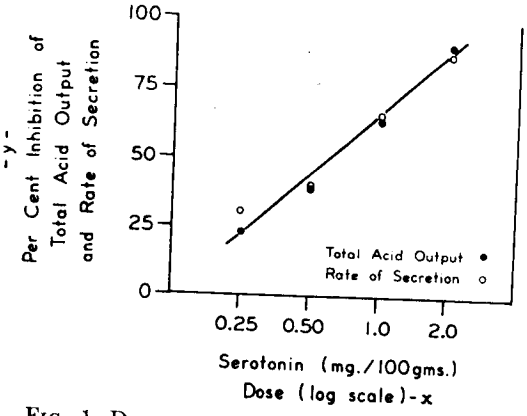

FIG. 1. Dose response curve of serotonin on rate of secretion and on total acid output of spontaneous gastric secretion in the rat.

We sought in these studies to determine whether the gastric secretory depression produced by this drug was through purely a peripheral mechanism or whether a central action as well might be involved. The findings of Weissbach *et al.*,[15] indicating that

TABLE 2

Effect of 5-hydroxytryptophan on interdigestive secretion in the rat

	1.0 mg.*					2.0 mg.*				
	Control		Drug			Control		Drug		
	n†	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*
Body weight (gm.)	17	141.4 11.6	18	142.2 15.0	0.191	20	135.9 14.3	19	142.1 10.4	1.514
Rate (ml./100 gm./4 hr.)	17	3.81 1.37	18	2.28 1.04	3.656‡	20	3.74 0.85	19	1.74 0.69	8.062‡
Free acid concentration (mEq./L.)	17	80.4 19.07	18	65.7 36.25	1.490	20	88.6 15.86	19	50.1 27.76	5.352‡
Total acid concentration (mEq./L.)	17	114.4 17.52	18	100.4 37.71	1.291	20	118.5 13.96	19	88.6 27.15	4.365‡
Total acid output (mEq./100 gm./4 hr.)	17	0.437 0.173	18	0.257 0.166	3.129§	20	0.446 0.118	19	0.164 0.098	8.105‡
Pepsin output (Mett units/100 gm./4 hr.)	17	28.0 11.68	17	15.1 8.58	3.674‡	20	31.8 10.85	19	12.6 8.75	6.079‡

* Dose (milligrams per 100 gm. of body weight).
† *n*, number of observations.
‡ Significant at probability <0.001.
§ Significant at probability of <0.01.

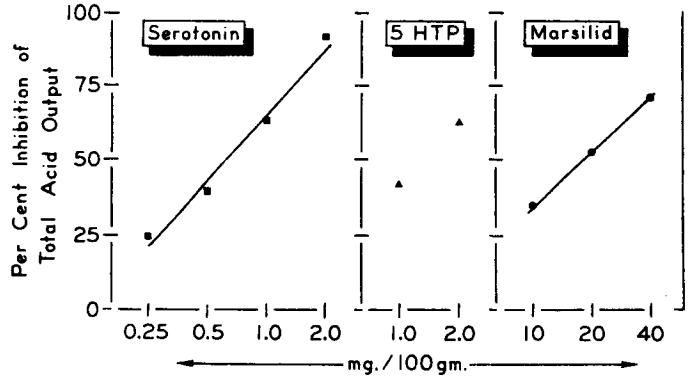

FIG. 2. Per cent inhibition of total output of gastric secretion in rats following serotonin, 5-hydroxytryptophan (5-HTP), and Marsilid.

TABLE 3

Effect of Marsilid on interdigestive gastric secretion in the rat

	10 mg.*					20 mg.*					40 mg.*				
	Control		Drug			Control		Drug			Control		Drug		
	n†	Mean ± S.D.	n	Mean ± S.D.	t	n	Mean ± S.D.	n	Mean ± S.D.	t	n	Mean ± S.D.	n	Mean ± S.D.	t
Body weight (gm.)	17	135.0 16.1	21	124.9 18.0	1.791	20	134.3 21.4	21	134.8 22.3	0.067	20	131.5 10.8	20	127.0 13.6	1.159
Rate (ml./100 gm./4 hr)	17	3.21 0.94	21	2.45 1.07	2.329‡	20	3.47 0.95	21	2.15 0.83	4.801§	20	3.41 1.30	20	1.23 0.56	6.846§
Free acid concentration (mEq./L.)	17	79.1 16.44	21	50.9 33.84	3.139¶	20	76.9 22.26	21	42.4 29.53	4.207§	20	78.8 25.58	20	37.2 25.33	5.161§
Total acid concentration (mEq./L.)	17	108.1 15.37	21	83.5 33.08	2.828¶	20	108.3 18.71	21	81.2 31.19	3.347¶	20	107.6 20.46	20	87.5 23.45	2.892¶
Total acid output (mEq./100 gm./4 hr.)	17	0.341 0.125	21	0.223 0.158	2.520‡	20	0.384 0.140	21	0.182 0.113	5.085§	20	0.386 0.183	20	0.112 0.071	6.254§
Pepsin output (Mett units/100 gm./4 hr.)	17	26.1 11.7	20	16.9 11.0	2.448‡	20	34.8 11.1	21	16.6 8.0	6.043§	20	34.4 12.7	19	10.8 7.3	7.074§

* Dose (milligrams per 100 gm. of body weight).
† *n*, number of observations.
‡ Significant at probability of 0.05.
§ Significant at probability of 0.001.
¶ Significant at probability of 0.01.

Marsilid inhibited monoamine oxidase in the brain only, therefore increasing brain serotonin alone, enabled us to evaluate the effect of increased brain serotonin on gastric secretion. The results again paralleled those observed with an increase in peripheral serotonin. It would appear, therefore, that serotonin inhibits gastric secretion by a central as well as by a peripheral action. Furthermore, although there is evidence for the central action of reserpine[16] probably located in the region of the hypothalamus. it is clear that the increase in gastric secretion by reserpine cannot be the result of either a central or a peripheral increase of serotonin. Too, serotonin must influence gastrointestinal motility through a mechanism that is different from the one through which it affects gastric secretion, since it increases the former and inhibits the latter.

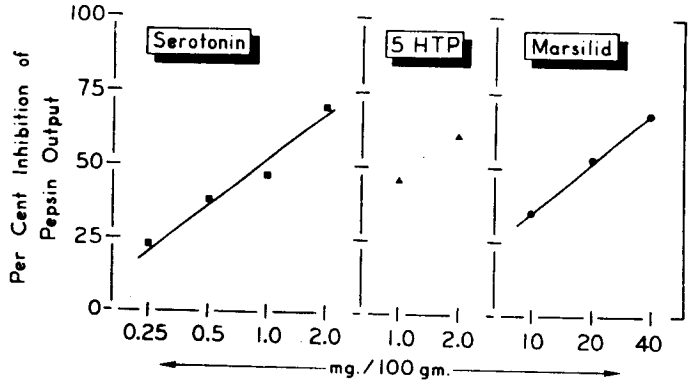

FIG. 3. Per cent inhibition of pepsin output of gastric secretion in rats following serotonin, 5-hydroxytryptophan (T-HTP), and Marsilid.

TABLE 4

Effect of brom-lysergic acid diethylamide on interdigestive gastric secretion in the rat

	5 μg.					20 μg.*					80μg.*				
	Control		Drug			Control		Drug			Control		Drug		
	n†	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*
Body weight (gm.)	19	119.4 11.9	22	124.6 12.3	1.350	20	121.5 13.8	21	119.8 13.4	0.408	19	128.9 9.7	21	135.5 13.1	1.789
Rate (ml./100 gm./4 hr.)	19	4.49 0.64	22	4.34 1.42	0.429	20	3.31 1.01	21	3.45 1.332	0.364	19	3.24 1.22	21	2.93 1.03	0.876
Free acid concentration (mEq./L./)	19	91.3 7.97	22	88.3 12.23	0.920	20	83.0 17.35	21	79.8 19.89	0.554	19	73.2 27.23	21	82.0 23.00	1.116
Total acid concentration (mEq./L.)	19	123.8 10.55	22	122.5 11.21	0.385	20	115.9 16.83	21	111.7 13.68	0.881	19	108.2 29.78	21	114.4 22.26	0.756
Total acid output (mEq./100 gm./4 hr.)	19	0.556 0.087	22	0.535 0.193	0.425	20	0.391 0.153	21	0.395 0.179	0.069	19	0.374 0.198	21	0.344 0.152	0.545
Pepsin output (Mett units/100 gm./4 hr.)	19	54.5 25.8	21	50.5 14.5	0.609	20	41.8 13.2	21	39.4 14.9	0.558					

* Dose (micrograms per 100 gm. of body weights).
† *n*, number of observations.

Hendrix *et al.*,[17] from studies on intestinal motor function in man, concluded that serotonin stimulates intestinal motor activity through cholinergic nerves at a site distal to the ganglionic synapse. Our results of the effect of serotonin both peripherally and centrally on gastric secretion in the rat, if the same is true in man, would not support our supposition that serotonin might represent the cholinergic factor which we believe operates in the mechanism that produces an increase in gastric secretion following emotional stress, nor does it support its possible action as a central parasympathetic neurohumoral activator.

5-HTP injected subcutaneously produced effects on gastric secretion that were similar in kind, but different quantitatively, from those of serotonin. Udenfriend and co-workers[18] have reported measurable increases of serotonin in the blood and tissue within 15 minutes after intraperitoneal injection of 5-HTP and a maximal rise in about 60 minutes which persisted for several hours after

TABLE 5

Effect of chlorpromazine on interdigestive gastric secretion in the rat

	0.025 mg.*					0.050 mg.*					0.1 mg.*					0.2 mg.*				
	Control		Drug			Control		Drug			Control		Drug			Control		Drug		
	n†	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*	*n*	Mean ± S.D.	*n*	Mean ± S.D.	*t*
Body weight (gm.)	20	120.3 17.8	22	116.2 9.7	0.942	18	128.7 35.0	20	140.7 16.1	1.379	20	126.6 13.8	22	123.3 19.6	0.621	20	116.7 15.4	19	123.2 18.1	1.210
Rate (ml./100 gm./4 hr.)	20	3.69 1.45	21	3.39 1.17	0.749	18	2.93 1.07	20	2.13 0.77	2.641‡	20	3.22 0.82	22	1.89 1.05	4.515§	20	3.05 1.03	19	1.27 0.71	6.219§
Free acid concentration (mEq./L.)	20	79.4 24.10	21	79.0 23.0	0.061	18	68.3 17.54	20	67.3 25.17	0.137	20	84.9 12.46	22	67.9 22.49	2.969¶	20	80.4 17.88	17	64.7 24.80	2.231‡
Total acid concentration (mEq./L.)	20	105.3 20.45	21	108.2 22.29	0.447	18	102.7 11.65	20	103.0 19.22	0.064	20	106.9 12.46	22	97.8 21.16	1.691	20	105.2 16.30	17	99.7 19.87	0.916
Total acid output (mEq./100 gm./4 hr.)	20	0.409 0.221	21	0.379 0.173	0.470	18	0.304 0.143	20	0.228 0.105	1.885	20	0.346 0.103	22	0.190 0.127	4.343§	20	0.324 0.135	17	0.137 0.090	4.737§
Pepsin output (Mett units/100 gm./4 hr.)	19	123.4 57.7	21	117.3 47.9	0.361	18	111.3 63.4	20	76.3 30.3	2.208‡	20	108.8 40.8	21	81.3 42.9	2.105‡	20	133.6 53.6	12	68.2 36.9	3.721§

* Dose (milligrams per 100 gm. of body weight).

† *n*, number of observations.

‡ Significant at probability of <0.05.

§ Significant at probability of <0.001.

¶ Significant at probability of <0.01.

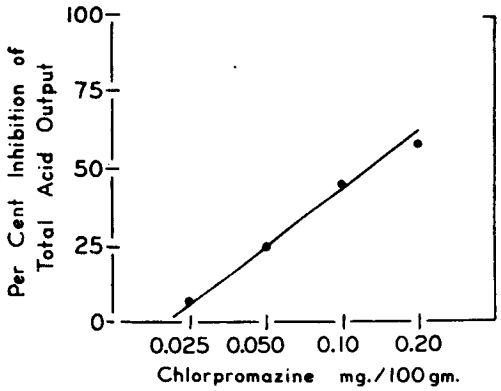

FIG. 4. Dose response curve of total acid output after chlorpromazine.

the administration. Our results would indicate that in the rat the action of 5-HTP on gastric secretion as compared with serotonin weight for weight, produces approximately one-half the effect of that caused by a similar dose of serotonin.

Marsilid, by increasing the serotonin level in the brain only, was found to inhibit gastric secretion. These results supply evidence for a central inhibitory action of serotonin on such secretion.

brom-LSD and LSD as used in these experiments produced no effect on gastric secretion. However, Haverback *et al.*[14] have observed stimulation of secretion in the dog with LSD.

The action of chlorpromazine on gastric secretion in the rat parallels the effects in the dog and in man.[19] Although this depressive action of chlorpromazine is not yet accurately localized, our studies[20] of its effect on sham feeding secretion in dogs with esophagostomy and in Heidenhain pouch dogs receiving intermittent Mecholyl injections indicate that the depressive action of this drug on gastric secretion is the result of a central and not a peripheral one.

Summary

1. The effect of serotonin on gastric secretion, of 5-hydroxytryptophan (5-HTP) its precursor, of iproniazid (Marsilid), the inhibitor of its metabolizing enzyme monoamine oxidase, of lysergic acid diethylamide (LSD), an antagonist of serotonin, and of chlorpromazine, were studied in our preparation of the pylorus-ligated rat.

2. Serotonin, in a dose of 0.0625 or 0.125 mg. per 100 gm. of body weight subcutaneously, produced no significant changes in gastric secretion. However, the dose response curves of inhibition of rate of secretion and total acid output were obtained with serotonin in doses of 0.25, 0.5, 1.0, and 2.0 mg. per 100 gm. of body weight.

3. 5-HTP injected subcutaneously produced a similar inhibition of gastric secretion. Its action as compared with serotonin, weight for weight, produced approximately one-half the effect of that caused by a similar dose of serotonin.

4. Iproniazid, in doses of 10, 20, and 40 mg. per 100 gm. of body weight subcutaneously, by increasing the serotonin level in the brain only, was found to inhibit gastric secretion. This supplies evidence for a central inhibitory action of serotonin on gastric secretion as well as a peripheral one obtained with serotonin administered subcutaneously.

5. *brom*-LSD and LSD as used in our experiments produced no effect on gastric secretion.

6. A dose response curve of inhibition of total acid output was obtained with chlorpromazine subcutaneously in doses of 0.025, 0.05, 0.1, and 0.2 mg. per 100 gm. of body weight.

7. The action of chlorpromazine in suppressing gastric secretion in the rat compared with that of serotonin when administered subcutaneously appears to be about five times greater on a weight for weight basis.

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