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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

L. STUDIES ON THE CONTROL OF HUNGER BY DRUGS *

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The hunger mechanism is a local mechanism within the stomach itself, subject to central regulation. A great accumulation of well established data points to the fact that hunger is a sensation produced by an increase in intragastric tension.¹ This is produced by characteristic contractions of the empty or nearly empty stomach beginning in the fundic region. Physical attitudes and local pathologic conditions, as ulcer or pyloric constriction, interpret tension as pain.²

Stomach activity is influenced by peripheral nervous control.³ The vagus nerve carries impulses stimulating tone and peristalsis; the splanchnics contain inhibitory fibers. By these two paths central action is exerted. It has been found, however, that with both vagi and splanchnics sectioned the stomach regains the tone temporarily lost, and the typical muscular activity of the stomach is resumed. This suggests a mechanism inherent in the stomach itself which regulates motor activity. The anatomic basis of such a system may be found in a nodal system which Keith⁴ has recently described in the stomach wall comparable to the nodal system of the heart.

Manipulation of the hunger contractions has been carried out by changing mental states and the administration of various substances. Excitement, fear and anger inhibit hunger.⁵ This comes well within the experience of the individual. Tracings from the stomach demonstrate that the hunger contractions in these conditions are inhibited. Water, acids, alkalis, and food taken by mouth or placed directly into

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† Mr. Ginsburg died during the course of the work for which he furnished the inspiration.

1. Carlson: Am. Jour. Physiol., 1913, **31**, 175.

2. Haytz: Sensibility of the Alimentary Canal, London, 1913, p. 47. Ginsburg, Tumpowsky and Hamburger: Jour. Am. Med. Assn., 1916, **67**, 990. Hardt: Jour. Am. Med. Assn., 1918, **70**, 837.

3. Carlson: Am. Jour. Physiol., 1913, **32**, 369.

4. Keith: Lancet, London, 1915, **2**, 371.

5. Carlson: Am. Jour. Physiol., 1913, **32**, 376.

the stomach by tube or through a fistula also inhibit contractions.⁶ Fever associated with anorexia inhibits contractions,⁷ while in the cachexia of advanced pulmonary tuberculosis with chronically high temperature they may be extremely vigorous.⁸ In starvation⁹ and experimental pancreatic diabetes¹⁰ contractions are marked. The effects of drugs on stomach activity has not been emphasized nearly to the degree that the intestine has been studied from this standpoint. Some facts in this regard have already been established clinically. The present work was undertaken to determine the effects of various common drugs on the hunger contractions by the use of the balloon method.

EXPERIMENTAL METHODS

Gastric fistulae were produced in twelve dogs, and in four of these both vagi and splanchnics were cut. In the latter cases it has been found advisable to section the splanchnics first, inasmuch as this part of the preparation is the most difficult and attended with the greatest fatality. The major splanchnic is severed as it emerges from the diaphragm. On the left side it lies lateral to the adrenal, running toward the gland parallel with the large adrenal vein. The right splanchnic is more difficult to obtain because the liver hampers good exposure and the nerve very frequently lies beneath the vena cava. Hemorrhage from the many small retroperitoneal veins about the adrenal makes the operation more difficult because other structures are easily mistaken for the nerve. Occasionally pneumothorax is produced by exploring the edge of the diaphragm, but this is not fatal. In about two weeks the vagi may be severed. Incision is made in the eighth or ninth interspace on the left side and somewhat posteriorly. The esophagus is hooked up through the interspace; the right and left vagus lying posteriorly and anteriorly, respectively, are grasped in a hemostat and a piece excised. All branches are similarly treated, and the wound is quickly closed. If the operation is done hurriedly, that is to say, two or three minutes elapsing from opening to closure of the pleural cavity, artificial respiration is not necessary. In fact, we used artificial respiration but twice, and lost but one animal at this stage, an accident which, with the technic developed subsequently, might have been avoided. If the animal shows signs of difficulty the edges of the wound may be approximated with the fingers until respirations become more regular, and the operation may then pro-

6. Carlson: *Am. Jour. Physiol.*, 1912, **31**, 151, and 1913, **32**, 389.

7. Meyer and Carlson: *Am. Jour. Physiol.*, 1917, **44**, 222.

8. Meyer, Jacob: *Contribution, Hunger in Tuberculosis*, to be published.

9. Carlson: *Am. Jour. Physiol.*, 1914, **33**, 95.

10. Luckhardt: *Am. Jour. Physiol.*, 1914, **33**, 313. Luckhardt and Hamburger: *Jour. Am. Med. Assn.*, **66**, 1831.

ceed. In one case the heart stopped pulsating for about one minute. By rapid and vigorous massage of the heart directly with two fingers through the intercostal space to imitate as nearly as possible the force and rate of the heart, pulsations recovered slowly and very feebly at first, finally at the usual rate and strength as near as one could determine. The dog recovered and lived many weeks, dying from respiratory infection. This result could not be repeated in other conditions and was probably due to recovery from reflex stimulation of the vagus. The gastric fistula was made through the left rectus to make use of the valve action of that muscle. A cone of stomach was drawn through the opening and the serosa stitched to the peritoneum, fascia and skin by three or four stitches in each layer. The apex was opened and the mucosa tacked to the serosa by three loose stitches.

The drugs were used on both sets of animals, those with the "intact" stomach having the nerves intact, and those with the "isolated" stomach having the peripheral nerves sectioned. The animals were easily trained to lie on the laboratory tables in a moderately darkened room with a towel covering the head to keep out the light and prevent their disturbance from such outside factors as the presence of others in the laboratory and the manipulations of the observer. It was possible in this way to have four animals running together while a single observer manipulated the kymographs, administered the drugs and recorded observations. One finds that the dogs will lie on the plain, uncovered table, not requiring soft blankets. They become so accustomed to the routine that they choose the proper laboratory by preference when released from the kennels, and lie quietly until the balloon is removed from the stomach at the end of the observation, when they sense their liberty and jump from the table. The animals are so astonishingly quiet during observations that other workers coming into the room unfamiliar with the work think the dogs are anesthetized. Subcutaneous and even intravenous injections may be made without disturbing the animal. One can, unassisted, apply the constrictor to the leg, plunge the needle into the vein, remove the constrictor and inject without causing the animal to change his position. Hypodermic and intramuscular injections require no assistance.

RESULTS

Atropin.—Auer and Meltzer¹¹ assert that atropin causes paralysis of the vagus endings connected with the ganglia of Auerbach's plexus and that the action is on the myoneural junction. Cushny¹² believes that the terminations are not paralyzed, because small doses only arrest

11. Auer and Meltzer: *Am. Jour. Physiol.*, 1906, **17**, 17.

12. Cushny: *Pharmacology and Therapeutics*, Philadelphia and London, 1913.

Fig. 1 Atropine 1 mg given subcutaneously, causing complete abolition in seven minutes lasting hours

certain abnormal violent forms of contractions without interfering with normal peristalsis. He also says that larger doses increase, and very large doses paralyze, the latter probably never occurring in the intact animal. Clinically, belladonna relieves some spasmodic conditions of the stomach by paralyzing the vagus and allowing unopposed action of the splanchnics.¹³ Fluoroscopic examination has shown that

TABLE 1.—ATROPIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/80	Inhibition	7		
Intact	Subcuta- neous	1/80	Inhibition	10		
Intact	Subcuta- neous	1/80	Inhibition	14		Eserin, 1/80 grain given 23 minutes after inhibition began yielded contractions in 23 minutes
Intact	Subcuta- neous	1/70	Inhibition	8	3 hrs. 40 min. then contractions	Occasional contractions "escaped"
Intact	Subcuta- neous	1/70	Inhibition	5		
Intact	Subcuta- neous	1/60	Inhibition	7	1 hr. 40 min. +	
Intact	Subcuta- neous	1/60	Inhibition	5	1 hr. +	36 minutes after pilocarpin 1/6 grain
Intact	Subcuta- neous	1/60	Inhibition	5		1 hour 30 minutes after eserine 1/60 grain
Intact	Subcuta- neous	1/50	Inhibition	4	30 min. +	
Intact	Subcuta- neous	1/100	Inhibition	8		50 minutes after pilocarpin 1/12 grain
"Isolated"	Subcuta- neous	1/50	Inhibition	8	1 hr. +	17 minutes after pilocarpin 1/6 grain
"Isolated"	Subcuta- neous	1/40	Inhibition	8	4 hrs. +	Pituitary extract (Armour) ampule intravenously; 3 hours after followed by small infrequent contractions
"Isolated"	Subcuta- neous	1/40	Inhibition	10	1 hr. 20 min. +	1 hour 52 minutes after pilocarpin 1/6 grain

often the spasm is suddenly relieved, while in other cases shown to be spasmodic by the massage test, it has no effect. Hertz¹⁴ says that belladonna is remarkably efficient in hour glass contractions of spasmodic origin and may even relieve spasm in the presence of active ulceration. In our work atropin sulphate in doses from $\frac{1}{80}$ to $\frac{1}{40}$ grain hypodermically invariably inhibited contractions and counteracted the

13. Barclay: Alimentary Tract: A Radiographic Study, New York, 1915, p. 17.

14. Hertz: See reference Footnote 2, p. 76.

effect of pilocarpin and eserine in this regard. The time of action is quite constantly between five and ten minutes. The inhibition is sudden, decisive and persists for hours. Occasionally a few undulations "escape." Otherwise the tracing records only the respiratory oscillations. The fact that the same results obtain in "isolated" stomach indicates that the action is on the myoneural junction.

TABLE 2.—PILOCARPIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/5	Increased tonus	8	20 min.	35 minutes after epineph- rin (adrenalin), 2 c.c. 1:10,000 intravenously and subcutaneously
Intact	Subcuta- neous	1/5	Contraction- s	5	45 min. +	
Intact	Subcuta- neous	1/75	No effect			Gradual increase after second dose
Intact	Subcuta- neous	1/75	Slight in- crease		2 hrs. +	
Intact	Subcuta- neous	1/6	Contraction- s	8	1 hr. 30 min. +	Gradual increase in tonus preceded the contraction- s, later inhibited by atropin
Intact	Subcuta- neous	1/12	Contraction- s	15	50 min.	Inhibited by subsequent atropin
Intact	Subcuta- neous	1/12	Contraction- s	9		40 minutes after pituitary extract
"Isolated"	Subcuta- neous	1/6	Contraction- s	8	1 hr. 30 min. +	Increase in tonus preced- ed contraction- s; inhibited by subsequent atropin
"Isolated"	Subcuta- neous	1/5	Contraction- s	6	1 hr.	46 minutes after eserine 1/40 grain
"Isolated"	Subcuta- neous	1/6	Contraction- s	3		Inhibited by atropin 20 minutes later

Pilocarpin.—Sollmann¹⁵ says that the myoneural junctions paralyzed by atropine are stimulated by pilocarpin. In doses from $\frac{1}{12}$ to $\frac{1}{5}$ grain hypodermically the contractions are augmented, accompanied by diminished pulse rate. With the change in pulse rate as a criterion for absorption it could be determined that absorption occurred in seven to ten minutes. The contractions were inhibited by subsequent atropine in the usual five to ten minutes. The same effect was noted with section of the nerves, confirming Sollmann's opinion that pilocarpin is effective even after degeneration of the nerves.

Eserine.—Stimulation is produced by eserine, particularly by intravenous administration. In subcutaneous injections there is often a long latent period before activity begins, but activity remains as long as four hours. Again, as with pilocarpin, coincident with the gastric

15. Sollmann: Manual of Pharmacology, 1917, p. 299.

Fig. 2A. Film, 10 gram substance only, causing marked contractions lasting an hour and a half.

Figure 2B.

manifestations, in the experiments the pulse rate fell as low as 50 beats per minute, and gradually returned to normal with abolition of the gastric effects. Inasmuch as similar effects were obtained on the "isolated" stomach, the work confirms the belief that eserine also acts on the nerve endings.

TABLE 3.—ESERIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/60	Contraction	6	1 hr. 30 min.+	For 1 hour contractions unusually strong
Intact	Subcuta- neous	1/100	Contraction	6	2 hrs.+	
Intact	Subcuta- neous	1/50	Contraction	2	40 min.	Very strong contractions; may have been oncoming regular period
Intact	Subcuta- neous	1/60	Contraction			
Intact	Subcuta- neous	1/60	No contraction			Administered 19 minutes after atropin 1/60 grain
Intact	Subcuta- neous	1/60	Contraction	6	1 hr. 35 min.	Inhibited by atropin
Intact	Subcuta- neous	1/100	Contraction	5		
Intact	Subcuta- neous	1/80	Contraction	20	30 min.	37 minutes after atropin 1/80 grain
Intact	Subcuta- neous	1/80	Contraction	23	4 min.	2 hours 32 minutes after preceding eserine
Intact	Subcuta- neous	1/60	Contraction	14	12 min.	39 minutes after preceding eserine
Intact	Intrave- nous	1/100	Contraction	5		Moderate increase with tonus undulations
Intact	Intrave- nous	1/100	Contraction	4		Large tonus undulation
"Isolated"	Intrave- nous	1/100	Contraction	35		Periodic sequence
"Isolated"	Intrave- nous	1/50	Contraction	7	4 hrs.+	Marked increase
"Isolated"	Subcuta- neous	1/40	Contraction	5		Increased tonus
"Isolated"	Subcuta- neous	1/40	Contraction	15	2 hrs.+	
"Isolated"	Subcuta- neous	1/50	Contraction	5	3 hrs. 15 min.+	
"Isolated"	Subcuta- neous	1/40	Slight contraction	20		

Cocain.—In general, it is asserted that cocaine first stimulates, then depresses smooth muscle regardless of innervation.¹⁶ Cushny¹⁷ believes that it paralyzes the local nervous mechanism. Profound inhibition occurs with doses of 1 c.c. of 0.5 per cent. solution of cocaine per

16. Sollmann: Manual of Pharmacology, 1917, p. 252.

17. Cushny: Pharmacology and Therapeutics, 1913, p. 308.

Fig. 3.—Cocain, 1 c.c. of 1 per cent. per kilogram subcutaneously, causing profound inhibition lasting over two hours.

kilogram. The tracings give a striking picture demonstrating why cocain allays the hunger pangs.

TABLE 4.—COCAIN

Stomach	Adminis- tration	Dose	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Intrave- nous	3 c.c. 0.5% 7.8 kg.	Inhibition	1	30 min.+	Lowered tonus; increased respiratory rate
Intact	Subcuta- neous	1 c.c. 0.5% per kg.	Inhibition	10	2 hrs.+	Lowered tonus; active period shortened
Intact	Subcuta- neous	1 c.c. 0.5% per kg. 14 c.c.	Inhibition	26	1 hr. 30 min.+	Given in active period; preliminary rise in tonus and contractions; then lowered tonus and con- tractions and increased respirations
Intact	Subcuta- neous	0.5 c.c. 1% per kg. 5 c.c.	Slight in- hibition	45	1 hr.+	Given in moderately ac- tive period; low degree contractions
Intact	Subcuta- neous	1 c.c. 1% per kg. 9.2 c.c.	Inhibition	15	2 hrs.+	Marked salivation; ani- mal licking nose
Intact	Subcuta- neous	1 c.c. 1% per kg. 8 c.c.	Inhibition	10	2 hrs. 30 min.+	Never regains usual vig- orous contractions
Intact	Subcuta- neous	1 c.c. 1% per kg. 7 c.c.	Inhibition			Gradually appearing low- ered tonus and increased respirations
Intact	Subcuta- neous	1 c.c. 1% per kg. 11 c.c.	Inhibition	18	2 hrs.+	Marked result
Intact	Subcuta- neous	1 c.c. 1% per kg. 9 c.c.	Inhibition	6	2 hrs.+	Marked result
Intact	Subcuta- neous	1 c.c. 1% per kg. 9.2 c.c.	Inhibition	10	2 hrs.+	Marked result
"Isolated"	Subcuta- neous	1 c.c. 1% per kg. 11 c.c.	Slight in- hibition	15	2 hrs.+	Lowered tonus 15 min- utes; active 30 minutes then rest 2 hrs.+
"Isolated"	Subcuta- neous	1 c.c. 1% per kg. 11 c.c.	Slight in- hibition			Increased tonus at first as if remnant of an ac- tive period; then lowered tonus and inhibition
"Isolated"	Subcuta- neous	0.5 c.c. 1% per kg. 5.5 c.c.	Slight in- hibition	12	1 hr. 30 min.+	Increased respiration; lowered tonus; later complete inhibition for 1 hour 30 minutes

Camphor.—Camphorated oil was administered to determine whether its stimulating effect on the central nervous system is reflected in any manner in the activity of the stomach. The stimulating effect observed is only obtained when the drug is administered intramuscularly. In large doses the contractions appear to become more frequent and intense, and the period of activity is prolonged.

Strychnin.—As widely employed as strychnin is for its tonic value, there has been no experimental evidence for its supposed gastric effect.

TABLE 5.—CAMPBOR

Stomach	Adminis- tration	Dose, Grain	Result	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1	No change		Given at beginning of active period contractions began lasting 1 hour 20 minutes
Intact	Subcuta- neous	2	Increased activity	2 hrs.+	Given at beginning of increased tonus; contractions began in 4 minutes and lasted 2 hours +
Intact	Intramus- cular	3	No change		Given during rest period and ob- served for 45 minutes
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr.+	Given in active period; contrac- tions became more frequent and intense and period prolonged
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contrac- tions became more frequent and intense and period prolonged
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contrac- tions became more frequent and intense and period prolonged
Intact	Intramus- cular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contrac- tions became more frequent and intense and period prolonged
"Isolated"	Intramus- cular	3	Increased and prolonged activity	2 hrs.+	Given in active period; contrac- tions became more frequent and intense and period prolonged
"Isolated"	Intramus- cular	3	Increased and prolonged activity	1 hr. 30 min.+	Given in active period; contrac- tions became more frequent and intense and period prolonged
"Isolated"	Intramus- cular	3	Contractions	2 hrs.+	Given during rest period; contrac- tions began in 10 minutes, lasting 2 hours +

TABLE 6.—STRYCHNIN

Stomach	Adminis- tration	Dose, Grain	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1/60	Contra- ctions	5	3 hrs.	Increased excitability
Intact	Subcuta- neous	1/60	Contra- ctions	2	1 hr. 30 min.	Prolonged active period
Intact	Subcuta- neous	1/60	Contra- ctions	5	2 hrs.	Moderate but prolonged increase
Intact	Subcuta- neous	1/60	Contra- ctions		45 min.	Given in active period; in- creased contractions but diminished when mild spasms began
Intact	Subcuta- neous	1/60	Contra- ctions	15	1 hr.	Moderate increase; dimin- ished when spasms began
Intact	Subcuta- neous	1/60	Contra- ctions	5	2 hrs.+	Marked increase; given in active phase
Intact	Subcuta- neous	1/90	Contra- ctions	10	1 hr.	Given 1 hour after 1:30,000 epinephrin applied to surface of gastric fistula
Intact	Subcuta- neous	1/100	No con- traction			Given 1 hour after 1:30,000 epinephrin to nasal mu- cosa
"Isolated"	Subcuta- neous	1/60	Slight con- traction			Low grade contractions with no definite active or inactive periods for 2½ hours
"Isolated"	Subcuta- neous	1/60	Contra- ctions		1 hr. 30 min.	Given in active period; increased tonus and con- tractions
"Isolated"	Subcuta- neous	1/60	Contra- ctions	6	1 hr. 30 min.	
"Isolated"	Subcuta- neous	1/90	Contra- ctions	8	2 hrs.	

It is the usual conception that it increases the tone of the centers regulating the gastro-intestinal tract. With doses of $\frac{1}{90}$ to $\frac{1}{60}$ grain subcutaneously, stomach tonus was increased, but at the same time the general excitability of the animal was increased so that the increased height of the writing level may have been due to the increased tonus of the abdominal muscles. At the same time, however, there appears to be a definite increase in the hunger contractions themselves. Pollak¹⁸ says that strychnin probably has no effect in ordinary doses given hypodermically. Direct application to Auerbach's ganglia causes stimulation.¹⁹

TABLE 7.—AMYL NITRITE

Stomach	Adminis- tration	Dose, Minims	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Inhala- tion	10	Temporary inhibition	Imme- diate	5 min.	Slightly lowered tonus
Intact	Inhala- tion	10	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min.	
Intact	Inhala- tion	10	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min.	
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min.	Inhibition while animal struggled against inhal- ing the drug; but a large contraction; "escaped"
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate		Only one of the regularly appearing contractions was inhibited 15 minutes after preceding dose
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min.	
Intact	Inhala- tion	5	Temporary inhibition	Imme- diate	$\frac{1}{2}$ min.	
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	5 min.	Lowered tonus slowly restored
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	5 min.	Given in active phase; lowered tonus quickly restored
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate		Persistent low tonus; no contractions
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	15 min.	Given 55 millimeters after preceding dose
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	4 min.	
"Isolated"	Inhala- tion	5	Temporary inhibition	Imme- diate	10 min.	Original tonus very slowly restored

Amyl Nitrite.—Hirschfelder²⁰ says that systemic administration of nitrites relaxes the constriction produced by lead salts, although this

18. Pollak: Biochem. Centralbl., 1910, **10**, 199.

19. Langley and Magnus: Jour. Physiol., 1905-1906, **33**, 37.

20. Hirschfelder: Jour. Am. Med. Assn., 1915, **65**, 516.

Fig. 4. Strychnine, 100 grain subcutaneously, causing increase in tone and contractions.

Fig. 5. Amyl nitrite, 5 minutes by inhalation, causing only slight temporary inhibition, as shown between 2 and 3.

treatment for lead colic is not successful. Inhalation of 5-minim pearls often repeated after short intervals causes only a temporary inhibition which disappears as soon as the drug is removed from the nostril. The effect may be psychic, but the contractions which follow are not reduced in frequency, intensity or duration. In animals with the nerves sectioned the same inhibition is observed, but after removal of the drug the tonus remains depressed for a long time, only gradually returning to its original height.

TABLE 8.—EPINEPHRIN

Stomach	Adminis- tration	Dose	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Intrave- nous	1 c.c. 1:10,000	Inhibition	Imme- diate	1 hr.+	
Intact	Intrave- nous	1 c.c. 1:10,000	Inhibition	Imme- diate	1 hr.	
Intact	Intrave- nous	1 c.c. 1:10,000	Inhibition	1		Also lowered tonus
Intact	Intrave- nous and subcut.	2 c.c. 1:10,000	Inhibition	8	2 hrs.+	Lowered tonus; later complete inhibition
Intact	Raw sur- face of fistula	1:30,000	Inhibition	3	2 hrs.+	Lowered tonus
Intact	Nasal mu- cosa	1:30,000	No effect			
"Isolated"	Subcuta- neous	1 c.c. 1:10,000	Lowered tonus	10		
"Isolated"	Intrave- nous	10 min. 1:10,000	Inhibition	Imme- diate	40 min.	
"Isolated"	Intrave- nous	10 min. 1:10,000	Inhibition	1	1 hr.+	
"Isolated"	Intrave- nous	20 min. 1:15,000	Inhibition	2	1 hr.	
"Isolated"	Intrave- nous	4 c.c. 1:25,000	Inhibition	5	1 hr.+	Period of tetany pre- ceded inhibition

Epinephrin.—Administration of adrenalin (Parke, Davis & Co.) causes prompt and marked inhibition of the hunger contractions. This action should be expected because of its property of stimulating the nerve endings of the sympathetic system. The consequent stimulation of the splanchnic endings counteracts the augmentatory effects acting through the vagi. Meyer and Gottlieb²¹ say that epinephrin by mouth and by hypodermic injection is ineffective, and when given intravenously acts only a few minutes. Our tracings show that the inhibitory effect on the hunger contractions when the drug is given intravenously may last much longer. Enough of a 1 to 30,000 solution was absorbed from the eroded surfaces about the gastric fistula to

21. Meyer and Gottlieb: Text Book, Philadelphia and New York, 1914, p. 188.

cause inhibition. Subcutaneous injection gives a slower response. Inhibition also occurs with the "isolated" stomach, since it is known that the physiologic nerve endings stimulated by epinephrin do not degenerate on section of the nerves, so that the epinephrin effect may persist for weeks.

TABLE 9.—ERGOT

Stomach	Adminis- tration	Dose, Ampule	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1	Increased contract	5	1 hr.	Increased tonus undula- tions
Intact	Intramus- cular	1	Marked in- crease	21	1 hr. 30 min.	Unusual steplike rise with great tonus, short rest, then activity
Intact	Intrave- nous	½	No effect			Two large contractions, then inhibition followed by active period
Intact	Intrave- nous	1	Temporary inhibition	1	3 min.	Given in active period; subsequent contractions lowered tonus
Intact	Intrave- nous	1	Temporary inhibition	1	3 min.	Lowered tonus for 30 min- utes; return of contrac- tions for 2 hours +
Intact	Intrave- nous	1	Temporary inhibition	1	3 min.	Lowered tonus following
"Isolated"	Intrave- nous	1	Temporary inhibition	1	3 min.	
"Isolated"	Intrave- nous	1	Contra- ctions	1	1 hr. 30 min.	Almost immediate step- like rise with enormous tonus well sustained
{ "Isolated"	Intrave- nous	½	No effect			
	Intrave- nous	1	Contract	3	2 hrs.+	28 minutes after preced- ing, followed by steplike rise lasting 2 hours +
	Subcuta- neous	1	No effect			Given in midst of active period; contractions fol- lowed 1½ hours +

Ergot.—It has been found that intravenous injections of the fluid-extract of ergot causes an increase in the spontaneous movements of the alimentary tract.²² The motor responsiveness to vagus stimulation was also increased. Later, Meltzer and Githens²³ injected 10 mg. of ergotoxin into rabbits and obtained the same results. Using ampoules of ergot intravenously, we usually obtained a temporary inhibition followed by lowered tonus, although contractions ensued. Intramuscular injection in one instance gave a tremendous steplike rise, with extremely high tonus level, followed by a short rest, and then another active period. The same observation was made on injection of an ampoule intravenously in an "isolated" stomach twenty-eight minutes after a similar injection of one-half ampoule.

22. Meltzer and Auer: Am. Jour. Physiol., 1906, **17**, 143.

23. Meltzer and Githens: Proc. Soc. Exper. Biol. and Med., 1916, **13**, 87.

Fig. 6. Ergot, 1 ampoule intravenously, with almost immediate steplike rise, with well-sustained, marked tonus.

Fig. 7. Pituitrin (P. D. & Co.), 3 minims intravenously, with prompt inhibition.

Pituitary Extract.—It is commonly believed that pituitary extracts stimulate smooth muscle regardless of innervation, and it is given in paralytic distentions.²⁴ In the experiments reported the effect of pituitary preparations was remarkably like that of epinephrin. Immediately after injection inhibition occurs. Parke, Davis & Co.'s pituitrin and Armour's pituitary liquid were used with similar results, although

TABLE 10.—PITUITARY EXTRACT

Stomach	Adminis- tration	Dose	Result	Latent Interval, Minutes	Dura- tion of Effect	Remarks
Intact	Subcuta- neous	1 c.c. (P.D.Co.)	Slight in- hibition	7	30 min. +	Given during moderate contractions
Intact	Subcuta- neous	1 c.c. (Armour)	No effect		30 min.	Given in quiescent period
Intact	Intrave- neous	1 c.c. (P.D.Co.)	Inhibition	Almost Imme- diate	30 min. +	
Intact	Intrave- neous	5 min. (P.D.Co.)	Inhibition	Almost Imme- diate	1 hr.	
Intact	Intrave- neous	3 min. (P.D.Co.)	Inhibition	Almost Imme- diate	30 min. +	
Intact	Intrave- neous	0.5 c.c. (Armour)	Inhibition	Almost Imme- diate	30 min.	After 30 minutes slowly developing contractions appeared
Intact	Intrave- neous	1.0 c.c. (Armour)	Inhibition	Almost Imme- diate	1 hr.	Occasional low grade con- tractions appeared
"Isolated"	Subcuta- neous	1.0 c.c. (Armour)	No effect			Given in an active period
"Isolated"	Subcuta- neous	1.0 c.c. (P.D.Co.)	Inhibition	16		Given in an active period
"Isolated"	Intrave- neous	1.0 c.c. (Armour)	No inhibi- tion			Periodic contractions although infrequent, oc- curred after administra- tion
"Isolated"	Intrave- neous	1.0 c.c. (P.D.Co.)	Inhibition	Almost Imme- diate	1 hr.	Subsequent active period short
"Isolated"	Intrave- neous	10 min. (P.D.Co.)	Inhibition	Almost Imme- diate	2 hrs.	Given in middle of active period
"Isolated"	Intrave- neous	5 min. (P.D.Co.)	Inhibition	Almost Imme- diate	1 hr.	Given in beginning of ac- tive period

both preparations caused a rise in blood pressure when tested on crucial animals. In accordance with these results are the results of Bayer and Peter,²⁵ who noted that pituitrin and also fresh extract of the pituitary body might inhibit the movements and tone of rabbits' isolated intestinal loop. Shamoff²⁶ and Hoskins²⁷ found that the intes-

24. Sollmann: Manual of Pharmacology, 1917, p. 339.

25. Bayer and Peter: Arch. f. exper. Path. u. Pharmacol., 1911, **64**, 209.

26. Am. Jour. Physiol., 1915-1916, **39**, 268.

tinal action varies greatly in different preparations, some even relaxing like epinephrin. Even extracts of fresh glands gave this result, although blood pressure tests were normal. The effects of pituitrin were remarkable in their inhibitory effects. Having determined the length of the periods by mere recording without administering the drug, one could observe that administration of pituitrin cut short the active period so that the subsequent rest period equaled the rest period usual for that animal on that particular day plus the "inhibited" portion of the previous active period arrested by pituitrin. By repeating the drug one could predict with surprising accuracy about the time of onset of the next active period. It appears, therefore, that the action of pituitrin is of short duration.

COMMENT

To preserve the conditions of experimentation as nearly constant as possible the records were taken about 1 p. m., running on until about 5 p. m. The dogs were then fed and given nothing else but water until after the next observation at the same hour on the next day. To obtain more accurate results the drugs were given by routes enabling prompt absorption and action so that the change in the picture of gastric motility might be referred to the manipulation. Observations were made for some time before injections to determine whether the stomach was in a period of rest or activity. Only in this way, recording several periods, can the observer decide that he is dealing with the beginning of a rest or active period as the case may be. By observing the periodicity the time interval may be determined so that one may conclude fairly regarding the effects of the drug. For instance, if a drug is administered at the end of an active period the subsequent rest period may be fallaciously ascribed to the drug. In any work involving the hunger contractions it is of prime importance to determine the phase of gastric motility and repeat the manipulation during different phases. There still remains a large field for intensive experimentation with drugs by varying the preparations and dosages, studying the intestinal movements simultaneously and checking results with observations on the other pharmacologic effects of the drug employed, which the exigencies of the present situation prevent the authors from surveying.

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27. Hoskins: Jour. Am. Med. Assn., 1916, **66**, 732.