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CARDIOVASCULAR AND BLOOD VOLUME ALTERATIONS RESULTING FROM INTRAJEJUNAL ADMINISTRATION OF HYPERTONIC SOLUTIONS TO GAS-TRECTOMIZED PATIENTS: THE RELATIONSHIP OF THESE CHANGES TO THE DUMPING SYNDROME*

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THE SIGNS AND SYMPTOMS associated with the dumping or postgastrectomy syndrome consist of a sensation of fullness and churning in the epigastrium followed by or associated with weakness, sweating and tachycardia, and tachypnea, pallor and an elevated blood pressure. The onset of symptoms, in most instances, occurs within 15 to 20 minutes after the ingestion of food or hypertonic solutions, and lasts approximately 60 to 90 minutes. In more severe cases, there may be an associated diarrhea and vomiting.^{3, 4, 15, 19, 20, 22, 24, 28, 32, 33} Although it has become increasingly apparent that the cardiovascular manifestations and the associated sweating, pallor and weakness are sympathetic in nature, the mechanism whereby this sympathetic response is elicited has not been clearly defined.

It has been shown that the ingestion of a variety of hypertonic solutions accurately re-

produces the dumping syndrome in partially gastrectomized patients.^{13, 19, 20} Intrajejunal administration of hypertonic solutions in patients with a jejunostomy or in patients with stomach intact produces a similar chain of events.^{19, 20} On the basis of the intestinal distention and increased motility consequent to the dilution of the hypertonic solution, it has been postulated that there is mechanical stimulation of the splanchnic nerves resulting in a sympathetic response.³³ Impetus to the theory implicating mechanical distention of the jejunum is given by those reports which state that balloon distention of the jejunum results in the characteristic symptomatology.^{2, 19} Attempts to block the splanchnic stimulus by means of splanchnicectomy or the use of pharmacologic blocking agents have not, however, been uniformly successful,^{3, 4, 24} nor does mechanical distention of the jejunum consistently result in typical dumping symtoms.³

Evidence that the dumping syndrome may result from metabolic disturbances has been presented; Smith²⁹ has shown a drop in plasma potassium and phosphate, as well as electrocardiographic changes characteristic of hypokalemia in partially gastrectomized patients following carbohydrate meals; from such findings he has postulated that the symptomatology is related to hypo-

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Case	Solution Administered	Control Values				Maximum Change			
		Plasma Volume c.c.	Hemato- crit Se	Blood Volume c.c.	Red Cell Mass	Plasma Volume c.c.	Hemato- crit %	Blood Volume c.c.	Red Cell Mass
L. C.	150 c.c. 50% glucose	2700	36	4219	1519	2180	38.5	3545	1365
N. Z.	150 c.c. 50% glucose	2660	35	4095	1435	1843	39.0	3020	1177
J. M.	200 c.c. 50% glucose	3500	44	6250	2750	2780	49.0	5451	2671
B. M.	100 c c. 9% saline	3140	41	5320	2180	2610	46.0	4830	2220
A, C.	130 c.c. 9% saline	2200	48	4230	2630	1795	51.0	3660	1865
ejunostomy)								
N. F.	200 c.c. 50% glucose	3320	38	5355	2035	2540	42.0	4380	1840
			Patients wi	ith Stomach	Intact				
M. W.	150 c.c. 50% glucose	2200	38	3545	1345	2200	38.0	3545	1345
O. A.	150 c.c. 50% glucose	2400	40	4000	1600	2400	40.0	4000	1600
W. M.	150 c.c. 50% glucose	2520	42	4345	1825	2520	42.0	4345	1825
P. P.	150 c.c. 50% glucose	3480	43	6100	2620	3480	43.0	6100	2620

*Maximal alterations in red cell volume, plasma volume, and blood volume which occurred following injection of hypertonic solutions. Explanation in text.

kalemia. Pontes²³ has implicated the adrenal cortex in the dumping syndrome on the basis of a drop in eosinophile counts and urinary retention of sodium and chloride.

Such varied and diverse reports concerning the mechanism of the dumping syndrome serve to emphasize the complexity and the possible interrelationship of events which occur following the intrajejunal administration of foodstuffs. It occurred to us that all of the factors implicated in this syndrome might profitably be studied with an attempt to correlate mechanical, metabolic and subjective factors. With this in mind the studies described below were undertaken in a group of gastrectomized and normal patients: (1) to define the time sequence in which the physiological alterations occur, and (2) to inquire into the mechanisms implicated in bringing about the cardiovascular and sympathetic manifestations of the dumping syndrome.

METHODS

Forty-seven experiments were performed on a total of 21 patients. Ten of these patients had undergone total gastrectomy, four were subtotal gastrectomies, one had a feeding jejunostomy, and the remaining six patients had intact stomachs and served as controls. The studies consisted of serial electrocardiograms, blood pressure measurements, plasma volume, hematocrits, pH and plasma concentrations of sodium, potassium, chloride, glucose, phosphate and bicarbonate. In four gastrectomized patients, simultaneous studies of renal function, electrolyte excretion and eosinophiles were measured.

Following the control period, the patients were given hypertonic solutions or a test meal; and blood samples and electrocardiograms were taken at appropriate intervals. The solutions used in these experiments were: (1) 9 per cent sodium chloride, (2)50 per cent glucose, (3) a commercial dietary supplement (Sustagen),* or (4) starch. In some cases electrocardiograms were taken before and after a routine hospital meal; in these instances, no measurement of plasma volume could be made because of the interfering lipemia. Of major importance was the amount of solution used to precipitate the physiological alterations studies. To avoid the diarrhea which occurred with excessive amounts, it was necessary to quanti-

^{*} We wish to acknowledge the gift by the Mead Jolinson Company of a generous supply of Sustagen used in these experiments. This dietary supplement is composed of carbohydrates, 66.5 per cent; protein, 23.5 per cent; minerals, 4.0 per cent; fat, 3.5 per cent.

		Тав	le II.*		
		Plasma	-	Electro- cardio-	
Time	Sodium	Potassium mEq/L	Phosphat mg. %		
		J. M. (Ge	strectomiz	ed)	
Control	143.0	5.0	107	4.4	(
	142.0	5.0	108	4.4	(
		150 c.c. of	50% Glu	cose	
15	143.0	4.7	108	4.16	+++
30	143.0	4.35	107	4.16	++++
45	138.0	4.2	108		++++
60	137.5	4.1	107	3.5	+++
75	143.0	3.75	107	3.3	+ +
90	141.0	3.8	107	3.0	+
		A. C. (J	ejunostom	y)	
Control	142.0	4.1	104	4.54	C
	143.0	4.2	104	4.5	(
	15	0 c.c. of 9%	Sodium (Chloride	
10	140.0	4.15	104	4.54	+
20	145.0	3.9	107	4.56	+++
30	146.0	3.9	108	4.4	++++
60	149.0	3.8	112		++
90	147.0	3.9	112	4.4	(
		M. W. (St	omach Int	act)	
Control	141.0	4.2	116	4.6	(
	141.0	4.2		4.56	(
		150 c.c. of			
20	142.0	3.7	116	3.8	C
40	145.0	3.5	115	3.7	C
60	142.0	3.8	114	3.4	C
80	144.0	3.7	114	3.4	C

*Plasma Electrolytes and electrocardiographic alterations following: (1) oral administration of 50 percent glucose (150 cc.) to a patient with gastrectomy (J. M.), and a patient with intact stomach (M. W.) and (2) intrajejunal administration of 130 cc. of 9 perce⁻⁺t c⁺loride to a patient with a feeding jejunostomy (A. C.).

tate the solution given to each patient as that amount necessary to produce the sympathetic component without diarrhea; the amount of hypertonic solutions necessary in most instances ranged between 130 and 200 ml.

Plasma volume was determined with the use of Evans Blue dye, according to the indirect method of Gibson, *et al.*^{11, 12} The Evans Blue was given several hours previous to the time of study to ensure a steady falloff curve over a period of time approximately equal to the length of the experimental period. During the control period, three to four determinations of dye in the plasma were done to establish the slope of dye disappearance; following the adminis-

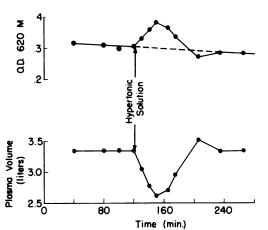


FIG. 1. Changes in plasma concentration of the dye (upper half) and in plasma volume (lower half) following the administration of hypertonic solution. Explanation in text. (Reproduced from Surgical Forum, 4: 301, 1945, by courtesy of W. B. Saunders and Company.)

tration of hypertonic solution, plasma values for dye concentration were determined at intervals of ten to 15 minutes for an appropriate length of time. During the dumping episode the deviation in dye concentration of plasma from the control disappearance slope represented the decrease in plasma volume (Fig. 1).

Serial electrocardiograms, including standard limb leads and augmented unipolar extremity leads, were taken with a Sanborn viso-cardiette; the electrodes were strapped in position during the control period and were not removed throughout the experimental period. Hematocrits were determined with the use of Van Allen hematocrit tubes. Blood and urinary constituents were done according to the following methods: chloride by the method of Van Slyke and Hiller;³¹ phosphate by the method of Fiske and Subbarow;⁹ inulin by the method of Roe;27 total carbon dioxide by the method of Van Slyke and Neill;³⁰ bicarbonate was determined utilizing the Henderson-Hasselbach equation; pH of whole blood and urine was determined with a Cambridge condenser-type glass electrode surrounded by a constant-temperature water jacket at 37 degrees C.; sodium and potassium were determined with an internal standard flame photometer.

RESULTS

Alterations in Blood Volume. Figure 1 shows graphically the method of study and the changes which occurred in the plasma concentration of dye and in plasma volume following the administration of hypertonic solutions. In the upper part of the graph, the optical density of the dye in the plasma

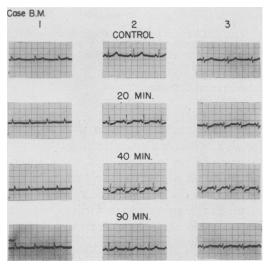


FIG. 2. Electrocardiographic alterations occurring in leads 1, 2, and 3 following hypertonic solution to a gastrectomized patient (B. M.).

is plotted; in the lower part are shown the changes in plasma volume, as calculated from the deviation in dye concentration of plasma from the prolongation of the control disappearance slope. From this it can be seen that there was a marked decrease in plasma volume which occurred within ten minutes, reached a maximum in 30 to 40 minutes, and returned to normal within a period of 100 to 120 minutes. Table I summarizes the maximum alterations in plasma volume, blood volume, and red cell volume which occurred following hypertonic solutions in five gastrectomized patients, one patient with a jejunostomy and four patients with intact stomachs. As shown in this table,

alterations in total blood volume and red cell volume occurred in conjunction with the loss of plasma volume. It was repeatedly observed that the hematocrit rose during the dumping episode; however, the rise in hematocrit, in many experiments, was not always in proportion to the change in plasma volume. Consequently, the red cell volume in these patients was also found to be slightly decreased. Although the cause of the apparent diminution of red cell mass is obscure, the observations of Bane, et al.,16 indicate that there may be a considerable number of red cells "trapped" in the vascular bed of the intestinal tract following the direct instillation of hypertonic solutions in dogs.

In those patients with intact stomachs, no change in plasma volume, hematocrit or blood volume occurred following the administration of hypertonic solutions in the amounts used in these experiments. Moreover, no symptoms were displayed by this group of patients.

Electrocardiographic Alterations. Within ten to 15 minutes following the administration of hypertonic solutions (or a routine hospital meal in some patients), alterations occurred in the electrocardiogram in patients exhibiting the dump syndrome. These changes were seen in all leads and consisted of an increase in cardiac rate, flattening of the T wave, elevation (or occasionally depression) of the ST segments, and sometimes the appearance of a U wave. These changes usually occurred within ten minutes, were maximal in 30 to 40 minutes, and returned to normal within a period of 80 to 120 minutes. In Figures 2 and 3, electrocardiographic changes are demonstrated. Figure 2 illustrates the changes which occurred in one patient in leads 1, 2 and 3. Figure 3 shows the alterations which occurred in lead 2 in six of the patients studied, and demonstrates that electrocardiographic alterations may be seen following hypertonic saline, glucose, Sustagen or a hospital meal. Similar electrocardiographic alterations were not observed, however, in those patients with

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stomach intact, tested with a similar amount of hypertonic solution.*

Plasma Electrolytes. Following the administration of a glucose load, there was a progressive fall in plasma potassium and utes. However, this was not a consistent finding in all patients studied. No alteration occurred in plasma pH. A significant drop in plasma concentration of potassium and phosphate did not occur following the ad-

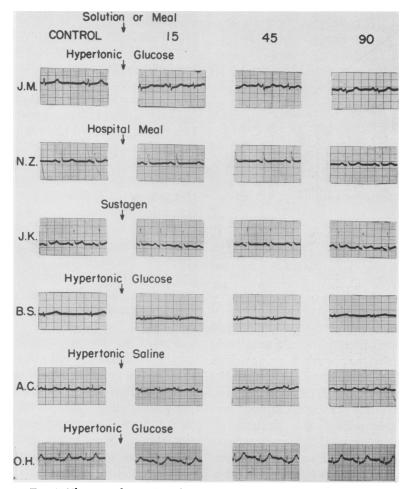


FIG. 3. Electrocardiographic alterations as illustrated in lead 2 at 15, 45, and 90 minutes, following the administration of various substances. (Reproduced from Surgical Forum, 4: 301, 1945, W. B. Saunders and Company.)

phosphate which reached its maximum in 75 to 80 minutes in the gastrectomized group and in the normal patients. In four patients studied, there was a transient drop in plasma chloride, sodium and bicarbonate at 60 min-

ministration of sodium chloride. Table II shows the typical plasma electrolyte alterations which occurred following the ingestion of: (1) hypertonic glucose in normals and in gastrectomized patients, and (2) saline in the gastrectomized group. Correlation of the electrocardiographic changes and the electrolyte alterations indicate that there is not a direct correlation between the two events. Although a decrease in plasma potassium

^{*} Although electrocardiographic alterations have been reported following meals and hypertonic solution in normal patients (14), amounts needed to precipitate these alterations were greater than the amount used in these experiments.

and phosphate occurred in the normal patients and in the gastrectomized group given glucose, only the latter patients showed electrocardiographic alterations. Furthermore, it was noted that electrocardiographic alterations occurred following the administration

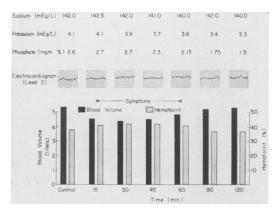


Fig. 4. Relationship between the changes in blood volume, the electrocardiogram, plasma electrolytes and symptomatology in a gastrectonized patient,* at 15, 30, 45, 60, 90, and 120 minutes, following oral ingestion of 200 cc. of 50% glucose. (Reproduced from Surgical Forum, 4: 301, 1945, W. B. Saunders and Company.)

of hypertonic saline to the gastrectomized group, although no significant alteration in plasma potassium or phosphate was evident.

Figure 4 summarizes the sequential changes which occurred in a patient who had a moderately severe dumping syndrome. In this patient, the electrocardiographic alterations, the blood volume changes and symptomatology occurred concurrently. Any alteration in plasma electrolytes occurred later, and were still evident at a time when the blood volume and electrocardiogram had returned to normal. Equivalent results were seen in 14 experiments on 11 patients.

Hypotonic Foodstuffs. Although the routine hospital meal given to these patients was found to be hypotonic or isotonic to the plasma, the electrocardiographic alterations and symptoms similar to those seen following hypertonic solutions were repeatedly observed following the meal. A decrease in blood volume following the ingestion of hypo- or isotonic substances would not be expected without rapid intrajejunal hydrolysis of food particles into smaller molecular components with a corresponding increase in osmolarity. For this reason, a series of experiments were carried out to determine the rate of breakdown of hypotonic solutions and the resultant effects on circulating blood volume. In these experiments, 150 to 200 Gm. of uncooked cornstarch was given to the patients, following which, serial determinations of blood glucose and blood volume were done for a period of two to three hours. Figure 5 shows the alterations which occurred in one of the patients studied. In this patient, as well as in five others, there was a decrease in blood volume and electrocardiographic alterations similar to those seen following the ingestion of hypertonic solutions. An indication of the rapidity of starch hydrolysis is shown by the closely paralleled blood glucose curves following the ingestion of equivalent amounts of starch or glucose.

Renal Excretion of Electrolytes. The renal excretion of sodium and chloride, as measured in four patients, was found to be decreased following the administration of hypertonic solutions. This finding is in keeping with reports already published.²³ That the decrease in the excretion of these ions was the result of increased reabsorption is evident from Table III. In the experiments shown here, an attempt was made to enhance the reabsorption of sodium and chloride by the administration of a sodium chloride load to precipitate the dumping syndrome. If the amount of electrolyte filtered is calculated as the product of the glomerular filtration rate and the plasma concentration, corrected for Donnan distribution, the amount reabsorbed is the difference between the quantities filtered and excreted. As shown in this table, the amount of sodium and chloride reabsorbed is increased whether calculated as total amount reab-

^{*} We are indebted to Dr. John Madden for referring this patient to us for study.

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DUMPING SYNDROME

			Urine					
		Plasma mEq/1	Filtered	Excreted	Reabsorbed			
Time Min.	Glomerular Filtration Rate c.c./min.		mEq/min.	mEq/min.	mEq/min.	mEq/100 c.c. Glomerular Filtrate	% of Filtered	
			(1)					
			SODIUM					
Control	68.7	138.0	9.007	0.116	8.89	12.94	98.7	
		150	c.c. 9% Sodium	Chloride				
30	49.6	142.0	6.91	0.092	6.60	13.29	98.7	
60	80.3	142.0	10.832	0.062	10.77	13.43	99.4	
			POTASSIUI	М				
Control	68.7	4.0	0.261	0.019	0.242	0.353	92.8	
		150	c.c. 9% Sodium	Chloride				
30	49.6	3.9	0.184	0.014	0.170	0.343	92.4	
60	80.3	3.8	0.290	0.015	0.275	0.344	94.8	
			CHLORIDE	3				
Control	68.7	108.0	7.8	0.118	7.68	11.17	98.5	
		150	c.c. 9% Sodium	Chloride				
30	49.6	111.0	5.78	0.093	5.68	11.48	98.3	
60	80.3	111.4	9.39	0.055	9.335	11.62	99.4	
			(2)					
			SODIUM					
Control	65.0	138.0	8.52	0.047	8.47	13.03	99.4	
			c.c. 9% Sodium		••••			
30	36.0	145.0	4.96	0.01	4.95	13.74	99.8	
60	0.03	147.0	11.17	0.008	11.16	13.95	99.9	
			POTASSIU					
Control	65.0	4.2	0.259	0,038	0.220	0.34	85.3	
		100	c.c. 9% Sodium					
30	36.0	4.0	0.1368	0.022	0.114	0.316	83.4	
60	80.0	3.9	0.296	0.035	0.2611	0.326	88.2	
		0	CHLORIDE		0.2011	0.020	00.2	
Control	65.0	104.0	7.098	0.042	7.056	10.85	99.4	
	00.0		c.c. 9% Sodium		7.000	10.00	<i>,,,</i> ,	
30	36.0	109.0	4.12	0.010	4.11	11.42	99.8	
60. . 	80.0	112.0	9.405	0.005	4.11 9.40	11.42	99.8 99.99	
	00.0	112.0	9.105	0.005	9.40	11.70	yy. 99	

TABLE III. Changes in the Renal Excretion of Electrolytes and Glomerular Filtration Rate Following the Intrajejunal Administration of Hypertonic Saline.

sorbed or as percentage reabsorbed. Of some interest was the finding that the increased reabsorption occurred in the face of a rising plasma level of these ions.

Eosinophiles. Because of those reports²³ implicating the adrenal cortex in the dumping syndrome, eosinophile counts were studied in four patients. In one patient, a minimal drop in eosinophiles occurred at the end of 90 minutes. In three others, no change was noted during the period of 60 to 90 minutes following the ingestion of hypertonic solutions.

Jejunal Distention. In three patients, balloon distention with air or water up to 200 cc. produced vague abdominal discomfort and nausea. In no instance was there any alteration in plasma volume, hematocrit, plasma electrolytes or the electrocardiogram. Similarly, the rapid administration of tap water or a barium-water mixture in amounts of 200 to 800 cc. failed to produce any alteration in the plasma or the electrocardiogram.

Symptomatology. Correlation of the symptoms which occurred in the gastrectomized patients showed that they occurred concomitantly with the alterations in blood volume and the electrocardiogram. Because of the limited number of patients in this series, no attempt was made to correlate the severity of the dumping syndrome clinically with the plasma alterations or the electrocardiogram. Of the group who did show cardiovascular alterations, all gave a clinical history of having experienced dumping symptoms except one (L. C.). Four patients were studied, from whom a clinical history suggestive of a dumping syndrome could not be elicited; all four failed to show the electrocardiographic or blood volume alterations following the administration of hypertonic solutions.*

DISCUSSION

From the studies shown above and from those reported elsewhere,^{19, 22, 33} it would appear that the intrajejunal administration of hypertonic solutions accurately reproduces the symptomatology of the dumping syndrome and affords a convenient and simple method for measuring the physiological alterations which occur in this clinical en-Cognizance of the simultaneous tity. changes in the electrocardiogram, blood volume and symptomatology implicates the acute drop in blood volume as a causative factor. It has been well established that the introduction of hypertonic solutions into the upper jejunum results in a shift of extracellular water, and perhaps electrolytes as well, into the jejunal lumen; in this manner intestinal contents are brought into isotonicity with the plasma.^{18, 25, 26} Furthermore, it has been shown that this equalization of osmotic pressures may occur quite rapidly in the jejunum. It is reasonable to expect that the acute loss of circulating blood volume resulting from this shift would in turn result in sympathetic stimulation emanating from presso-receptors, which play an intricate role in the regulation of arterial blood pressure and are located mainly in the aortic arch, carotid sinus, and in juxtaposition to

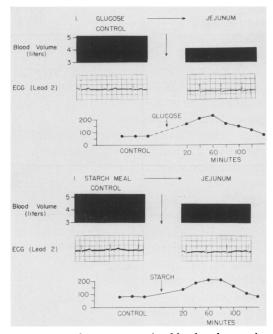


FIG. 5. Alterations in the blood volume, the electrocardiograph and the blood glucose curve following intrajejunal administration of 150 Gm. of starch and 150 Gm. glucose. Blood volume, ECG, and blood glucose levels are shown.

the mesenteric vessels.^{1, 10, 34} In accordance with this concept are the electrocardiographic findings. Although these alterations are not specific, it has been observed that similar changes may occur in such circumstances as: (1) acute coronary insufficiency, (2) hemorrhage, and (3) epinephrine administration.¹⁴ For this reason it is reasonable to assume that the cardiac changes might reflect the acute drop in blood volume and/or the sympathetic outflow.

Because similar electrocardiographic alterations may be seen in hypokalemia,^{5, 6, 14} the drop in potassium following glucose administration has been implicated in the symptomatology of the dumping syndrome.²⁹ In those studies in which saline was

^{*} Two of these patients had had subtotal gastrectomies, their clinical courses had been satisfactory. They showed no evidence of nutritional deficiency or symptomatology suggestive of a dumping syndrome. The third patient had had a total gastrectomy two and one-half years previously. This patient showed alterations similar to the other patients in the gastrectomized group only when the amount of solution used was double in amount or concentration of that given to the rest of the group. The fourth patient was three weeks post total gastrectomy and had a marked decrease in transit time; studies with barium-glucose mixture showed it to be in the ileum in 15 to 20 minutes. Repeated attempts to study this patient with hypertonic glucose were terminated by diarrhea.

given, no significant drop in potassium occurred, although cardiovascular alterations and symptomatology were evident. In those experiments showing a drop in plasma potassium and phosphate, the sequence was such that cardiovascular alterations and symptomatology occurred prior to the hypokalemia, and had returned to normal at a time when the plasma potassium was reduced. In addition, it was noted that the plasma concentration of potassium dropped in those patients with intact stomachs given glucose with no change in the electrocardiogram or blood volume. For these reasons, the potassium and phosphate changes are presumably secondary to the deposition of glycogen, which has been reported to occur as a result of glucose administration,8 and do not necessarily play a major role in the cardiovascular alterations or symptomatology of the dumping syndrome.

The alterations which were seen following the ingestion of hypotonic starch solutions focus importance on the enzymatic breakdown of foodstuffs exerting little osmotic force, into smaller molecular components with a corresponding increase in osmolarity.7, 17, 18 From the findings in these patients that the blood sugar levels and alterations in blood volume following starch paralleled those following hypertonic glucose, it would appear that the digestion of starch in the jejunum occurs rapidly. These observations implicate the "rate" of hydrolysis of foodstuffs in the jejunum in the sequential alterations of blood volume which occur in the dumping syndrome.

The finding that those patients with intact stomachs did not display physiological alterations or symptomatology in contrast to the gastrectomized group is presumably related to the rapidity with which the solution enters the jejunum, and hence the rapidity of hydrolysis or dilution. Although it has been shown that minimal dilution of hypertonic solutions may occur in the stomach, this dilution is neither so rapid nor so complete as in the jejunum.^{16, 18, 25, 26} In subserving its well-known function as a gastric reservoir, the stomach empties small aliquots of foodstuffs into the duodenum at intervals. In the case of hypertonic substances, gastric emptying time is markedly slowed.²¹ The studies reported here emphasize this function of the stomach in protecting the organism against rapid dilution or breakdown of foodstuffs.

CONCLUSIONS

1. Intrajejunal administration of hypertonic solutions or starch causes an acute decrease in circulating blood volume resulting from a shift of plasma water into the intestinal lumen.

2. The shift of fluid into the intestinal tract is mediated by differences in osmolarity between the administered solution and the plasma.

3. Electrocardiographic alterations and symptomatology typical of the dumping syndrome occur coincidental with the decrease in blood volume.

4. Similar alterations did not occur in patients with intact stomachs who were given equivalent amounts of hypertonic solution.

5. It is suggested that the acute drop in blood volume with subsequent stimulation of presso-receptors intimately associated with regulation of arterial blood pressure is implicated in the sympathetic component of the dumping syndrome.

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