The Effect of Gastrectomy on Serotonin Metabolism in the Human Portal Vein

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ALTHOUGH the etiology of the dumping syndrome remains unknown, evidence indicates the existence of a humoral factor(s) involved in the production of the dumping symptom complex. The similarities between the symptoms of the dumping syndrome and those of hyperserotonemia have led to investigations designed to determine whether increased release of serotonin occurs during the early postgastrectomy syndrome. Evidence has accumulated indicating increased release of serotonin from the proximal small bowel into the portal circulation in the experimental dumping syndrome. Increased portal vein serotonin levels have been demonstrated after hypertonic stimulation of proximal small bowel in dogs.[2] Decreased serotonin content of the proximal small bowel in animals after peptic ulcer type operations has been observed.[16] Loss of characteristic fluorescence, consistent with serotonin release, has been observed microscopically after exposure of human proximal small bowel to hypertonic glucose solution under anesthesia at the time of laparotomy.[21] Consistent increases in peripheral serotonin levels during human dumping syndrome have been demonstrated in peripheral blood.[15] Excretion of 5-hydroxyindoleacetic acid is variably increased in patients with most severe dumping symptoms.[20] Previously, no direct portal vein serotonin assays in the human dumping syndrome have been avialable to confirm intestinal release of this vasoactive amine into the circulatory system. In this study, serotonin assays were done directly on portal blood in unanesthetized postgastrectomy patients after induction of the dumping syndrome by hypertonic glucose solution.

Methods

Direct portal blood sampling in unanesthetized postgastrectomy and control patients was done through a previously placed large-bore polyethylene umbilico-portal catheter. In those patients tested in whom laparotomy was being done, the umbilical vein was cannulated after the abdomen had been entered, usually at the conclusion of the particular operation (Fig. 1). This open approach was used only in those patients requiring laparotomy for reasons other than umbilico-portal cannulation. Testing in these patients was not begun until adequate time for resolution of postoperative ileus had elapsed (usually 7–9 days). In patients not undergoing laparotomy, the umbilical vein was approached under local

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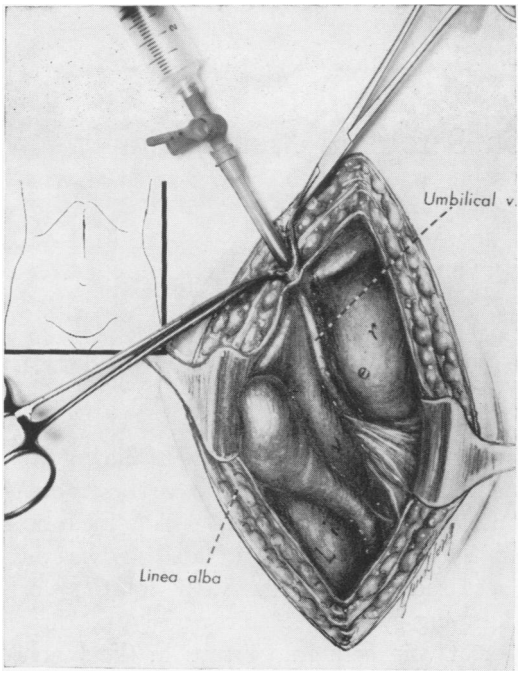

FIG. 1. Technic of incidental cannulation of the left portal vein by dilitation of the umbilical vein. The umbilical vein is dilated by successive Bakes dilators and a large bore polyethylene catheter is passed to the umbilico-portal junction. Daily infusion of dilute heparin maintains patency of the catheter until the time of testing. The catheter is subsequently used for portal venous blood sampling. This open approach to the umbilical vein is used only in those who require laparotomy for reasons other than umbilico-portal cannulation.

anesthesia. A small mid-line incision in the epigastrium was made through the skin and the linea alba. The umbilical vein was exposed and cannulated extraperitoneally (Fig. 2). Both control and gastrectomy groups included some patients in whom the umbilical catheter was placed at the time of laparotmoy. The patients tested included both nine control patients (normal pyloric sphincter mechanism) and six postgastrectomy patients. The postgastrectomy group included three patients with hemigastrectomy and vagotomy with gastrojejenostomy, two patients with hemigastrectomy and vagotomy with gastroduodenostomy, and one patient with subtotal gastrectomy with gastroduodenostomy. Control patients included patients with negative abdominal exploration for trauma and volunteers whose umbilical vein was dilated under local anesthesia. On the day of testing, 1 Gm. of glucose per pound of body weight was administered orally as a 50% dextrose in water solution. Because of the large amounts of glucose administered, patients included in this study were less than 50 years of age and without known cardiovascular disease. Fasting peripheral and portal venous blood samples were taken and at 10, 20, 30, 40, and 60 minutes after oral glucose administration. To insure a maximum of sensitivity and consistency of results, assays were carried out on platelet-rich plasma which was prepared according to the method of Hardisty and Stacey.[4] Isotonic anticoagulants and siliconized glass-

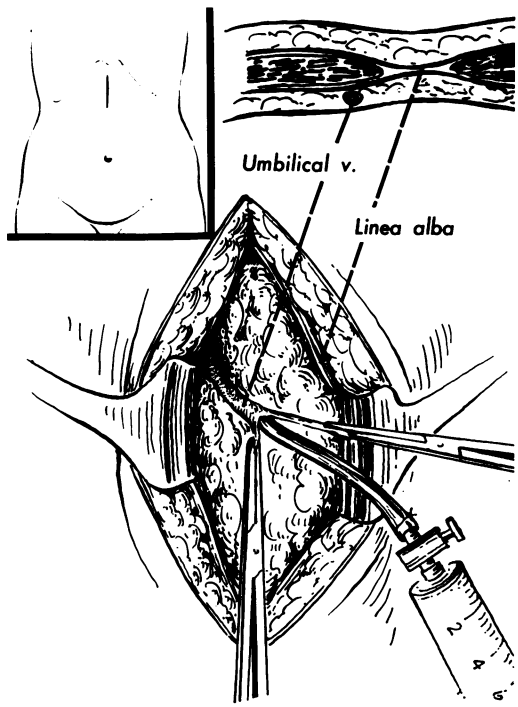

FIG. 2. Extraperitoneal umbilical vein cannulation. A midline incision is made through the skin and linea alba under local anesthesia. The umbilical vein is dilated with successive dilators, and a large bore polyethylene catheter is passed to the umbilico-portal junction for subsequent portal venous sampling.

TABLE 1. *Serotonin (5 HT) Changes in Postgastrectomy Patients after Oral Administration of Hypertonic Glucose**

Peripheral Platelet-rich Plasma**

	Fasting 5 HT	Maximum 5 HT	Increase 5 HT	% 5 HT Increase
A.	0.57	1.42	0.85	149
B.	0.32	0.53	0.21	66
C.	0.18	0.43	0.25	29
D.	0.12	0.15	0.03	17
E.	0.35	0.55	0.20	57
F.	0.27	0.44	0.17	63
		Maximum Average Increase		64 ± 47%

Portal Platelet-rich Plasma**

	Fasting 5 HT	Maximum 5 HT	Increase 5 HT	% 5 HT Increase
A.	0.50	3.20	2.70	540
B.	0.44	1.89	1.45	330
C.	0.18	1.10	0.92	511
D.	0.12	0.21	0.09	75
E.	0.40	0.60	0.20	50
F.	0.27	0.39	0.12	44
		Maximum Average Increase		258 ± 210%

* One Gm. glucose/pound of body weight dissolved in 2 cc. water/Gm. glucose.

** Micrograms serotonin/ml. platelet-rich plasma.

ware were used in the blood sample collections to maintain the integrity of the platelets until their separation from the erythrocytes, thus preventing the loss of serotonin to the red blood cells and red cell debris. Platelets were separated from the red blood cells by differential centrifugation at 5° C. Platelet-rich plasma was then aspirated from the red blood cell layer. Serotonin assays were done by multiple extractions and subsequent fluorescent analytical technic.[22]

Results

Following oral administration of hypertonic glucose to six postgastrectomy patients, the average maximum increase in platelet-rich plasma serotonin levels was 258 ± 210% in portal blood and 64 ± 47% in peripheral venous blood (Table 1). The average maximum per cent serotonin increase in nine patients with normal pyloric sphincter was 7 ± 9% in portal venous blood, and 16 ± 13% in peripheral venous blood. Following oral ingestion of hypertonic glucose solution, portal and peripheral venous serotonin changes are consistently greater in postgastrectomy patients than in patients with normal pyloric sphincter mechanism ($p < 0.01$) (Fig. 3). These changes in control and postgastrectomy patients are shown chronologically in portal blood (Fig. 4) and in peripheral blood (Fig. 5). Serotonin changes (both portal and peripheral) in postgastrectomy patients are considerably greater than the changes in hematocrit (Fig. 6). Hematocrit increases were consistently greater in postgastrectomy patients than in patients with a normal pyloric sphincter mechanism (Fig. 7). The difference in the hematocrit is significant at 40 minutes after ingestion of hyperosmolar glucose ($p < 0.001$). Portal serotonin changes reached a maximum at approximately 30 minutes after oral admin-

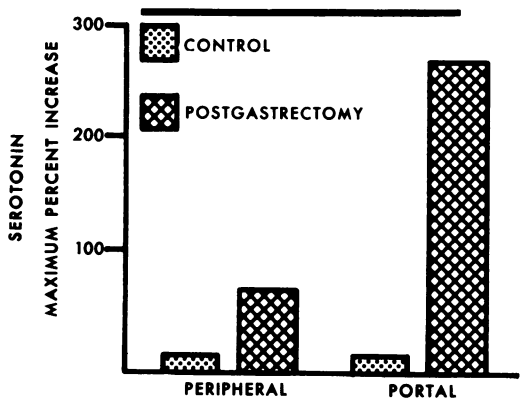

FIG. 3. Average maximum per cent increase of serotonin in peripheral and portal venous platelet-rich plasma in nine control patients (normal pyloric sphincter mechanism) and six postgastrectomy patients after oral administration of hypertonic glucose solution. The average serotonin changes are significantly greater in postgastrectomy patients in both portal vein (control: 7 ± 9%; postgastrectomy 258 ± 210%) and peripheral vein (control: 16 ± 13%; postgastrectomy: 64 ± 47%). ($p < 0.01$ in both portal and peripheral blood).

TABLE 2. *Average Fasting Serotonin in Control and Postgastrectomy Patients**

	Control (Normal Pyloric sphincter mechanism) **	Postgastrectomy
Portal	0.36 ± .15	0.32 ± .15
Peripheral	0.33 ± .14	0.30 ± .16

* Micrograms/ml. platelet-rich plasma.

** Although both the portal and peripheral average fasting serotonin levels were slightly higher in the control patients, the difference is not significant (portal $p < 0.7$; peripheral $p < 0.8$).

istration of hypertonic glucose solution. No difference between portal and peripheral average fasting serotonin levels was observed in either group of patients (Table 2). Although both the portal and peripheral average fasting serotonin levels were slightly higher in the control patients than in the postgastrectomy patients, the difference was not significant (Table 2).

Definite symptoms of dumping were experienced in patients with gastrectomy. All postgastrectomy patients experienced nausea, epigastric discomfort, weakness and a desire to lie down; most patients experienced diarrhea, borborygmus and tachycardia and some experienced flushing. The acme of symptomatology was felt to coincide chronologically with the maximum serotonin changes. The greatest serotonin changes were usually seen in those patients with the most severe diarrhea.

Discussion

Although release of serotonin from the proximal small bowel in response to hyperosmolar stimulus has been suggested in experimental dumping syndrome in animals, proof of postprandial serotonin release by direct serotonin assay in the human portal vein after loss of pyloric sphincter mechanism has not previously been reported. The safety and feasibility of umbilico-portal catheterization has been adequately demonstrated, and this has provided a means of direct portal venous study in the awake, unanesthetized patient. Peripheral serotonin elevations have been reported in the acute phase of human early postgastrectomy syndrome in earlier studies.[15] The assumption has been that the serotonin changes observed represent serotonin release from the bowel, but this has not been directly demonstrable because the portal vein had previously been inaccessible to sampling. Consistently and significantly elevated serotonin levels observed in the human portal vein during induced dumping syndrome thus confirm indirect experimental evidence of serotonin release from the intestinal tract into the portal circulation.

Evidence of serotonin release from the intestinal tract into the circulatory system has accumulated recently. Serotonin is present in greatest amounts in the enterochromaffin cells of the duodenum and jejunum.[17] Peskin and Miller[13] demonstrated loss of granular substance in the argentaffin cell mass upon exposure of proximal small bowel of dogs to hypertonic solution. Loss

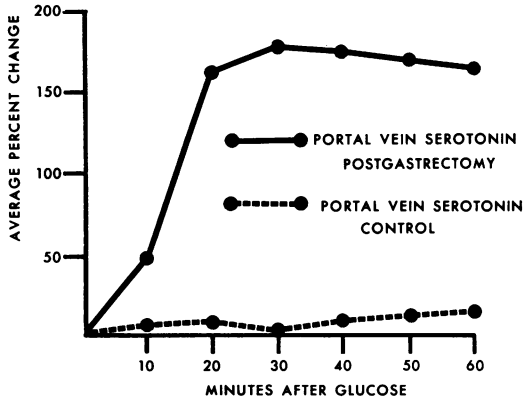

FIG. 4. Portal vein platelet-rich plasma serotonin changes after oral administration of hypertonic glucose solution (1 Gm. glucose/pound of body weight) in six postgastrectomy and nine control patients. Average portal vein serotonin per cent increases are consistently greater in the postgastrectomy patients than in patients with normal pyloric sphincter mechanism.

of characteristic fluorescence, consistent with serotonin release has been observed microscopically after exposure of proximal small bowel to hypertonic glucose solution in humans under anesthesia at the time of laparotomy.[21] Recently, we have observed decreased serotonin concentration in the proximal small bowel of animals following peptic ulcer type operations.[16]

Erspamer *et al.*[3] have estimated that serotonin stores of the proximal small intestine turn over and are replaced every 14 to 24 hours indicating that serotonin is readily released from the intestinal tract. The release of serotonin can be effected by various stimuli including increased intraluminal pressure [1] and application of hydrochloric acid.[18] Increased portal vein serotonin has been demonstrated in dogs after hypertonic stimulation of proximal small bowel.[2] Low levels of serotonin in patients with extensive large and small bowel resection is an indication that much circulating serotonin is derived from the enterochromaffin cells of the gastrointestinal tract.[5]

The evidence which has accumulated indicates that a humoral mechanism is involved in the pathogenesis of the dumping syndrome. Johnson and Jesseph [8] induced dumping parameters in normal dogs by cross-transfusion of portal vein blood from dogs with induced experimental dumping syndrome. Blood transfused from control dogs did not produce similar changes. Despite hypovolemia from intrajejunal plasma volume loss [19] and intravascular volume shift into the splanchnic bed, increased plethysmographic tracings have been demonstrated during the acute phase of the dumping syndrome.[6] This apparent selective dilitation of peripheral arteriolar pulsation concomitant with systemic hypovolemia is consistent with a circulating vasoactive humoral factor. The identity of such a humoral factor has not been established with certainty.

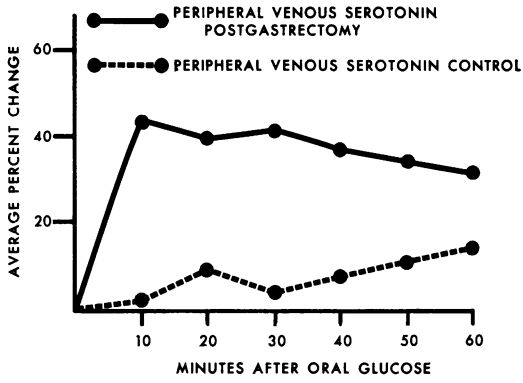

FIG. 5. Comparison of peripheral venous platelet-rich plasma serotonin of six postgastrectomy and nine control patients after oral administration of hypertonic glucose solution. Average peripheral venous serotonin per cent increases are consistently greater in the postgastrectomy patients than in patients with normal pyloric sphincter mechanism.

There is considerable evidence suggesting that serotonin is at least one humoral agent involved in initiating a series of pathophysiologic events known as the dumping syndrome.[14] Hyperserotonemia (as seen in the carcinoid syndrome) can cause both the vasomotor and the gastrointestinal symptoms seen in the dumping syndrome. The released serotonin may produce symptoms of flushing and sweating

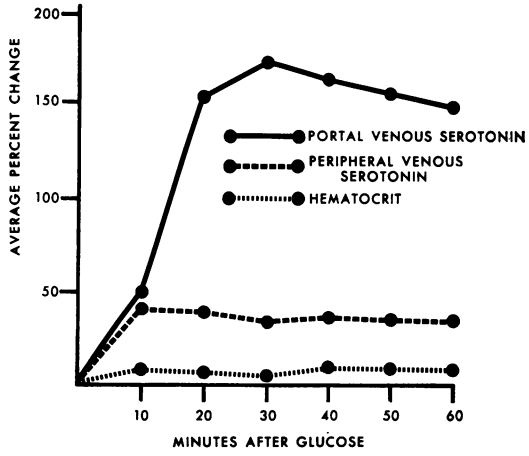

FIG. 6. Following oral administration of hypertonic glucose solutions, both portal and peripheral venous platelet-rich plasma serotonin changes are greater than hematocrit changes.

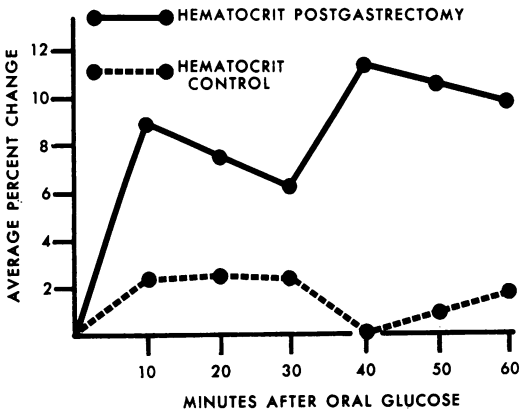

FIG. 7. Average change in hematocrit after administration of hypertonic glucose (1 Gm./pound of body weight) to six postgastrectomy patients and nine patients with normal pyloric sphincter mechanism. The difference between postgastrectomy and control patients is significant at 40 minutes ($p < 0.001$).

and stimulate the gastrointestinal tract, causing hypermotility manifested as cramps and diarrhea. The presence of serotonin may preclude vasoconstriction which would normally occur in response to intrajejunal plasma volume loss. If the patient is upright, he may experience hypotension and weakness. Serotonin may affect both the adrenal cortex and medulla, causing liberation of steroids and catecholamines which contribute to the dumping response.[12, 23] Serotonin may act on the liver to reproduce hyperglycemia by glycogenolysis and may also cause decreased pancreatic secretion, which is also observed in the experimental dumping syndrome. Infusion of serotonin into canine portal vein produced vasomotor changes which were not observed when the animals were pretreated with an antiserotonin compound (methylsergide).[14] Three types of antiserotonin drugs have been used successfully clinically for both vasomotor and gastrointestinal symptoms: reserpine, which depletes intestinal stores of serotonin, alphamethyl dopa, which blocks the formation of serotonin from its precursor; and cyproheptadine, which inhibits the response of tissues and organs to serotonin.[9]

Although fasting serotonin levels were the same in portal and peripheral venous platelet-rich plasma (Table 2), portal venous serotonin increased significantly more than peripheral venous serotonin after induction of dumping syndrome in postgastrectomy patients. The fact that fasting portal and peripheral serotonin levels are no different may indicate that minimal serotonin release from the gastrointestinal tract into the portal venous system occurs in the fasting state. It is also possible that serotonin destruction by hepatic or pulmonary monamine oxidase may proceed at an accelerated rate postprandially in response to the acute efflux of serotonin from the stimulated intestinal tract. Increased serotonin catabolism in the acute phase of the dumping syndrome could produce the observed differences between portal and peripheral serotonin levels after induction of the dumping syndrome. Continued comparison of the concomitant changes in portal and peripheral serotonin may provide evidence to help evaluate whether altered liver or lung enzymatic catabolism of serotonin may play a role in the genesis of the dumping symptom complex in some patients. Altered serotonin metabolism (release, formation or catabolism) could explain the variability and unpredictability of occurrence of the dumping syndrome.

Although hemoconcentration was consistently observed in patients with gastrectomy, serotonin increases were of much greater magnitude, indicating that the serotonin changes observed were not merely a reflection of hemoconcentration. Hematocrit changes were greater in postgastrectomy patients than in the patients with unaltered pyloric sphincter mechanism. Hemoconcentration is believed due to intrajejunal plasma volume loss secondary to influx of excessively hypertonic solution into the proximal small bowel because of

the loss of the pyloric sphincter mechanism. Karr *et al.*[10] demonstrated the elegance and importance of the pyloric sphincter mechanism in maintaining isotonicity of the proximal small bowel. The emptying rate of the intact stomach is decreased by hypertonic solutions, possibly mediated by duodenal osmoreceptors which regulate peristalsis and pyloric function.[7] Loss of pyloric sphincter mechanism, either by resection or bypass, is prerequisite for the dumping syndrome. In the postgastrectomy patients reported here, hemoconcentration and increases in serotonin concentrations occurred regardless of the extent of gastrectomy of the presence or absence of vagal function. No attempt is made here to relate the serotonin and hematocrit changes to the types or extent of gastrectomy or absence of vagal function because of the small number of patients in each group.

Although consistent elevations in portal and peripheral blood serotonin levels during dumping syndrome have been demonstrated, there is no proof that serotonin is related to the etiology of the dumping syndrome. The patients with the most severe diarrhea were found to have the greatest increase in portal and peripheral serotonin levels. At this time, it cannot be stated with certainty whether the serotonin elevations are the cause or the effect of the diarrhea. The consistent increases in peripheral serotonin levels indicates that the serotonin released into the portal system from the proximal small bowel is not entirely detoxified by hepatic or pulmonary monamine oxidase. Thus, serotonin, in increased concentrations, could recirculate to the bowel muscularis via the arterial system, and therefore could cause diarrhea. Similarly, recirculation to the other peripheral tissues in increased concentrations could also cause other vasomotor or gastrointestinal effects of elevated serotonin levels.

A combination of humoral factors may be involved in production of the alterations associated with the dumping syndrome. The cumulative effects of serotonin and bradykinin have been shown to be similar to the hemodynamic changes occurring in the experimental dumping syndrome.[24] The suggestion has also been made that the kallikrein-bradykinin system may mediate serotonin release, illustrating a possible interplay of more than one humoral agent.[11] Elevated bradykinin levels have been demonstrated in human dumping syndrome.[25] The role of other vasoactive compounds, e.g. histamine, catecholamines and dopamine is still being evaluated in relationship to dumping syndrome.

Summary

Direct portal blood sampling in unanesthetized postgastrectomy patients has confirmed precious indirect evidence of serotonin release from the intestinal tract into the portal circulation during induced dumping syndrome. Following hyperosmolar glucose ingestion, there is significantly greater serotonin increase in the portal venous blood of postgastrectomy patients than in patients with normal pyloric sphincter mechanism. This change is reflected in smaller but consistent peripheral venous serotonin increases in the postgastrectomy patients. Serotonin assays were done on platelet-rich plasma, which is believed to provide maximum sensitivity and reliability.

During the induced human dumping response in postgastrectomy patients, average potal serotonin levels increase to a greater extent than average peripheral serotonin levels. In the fasting state, no significant difference between portal and peripheral serotonin levels is observed. These findings suggest either a lack of measurable intestinal serotonin release in the fasting state, or accelerated hepatic or pulmonary catabolism in response to the acute efflux of serotonin from the stimulated intestinal tract during the acute phase of the dumping syndrome.

Greater hemoconcentration occurs following oral hyperosmolar ingestion in patients with gastrectomy than in patients with unaltered pyloric sphincter mechanism. However, hematocrit changes are smaller than concomitant serotonin changes, indicating that the serotonin increases are not merely reflections of hemoconcentration.

Thus, release of serotonin from the gastrointestinal tract into the portal venous system does accompany induced human dumping symptoms in the postgastrectomy patient; whether the increases are sufficient to account for all of the symptoms remains to be determined.

Acknowledgments

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Discussion

Dr. Theodore Drapanas (New Orleans): Eight years have passed since the role of serotonin in the dumping syndrome, experimentally, was documented in a report before this Association. I believe that Dr. Reichle has finally nailed down these observations in the human.

Arguments during the past few years have attempted to incriminate serotonin as the cause of possibly every component of the dumping syndrome. More importantly, however, we believe that no single mechanism or substance is responsible for all of the physiological derangements noted on the basis of further experimental work and clinical evidence.

First, the measured hemodynamic changes, as alluded to by Dr. Reichle, cannot be explained by serotonin alone or by alterations in blood volume alone.

Second, the timing of the observed changes lend further support to this. Serotonin levels peak at 20 minutes at a time when many of the vasomotor changes have already come and gone.

Third, we and others have replaced the measured plasma volume loss in patients and have not been able to abolish most of vasomotor symptoms.

Fourth, and perhaps most important, is the lack of correlation between the magnitude of the blood volume response, or indeed even of the peripheral serotonin response, to the symptoms of dumping.

As in the carcinoid syndrome, there is excellent evidence in the dumping syndrome that the early symptoms occurring within 5 to 10 minutes after ingestion of a hyperosmolar meal are due to bradykinin release.

The intermediate symptoms of cramps and diarrhea which occur in 20 to 40 minutes of cramps are probably due to serotonin and, finally, the later symptoms of weakness correlate nicely with the blood volume deficit.

If we dissect the dumping syndrome in this fashion, we find an excellent correlation between the physiologic alterations just reported and the symptoms. Certainly, the work in the carcinoid syndrome lends further support to primary rate of bradykinin in the vasomotor symptoms.

Dr. John E. Jesseph (Columbus): I would like also to commend Dr Reichle and his group on a very direct and technically well done piece of work that goes right to the core of one of the principal difficulties in the investigation of this complex problem. This difficulty has been to avoid the muddying effects of liver, extraction of serotonin from portal blood and a variety of other things involving dilution in the periphery. This direct portal vein study is the first, best definitive study to indicate clearly, as Dr. Drapanas has said, that there is an important role for serotonin in the explication of dumping. The problem divided into two parts; it was nearly 10 years ago that Lloyd Johnson and I, then working in Seattle, provided some little evidence that in animals at least there is evidence for these humoral influences. On review it became clear that the bradykinins are better incriminated in these difficult, often frustrating and hateful experiments to explain the complex cardiac, dynamic and vascular changes.

I would like to ask Dr. Reichle and his group if they have been able to or hope to do comparable studies and to study blood samples for the bradykinins of other humoral substances.

Dr. Robert E. Condon (Chicago): I wish to inquire in one area about the correlation between serotonin and symptomatology.

In the tests that we have done using provocation of dumping with a glucose load, we have been able to produce symptoms in a certain proportion of patients but unfortunately the patients who react to this test are very rarely those who have symptoms of clinical dumping.

I would like to ask Dr. Reichle two questions. One, is there any correlation between the portal blood, or even the peripheral blood, serotonin levels and the production of dumping symptoms in his test group? Two, has he been able to derive any evidence that those patients who are bothered