Serotonin Metabolism and the Dumping Syndrome

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SEVERAL POSTGASTRECTOMY SYNDROMES have been described to explain the variety of symptoms experienced by individuals following surgical operations for peptic ulcer. Some of these syndromes appear to have a mechanical etiology (afferent loop syndrome, efferent loop syndrome, small pouch syndrome, etc.) while the others are less definite as to etiology.

The *dumping syndrome* is one of the more common syndromes [9] with significant dumping occurring in 2 to 5 per cent of postoperative patients. There is a much higher incidence immediately postoperatively; however, the percentage falls rapidly within a very short time. Mild symptoms may be encountered in 10 to 15 per cent of postgastrectomy patients.

The dumping syndrome occurs either during a meal or within 20 to 30 minutes after eating. The same time relationship persists whenever a hypertonic solution is instilled into the proximal jejunum. The syndrome lasts 20 to 60 minutes and may be relieved by assuming the recumbent position. It has an intestinal component—hyperperistalsis, epigastric discomfort, bloating, fullness, cramps, nausea, vomiting, diarrhea; and a vasomotor component—weakness, dizziness, pallor, desire to lie down, palpitation, sweating, tachycardia and evidence of increased peripheral blood flow.

Since the early descriptions of the dumping syndrome,[5, 15] an intense experimental and clinical effort has been directed toward defining and establishing an etiology. Machella and associates in 1949 and 1950 [11, 12] differentiated the dumping syndrome from the postgastrectomy hypoglycemic syndrome by noting that the symptoms occurred during the early hyperglycemic period, the symptoms could not be relieved by intravenous glucose and virtually any hyperosmolic solution (greater than 300 milliosmols) instilled into the jejunum produced the symptoms. Simple distention of the jejunum by a balloon did not reproduce the syndrome.

Investigations on the vasomotor phenomenon have demonstrated that plasma volume decreases and returns to normal in 1 to 1½ hours,[8, 14] plasma expanders tend to decrease or occasionally eliminate the vasomotor component, and the vasomotor phenomena begin before significant changes in plasma volume can be detected.[3, 7, 8] This latter observation stimulated Johnson and Jesseph [7] to perform cross transfusion experiments in dogs, which established a humoral mechanism for initiating the dumping syndrome.

Serotonin (5-hydroxytryptamine, 5-HT) given intravenously will reproduce the dumping syndrome, causing serotonin to be suspected as the etiologic agent. Serto-

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tonin is present in great quantity in the enterochromaffin cells of the duodenum and jejunum.[19] Intraluminal hypertonic solutions and increased intraluminal pressures result in a release of serotonin from the enterochromaffin cells.[2, 17] Serotonin antagonists have been used experimentally[18] and clinically[8] in the prevention and treatment of the dumping syndrome. The reported results have been favorable, supporting the thesis that serotonin is the etiologic agent in the dumping syndrome.

Our close association with the Durham, North Carolina, Veterans Administration Hospital has afforded us the opportunity to follow a large group of patients (425) who have been operated upon for peptic ulcer disease. About one fifth of these patients had symptoms similar to those seen in the dumping syndrome. These observations, coupled with the information presented above, induced us to study serotonin metabolism as it relates to the dumping syndrome.

Materials and Methods

One hundred and twenty-four studies were performed on 88 male patients who had been operated upon for peptic ulcer disease. The studies fell into three major categories. The first was a subjective evaluation of the patient's symptoms before and after operation with special attention directed toward the dumping symptoms. The second was an objective evaluation of changes in blood pressure, pulse, sweating, diarrhea and vomiting during the time of testing. The third consisted of chemical studies of blood and urine before, during and after testing situations. These patients were not selected but were included in the series as they were admitted to the hospital for various reasons. Each patient's chart was carefully reviewed to ascertain the patient's preoperative course, the nature of the operation, and his postoperative course.

The 88 patients all had urinary 5-hydroxyendoleacetic acid (5-HIAA), blood plasma and platelet serotonin levels determined before, during and after a test for dumping. This test consisted of giving orally 150 cc. of 50% glucose mixed with lemon juice and recording subjective and objective reactions while measuring changes in blood pressure and pulse. Fourteen patients who were known "dumpers" were treated with methysergide maleate (Sansert*), a serotonin antagonist, and then restudied after two weeks of treatment. There were five patients in this group who had subjective improvement. These patients were given a "double blind" drug and studied again after two weeks.

Subjective Evaluation

Each patient was carefully questioned concerning the onset of symptoms which occurred within 30 minutes after eating. The symptoms particularly looked for included nausea, fullness, tremor, tachycardia, abdominal cramps, faintness or having to lie down. All patients were re-evaluated for these symptoms at the time of experimental testings. The relationship of these symptoms to various foods and the serotonin antagonists were noted.

Objective Evaluation

The patient was observed for 30 to 60 minutes prior to testing, during which control pulse and blood pressures were obtained; subjective feelings were also recorded. The patient then ingested 150 cc. of lemon-flavored 50% glucose. The blood pressure and pulse were monitored at 10-minute intervals up to an hour. Subjective symptoms were recorded, as was the onset of vomiting, diarrhea, sweating or flushing.

Chemical Studies

Urine samples were collected according to the following schedule: an 8-hour con-

* Kindly supplied by Dr. Ruedi Bircher of Sandoz Pharmaceuticals.

trol urine (1:00 a.m. to 9:00 a.m.), a 4-hour early test sample (9:00 a.m. to 1:00 p.m.), a second 4-hour test sample (1:00 p.m. to 5:00 p.m.) and a last 8-hour sample (5:00 p.m. to 1:00 a.m.). The 5-HIAA concentrations were determined according to the method of Udenfriend.[21] Blood samples for plasma and platelet serotonin concentrations were collected according to the following schedule: two control samples were obtained—one at 30 minutes before the testing and the other at 1 minute before the testing. Blood samples were drawn routinely at the time of peak reaction, and at 30 to 60 minutes after glucose ingestion. Some patients had samples drawn at 1, 3, 5, 10, 30 and 60 minutes after ingesting glucose. The blood plasma and platelet serotonin concentrations were determined according to the method of Kirshner.[10]

Five patients were tested in the usual manner and at the end of the first hour were given a repeat test.

All of the data was punched onto IBM cards and then transferred to a magnetic tape by the IBM 1401. The IBM 7072 computer was used to analyze the data. The programming and analyzing was performed at the Duke University Computer Center.

Classification of Patients

At the time of his first interview the patient was classified as a known *dumper* if he had any nausea, fullness, flushing, weakness, vomiting, tremor, tachycardia, sweating, abdominal cramps, diarrhea or faintness within 30 minutes after eating. Patients who did not experience these symptoms were called *non-dumpers*. There were 40 "dumpers" and 46 "non-dumpers." Two patients were not classified.

The patients were reclassified after their first testing into three groups. The first group contained the *non-reactors* (N.R.). These patients had no subjective symptoms and showed no change in pulse rate or blood pressure during the test situation. The pulse rate had to change ±10 beats per minute to be recorded as a change. A change in systolic and/or diastolic blood pressure of more than ±10 mm. Hg was required before a change was recorded. The second group contained the *subjective reactors* (S.R.). These patients experienced symptoms but had no change in blood pressure or pulse. The third group contained the *objective reactors* (O.R.). These patients had both subjective and objective reactions recorded. There were 11 non-reactors, 12 subjective reactors and 65 objective reactors.

During repeat testings the blood pressure and pulse were monitored. Methysergide maleate and the placebo did not alter the direction of the changes. The pulse curve for each patient remained virtually the same during the testing. Most of the patients on methysergide maleate showed a greater drop in blood pressure immediately after a test meal than they did during the control test. During a repeat challenge their blood pressure dropped (10–20 mm. Hg) further.

Six of these patients have had psychiatric evaluation. These patients were classified as having depression (2) or mixed psychoneurosis, all of which included depression as a major symptom.

Race, Age and Sex

All of the patients were males. Seventy of the patients were Caucasians and 17 were Negro. One patient was not classified. The average age of the patients at the time of their first interview was 48. The age range was from 32 to 74 years. The pretesting evaluation showed the Caucasians to be equally divided between known "dumpers" and "nondumpers" (35:35), while the Negroes were mainly "non-dumpers" (6:11). However, after testing, the majority of both groups were classified as objective reactors (Table 1).

TABLE 1. *Classification According to Race After First Testing*

	Caucasian	Negro
Objective reactors	50	14
Subjective reactors	11	1
Nonreactors	9	2

Preoperative Symptoms, Indications for Surgery, Operation Performed

The duration of symptoms prior to operation did not influence the post-testing classifications (Table 2). Comparison of indications for operation with the pretesting and the post-testing classification of patients (Table 3) indicates that patients who were operated upon for chronicity of symptoms or who had more than one indication were more prone to develop the dumping syndrome postoperatively.

The operations performed included 50 per cent gastrectomy, 60 per cent gastrectomy, 70 per cent gastrectomy, vagotomy and gastroenterostomy, vagotomy and gastrectomy, vagotomy and pyloroplasty, and vagotomy and antrectomy. The 50 per cent gastrectomy, vagotomy and pyloroplasty, and vagotomy and antrectomy had the lowest percentage of known "dumpers." However, when the post-test classifications were compared with the type of operation, most of the categories were similar, with greater than 67 per cent objective reactors. The 50 per cent gastrectomy had the lowest percentage (67%) of objective reactors. The highest percentage of non-reactors was in the vagotomy and pyloroplasty group (40%). The 70 per cent gastrectomy had the highest percentage of objective reactors (90%) and no non-reactors (Table 4).

The rate of gastric emptying postoperatively was compared with the patient categories. The rates of emptying were similarly distributed in the objective reactors, the subjective reactors and the non-reactors.

Postoperative Symptoms, Effect of Diet

Dumping symptoms occurred during the first postoperative month in 56 per cent of the patients. Thirty-four per cent of the patients experienced the onset of symptoms after 9 months. About 70 per cent of the patients were evaluated within 3 years of operation.

The most common postoperative symptoms were nausea (39.5%), fullness (18.4%), weakness (15.8%) and flushing (10.5%).

About one half of the patients had tried the usually prescribed diet (decreased carbohydrate, no liquids with meals, etc.) to control their symptoms. Twenty-seven per cent had no relief on the diet, 13.9 per cent had complete relief and 58.3 per cent had some relief.

Chemical Determinations

(Fig. 1). The normal blood serotonin concentration for our laboratory ranges from 0.15 to 0.80 μg. per 10^6 platelets. With only 13 exceptions, all the control blood serotonin concentrations fell within this range. Ten objective reactors, two subjective reactors and one non-reactor had higher levels. Because of the rather wide spread for normal serotonin concentrations, all results were expressed as per cent

TABLE 2. *Relationship of Duration of Symptoms Prior to Surgery to Post-Testing Classification*

Interval Postop.	1 mo.–1 yr.	1–2 yr.	2–3 yr.	3–4 yr.	4–5 yr.	5–10 yr.	10–15 yr.	15–20 yr.	20–25 yr.	>52 yr.
No. Patients	12	9	2	4	4	23	16	11	3	0
Objective reactors	10	6	1	3	2	17	13	7	2	0
Subjective reactors	1	1	1	0	0	3	1	4	1	0
Non-reactors	1	2	0	1	2	3	2	0	0	0

TABLE 3. *Indications for Operation and Patient Classification*

		Chronicity	Bleeding	Perforation	Obstruction	Intractability	Combination
No. Patients		43	9	1	3	1	31
Pre-test Class	Dumpers	20	1	1	1	0	17
	Non-dumpers	23	8	0	2	1	14
Post-test Class	Objective reactors	33	4	1	2	0	23
	Subjective reactors	7	2	0	0	1	3
	Non-reactors	3	3	0	1	0	5

change (±) of the control sample in order to facilitate the necessary comparisons.

In general, the "non-dumpers" tended to have higher control serotonin levels. However, after patients were given the test diet, the objective reactors had higher control serotonin levels. The serotonin concentrations changed in a similar manner in the "dumpers" and "non-dumpers" during the tests. The objective reactors had more positive changes than did the subjective reactors or non-reactors.

The use of methysergide maleate did not cause any persistent alteration in the serotonin levels. When compared to the earlier control tests, at least 33 per cent of the patients had no change, 12 to 45 per cent showed an increase and 12 to 55 per cent had a decrease. These changes were not seen consistently in any of the patient groups.

The normal range for the 24-hour 5-HIAA excretion in our laboratory is 1 to 15 mg. Values for all patients fell within this range. The distribution for "dumpers" and "non-dumpers" was the same. However the objective reactors had higher 24-hour urine 5-HIAA excretions as well as higher concentrations in each of the test samples. Methysergide maleate did not seem to influence the excretion of 5-HIAA in any of the patient groups.

Five patients, all objective reactors, had a repeat challenge. Graphs of serotonin concentrations for most of these patients were bell shaped curves with the highest values in the first sample after the second challenge. Most of these patients had an increase in their symptoms at this time.

Post-Treatment Symptoms

A comparison of the patients' symptoms while receiving methysergide maleate to their previous symptoms is shown in Table 5.

Several patients experienced improvement of their symptoms while on methysergide maleate for 2 to 3 weeks. However on repeated or prolonged treatment, the

TABLE 4. *Influence of Operative Procedure Upon Patient Classification*

Type Operation		50% Gast.	60% Gast.	70% Gast.	Vag. G. E.	Vag. Gast.	Vag. Pyloro.	Vag.
No. Patients		9	13	10	11	19	7	4
Pre-test Class	Dumpers	3	9	6	8	9	2	1
	Non-dumpers	6	4	4	3	10	5	3
Post-test Class	Objective reactors	6	10	9	8	14	5	3
	Subjective reactors	0	3	1	2	4	0	1
	Non-reactors	3	0	0	1	1	2	0

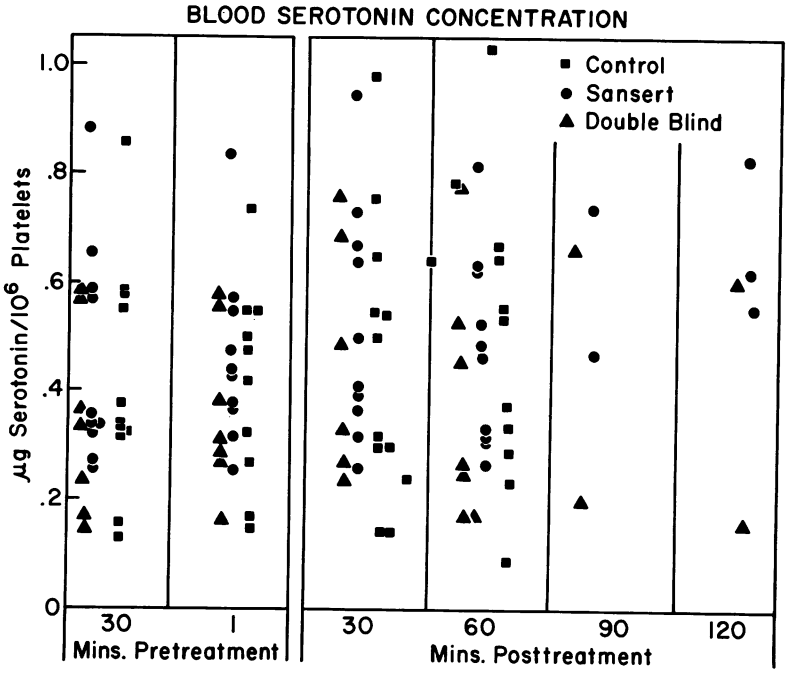

FIG. 1. Comparison of blood serotonin concentration on a single group of patients during Control, Sansert and Double Blind testing.

symptoms tended to recur. An equal number of patients noted their symptoms to be worse. Symptoms experienced at the time of repeat testing were not consistently better or worse.

Discussion

A reasonable explanation of pathophysiologic changes which occur during the dumping syndrome may be the rapid passage of hyperosmolar material into the proximal small intestine through a stomach-duodenal or jejunal arrangement created at operation. This material results in the release of a humoral agent from the enterochromaffin cells which is transported via the portal blood through the liver. Either the original humoral agent or a modification thereof is then distributed systemically, producing the myriad of symptoms known as the dumping syndrome. Other factors which influence postgastrectomy symptomatology, but which can and should be separated from their effect on the dumping syndrome, include distention of the jejunum and the hypoglycemic symptoms.

Similarities between the dumping syndrome and the well-known manifestations of an excess of serotonin in the peripheral blood have implicated serotonin as the etiologic agent. The largest known stores of serotonin are in the enterochromaffin cells of the jejunum. Serotonin is released by the small intestine in response to distention and intraluminal hypertonic solutions.[1, 17, 20]

If serotonin is the etiologic agent, then one would expect to find changes in blood concentrations of serotonin or changes in urinary concentrations of 5-HIAA following tests for dumping. Thus far the results of such testing are equivocal. No one has demonstrated altered systematic levels of serotonin, although rises in portal vein serotonin have been reported.[4, 18] Serotonin may be removed rapidly by enzymes (monamine oxidase) in the liver. However the rate of 5-HIAA excretion is not altered by inducing the dumping syndrome.[6]

Our peripheral blood determinations for serotonin failed to incriminate serotonin as the etiologic agent. Levels in almost all pa-

tients fell within the normal range. Serotonin concentrations during the test situation remained within the normal range. However the objective reactors had higher control serotonin concentrations and more positive changes during the test situations than did the subjective reactors or nonreactors. Results of 5-HIAA determinations were all within our normal range. However the objective reactors tended to excrete more per test sample.

Although trends were noted when changes in blood serotonin and urine 5-HIAA concentrations were compared to symptoms, no persistent pattern was found. Some patients with the severest symptoms had the lowest concentrations and some patients with no symptoms had quite high concentrations of serotonin and 5-HIAA.

Five patients were tested in the usual manner and then retested 1 hour later to determine if the etiologic agent responsible for the dumping syndrome could be exhausted. It has been suggested that shortly after a dumping episode the patient can eat with minimal or no symptoms.[8] All five patients had an equal or increased response to the second test meal, as well as slightly higher serotonin concentrations. We have been unable to obtain volunteers for a third or fourth consecutive test although this should be done.

Serotonin antagonists have resulted in improvement in the dumping symptoms.[8, 14] A potent serotonin antagonist, methysergide maleate, which is four times more potent than LSD-25[13] was given (8 mg. Spacetab, twice daily) to 14 patients. There were no patients who experienced consistent or prolonged improvement in symptoms. However five of these patients did have early relief which usually lasted only a month and which could not be reproduced by repeat usage of the drug. An occasional patient would report temporary relief from the placebo. We have to conclude that methysergide maleate used in the above manner did little to improve the dumping symptoms or alter the cardiovascular disturbances.

TABLE 5. *Comparison of Patients' Symptoms Before and After Receiving Methysergide Maleate*

Symptom	Per cent		
	No Change	Increase	Decrease
Nausea	40	20	20
Fullness	20		20
Flushing		10	40
Weakness	40	20	10
Vomiting	10	10	10
Sweating	10		10
Cramping		10	10
Diarrhea	10	20	10
Faintness	20	20	

Results of the study indicate that serotonin, although capable of producing the dumping syndrome, may not be the etiologic agent, or it may be only a link in the etiologic process, i.e., stimulating adrenal activity[14] or altering peripheral receptor organs by increasing their sensitivity to other agents.

There are other agents that should be investigated as the possible humoral agent. These include bradykinin, kallidin, the kinins and substance P.[16, 22] All are capable of reproducing parts or all of the changes seen in the dumping syndrome.

The 50 per cent gastrectomy had the lowest incidence of objective reactors (67%), while the 70 per cent gastrectomy had the highest (90%). All of the gastrectomies were reconstructed as anterior Hofmeister-Bilroth II's. Gastric emptying was not delayed in any patients and therefore could not be assessed. It has been demonstrated, however, that delay of gastric emptying, by decreasing the osmolarity of the gastric contents, helps control the dumping symptoms.[9]

Summary and Conclusions

The dumping syndrome is mediated by a humoral mechanism. Serotonin has been implicated by others as the humoral agent involved.

Serotonin metabolism was studied in 88 patients who had surgical procedures for peptic ulcer disease.

All patients had blood serotonin levels and urinary 5-HIAA levels within the normal range. Control values were slightly higher in the objective reactors than in the others.

No consistent changes were noted in any of the groups of patients during testing.

The "trigger" mechanism for the dumping syndrome cannot be exhausted by a single stimulus repeated in an hour.

A serotonin antagonist, while offering occasional temporary relief from symptoms, did not produce any persistent significant improvement.

Other agents to be investigated as etiologic agents are mentioned.

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