Role of 5-Hydroxytryptamine in the Dumping Syndrome after Gastrectomy:

Histochemical Study

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SINCE 1950 there have appeared many theories regarding the etiology of the dumping syndrome after gastrectomy, as summarized in Table 1. Among them the conclusions by Johnson *et al.*[7, 8] and Drapanas *et al.*[2] are noteworthy in that the syndrome is ascribed to a release of an endogenous, humoral agent, 5-hydroxytryptamine (5-HT). These authors demonstrated experimentally in dogs that hypertonic glucose solution administered through a Witzel's fistula into the proximal intestinal loop induced symptoms which resembled the dumping syndrome, and a simultaneous elevation of blood 5-HT levels in the portal vein. Supporting this view, cyproheptadine (Periactin), 5-HT antagonist, and α-methyldopa (Aldomet), aromatic amino acid decarboxylase inhibitor, have been found to be effective in counteracting the experimental dumping syndrome in dogs as well as its clinical manifestations in patients.

However, the cytologic distribution of 5-HT in the human gastrointestinal tract, its release mechanism and subsequent fate remain unknown, mainly because no specific histochemical method for demonstrating 5-HT at the cellular level has been available. Cellular 5-HT had been visualized only indirectly as an argentaffin material,[5] until it was found that it can be very clearly demonstrated as a highly specific fluorescence.[4]

The cellular distribution of 5-HT in the human gastrointestinal tract with the fluo-

TABLE 1. *Theories of Etiology of the Dumping Syndrome since 1950*

(A) Reduction in Serum Potassium	Smith, W. H., 1951[16]
(B) Adrenal Stimulation	Pontes, J. F. *et al.*, 1953[13]
(C) Hyperglycemia	Hobsley, M. *et al.*, 1960[6] Le Quense, *et al.*, 1960[9]
(D) Traction on the Residual Stomach	Capper, W. M. *et al.*, 1951[1]
(E) Sideropenia and Anemia	Wallensten, S., 1955[19]
(F) Distension of the Small Bowel	Machella, T. E., 1950[11]
(G) Hyperactivity of the Efferent Loop	Duthie, H. L. *et al.*, 1960[3] Liljedahl, S. O. *et al.*, 1959[10]
(H) Drop in Extracelluar Volume	Roberts, K. E. *et al.*, 1954[15]
(I) Serotonin	Johnson, L. P. *et al.*, 1961[7], 1962[8] Drapanas, T. *et al.*, 1962[2] Peskin, G. W. *et al.*, 1962[12]

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rescence method has been described in a previous report.[17] In order to find a causal relationship between the dumping syndrome and the change of gastrointestinal 5-HT, studies were done of the cellular distribution of gastrointestinal monoamines after the topical application of hypertonic glucose to the mucous membrane of the small intestine at laparotomy, and of the effect of the ingestion of hypertonic glucose on the glucose tolerance test in post-gastrectomized patients.[18]

Materials and Methods

Twenty ml. 50% glucose solution were placed directly into the jejunal lumen with an injection syringe in 20 patients during laparotomy. Thirty minutes later, fresh specimens of the jejunum near the site of injection were removed and cut into several pieces. They were freeze-dried, treated with formaldehyde gas, embedded in paraffin, sectioned and mounted for fluorescence microscopy, as described previously.[17] Control specimens were taken from jejuna injected with physiological saline alone. Non-glucose, and non-saline injected tissue specimens were also removed from the stomach and duodenum, and from the stomach and jejunum of patients during Billroth I or II operations.

In another series of studies, 50 Gm. glucose solution was given orally to 100 patients after gastrectomy. In such patients, hypertonic glucose can flow very rapidly from the stomach without a pyloric ring into the duodenum or jejunum. Thus, although the primary aim[18] of this test was to determine whether or not oxyhyperglycemia after gastrectomy was a sign of the prediabetic state, glucose ingestion by such patients served as a provoking agent

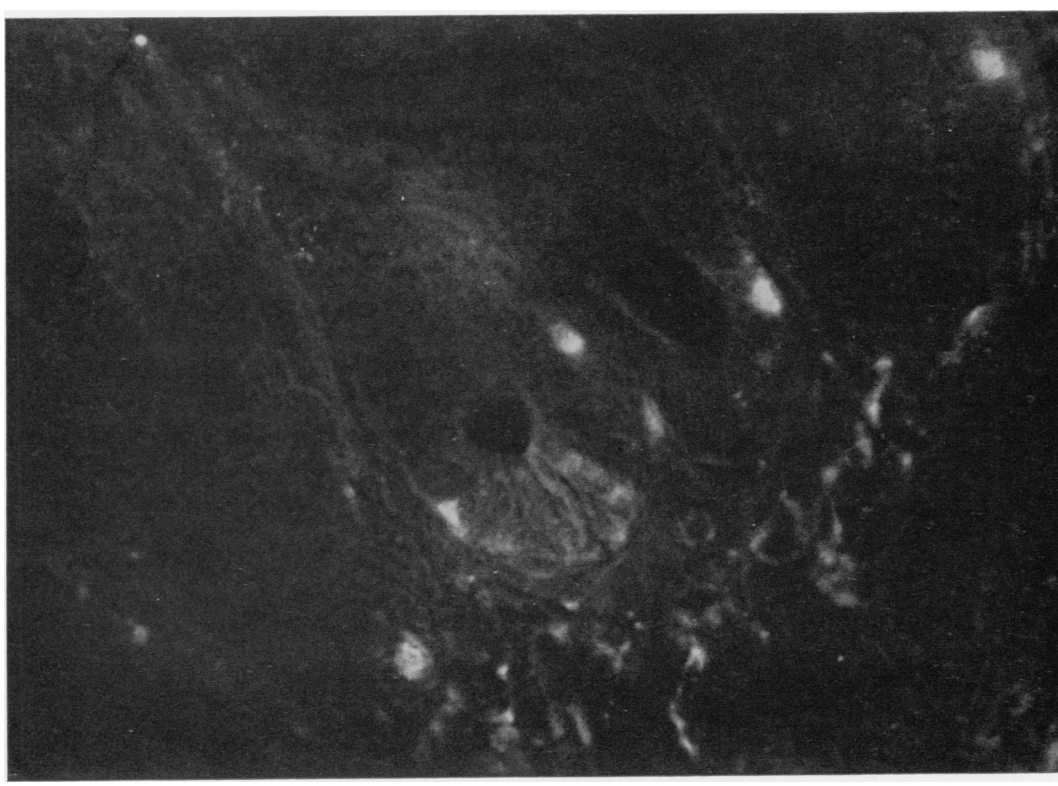

FIG. 1. Serotonin in the stomach. In the stomach throughout almost all the superficial mucous membrane there are no serotonin-containing cells, but in the deep layers adjacent to the submucosal tissue, near the pylorus, serotonin-containing cells can be found. (×160.)

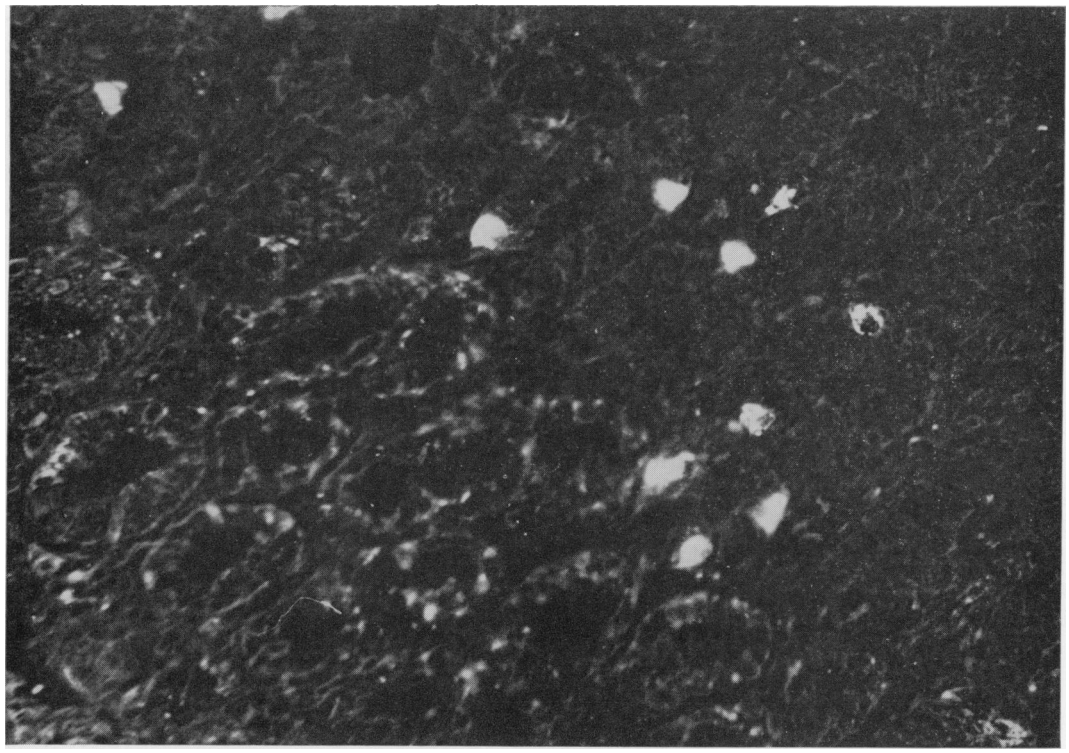

FIG. 2. Serotonin in the duodenum. The duodenum contains the largest number of serotonin-containing cells, and numerous serotonin-containing cells are demonstrated in Lieberkühn's crypts, 5 or 6 times more than in the stomach. No serotonin-containing cells can be found in Brunner's glands. (×160.)

for clinical manifestations following the topical application of hypertonic glucose to the intestinal tract.

Results

Although no fluorescence of 5-HT was found in the cells of the superficial layers of the gastric mucosa, some of the cells in the deep layer adjacent to the submucous tissue showed specific fluorescence, as shown in Figure 1. The number of specific fluorescent cells in the stomach was significantly smaller than in the duodenum or jejunum. The most dense distribution of fluorescent cells was found in the duodenum, and these cells were especially abundant in Lieberkühn's crypts. However, no specific 5-HT-containing cells were detectable in Brunner's glands of the duodenum, as shown in Figure 2. The distribution of 5-HT-containing cells in the jejunum was definite, but there were fewer than in the duodenum (Fig. 3).

In the submucous and myenteric plexuses of the duodenum and jejunum, there were networks of fiber structures exhibiting intense green to yellow-green fluorescence representing adrenergic nerves. As in many other tissues, the small arteries and arterioles were surrounded by adrenergic nerve terminals with an intense green fluorescence. Fluorescent fibers were also found in the muscle layer proper.

Tissue specimens taken from the jejunum, the mucous membrane of which had been bathed in hypertonic glucose 30 minutes previously, showed considerable to complete diminution of specific 5-HT fluorescence. Yellowish fluorescent cells in Lieberkühn's crypts disappeared totally, as

shown in Figure 4. On the other hand, non-significant changes were seen in the greenish fluorescent fibers due to catecholamines. Exposure to physiological saline of the mucous membrane of the jejunum did not cause a significant reduction of yellowish 5-HT fluorescence. The general appearance of saline-injected jejunal tissue was similar to that of untreated specimens. In accord with the diminution of intestinal 5-HT, many of the post-gastrectomized patients complained of nausea, diarrhea or abdominal pain with palpitation in response to ingestion of hypertonic glucose solution during the glucose tolerance test. The complaints developed soon after the ingestion and lasted for 60 minutes. There was considerable individual variation in the severity of response, and symptoms in severe cases resembled the dumping syndrome.

Discussion

The yellowish fluorescence seen in the mucous membrane of the stomach, duodenum and jejunum is in all probability derived from 5-HT, as described in a previous report.[17] The distribution of the fluorescent cells is restricted to the mucous membrane, and is more dense in the duodenum and jejunum than in the stomach. Furthermore, fluorescent cells were found in Lieberkühn's crypts but not in Brunner's glands. Such specific localization of the fluorescent cells suggests a physiological role of 5-HT in controlling the motility and tone of the gastrointestinal tract. In fact, the content of 5-HT in the gastrointestinal tract varies largely according to the time after food intake (Tobe: unpublished observations).

The view supporting an important role

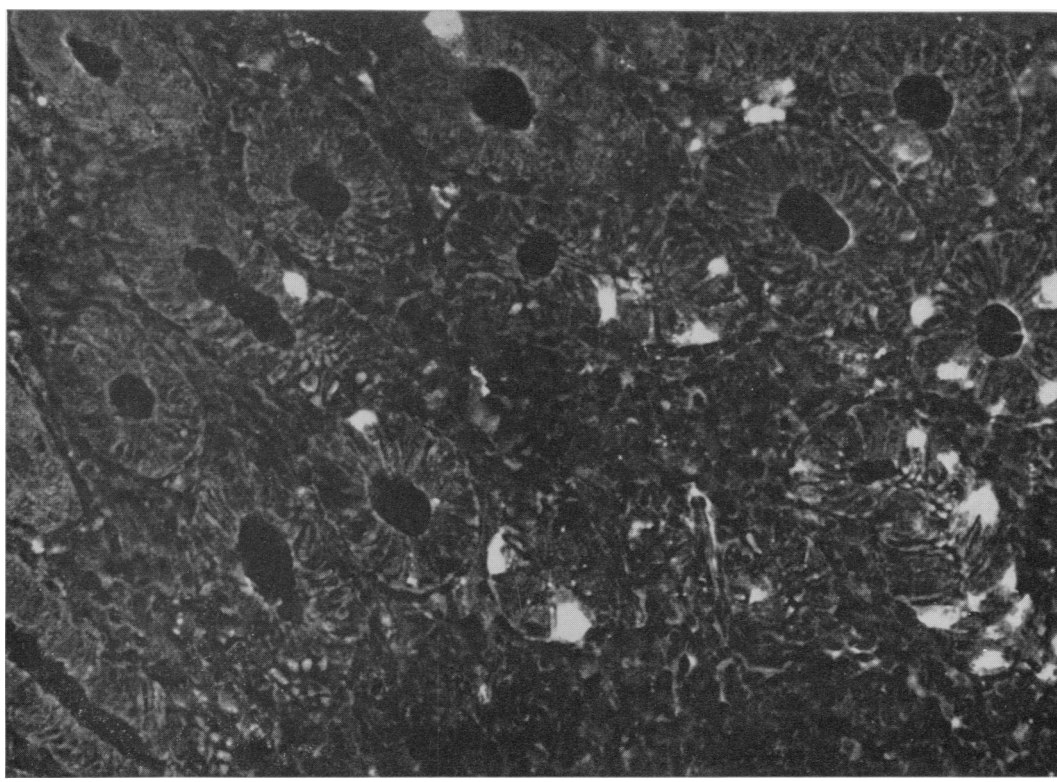

FIG. 3. Serotonin in the jejunum. In the jejunum many serotonin-containing cells can also be demonstrated in Lieberkühn's crypts, 4 or 5 times more than in the stomach. (×160.)

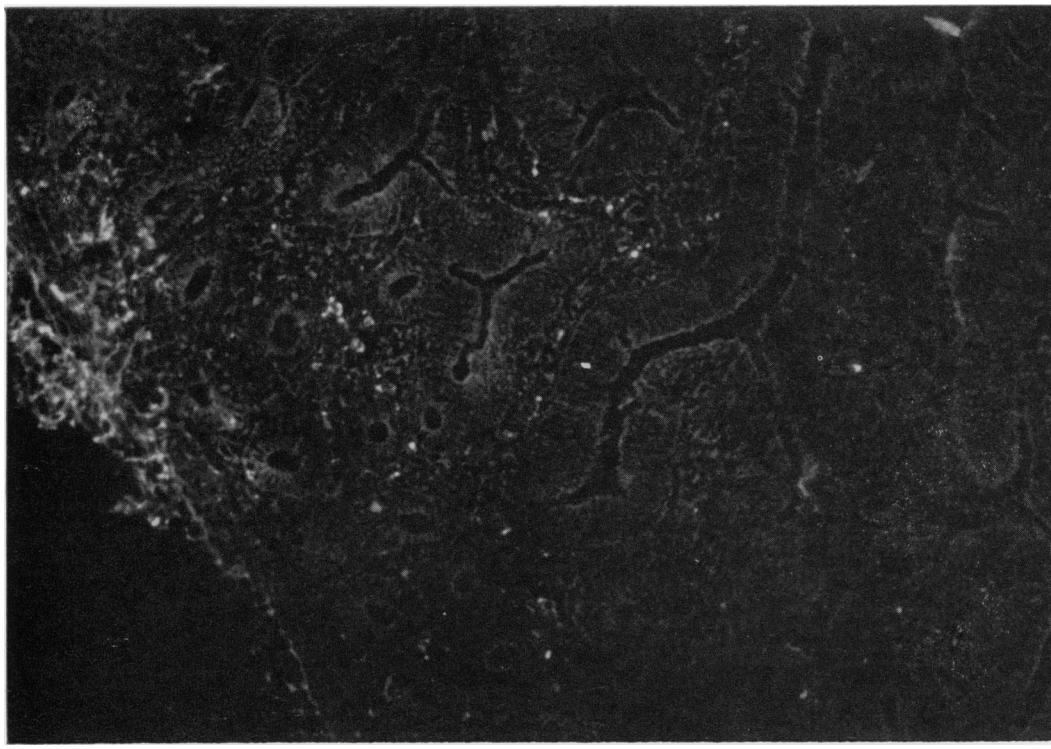

FIG. 4. Jejunum after the administration of 50% glucose. Complete release of serotonin can be identified. (×63.)

for 5-HT in the dumping syndrome has hitherto been based on the fact that hypertonic glucose induces symptoms resembling the dumping syndrome and an elevation of the blood 5-HT level in the portal vein in dogs.[2] The present study presents a morphological basis for the view that a humoral agent, 5-HT, may play an important role in the dumping syndrome of gastrectomized patients. 1) The distribution of 5-HT-containing cells is much larger in the duodenum and jejunum than in the stomach; 2) Jejunal 5-HT disappears completely or almost completely following topical application of hypertonic glucose to the mucous membrane, while catecholamines are not affected; and 3) Upon the ingestion of hypertonic glucose, many gastrectomized patients complain of nausea or abdominal pain with palpitation. In severe cases, the symptoms and signs resemble the dumping syndrome. It is considered that hypertonic glucose ingested by gastrectomized patients can flow very rapidly from the stomach without a pyloric ring into the duodenum or jejunum, which contains a large amount of 5-HT, causing the release of large amounts of 5-HT with the subsequent appearance of the dumping syndrome.

Although there have been several reports demonstrating that sucrose liberates endogenous monoamines or acetylcholine, the selective release of endogenous 5-HT in the gastrointestinal tract following the exposure of the mucous membrane to glucose needs more detailed study. It is assumed that the glucose is accessible to the 5-HT-containing cells in the mucous membrane more easily than to endogenous noradrenalin embedded in the deep structures.

The ingestion of hypertonic glucose by gastrectomized patients causes complaints resembling the dumping syndrome. How-

ever, no evidence has been presented to show that exogenously administered 5-HT produces similar symptoms in humans or that there is a quantitative relationship between the severity of the syndrome and the metabolism of 5-HT. Furthermore, it is not yet possible to state just how 5-HT causes the dumping syndrome after its release from the intestinal mucosa and transfer to the liver via the portal vein where 5-HT should be largely metabolized by monoamine oxidase.

Summary

With a specific fluorescence technic for demonstrating biogenic monoamines, the cytological localization of 5-HT and catecholamines in the human gastrointestinal tract has been demonstrated. In Lieberkühn's crypts in the duodenum and jejunum many 5-HT containing cells were found. Intrajejunally administered hypertonic glucose solution caused a complete to near-complete release of 5-HT in all cases. In accord with the 5-HT release, many gastrectomized patients to whom hypertonic glucose was administered during a glucose tolerance test complained of nausea or abdominal pain with palpitation. In severe cases, symptoms and signs resembled the dumping syndrome. It is suggested that after gastrectomy a liquid diet can flow very promptly from the stomach without a pyloric ring into the jejunum or duodenum, then induce considerable release of 5-HT which results in the dumping syndrome in 5-HT-sensitive patients.

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