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# Massive Submucosal Ganglia in Colonic Inertia

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**Context.**—Colonic inertia is a debilitating form of primary chronic constipation with unknown etiology and diagnostic criteria, often requiring colectomy. We have occasionally observed massively enlarged submucosal ganglia containing at least 20 perikarya, in addition to previously described giant ganglia with greater than 8 perikarya, in cases of colonic inertia. These massively enlarged ganglia have yet to be formally recognized.

**Objective.**—To determine whether such “massive submucosal ganglia,” defined as ganglia harboring at least 20 perikarya, characterize colonic inertia.

**Design.**—We retrospectively reviewed specimens from colectomies of patients with colonic inertia and compared the prevalence of massive submucosal ganglia occurring in this setting to the prevalence of massive submucosal ganglia occurring in a set of control specimens from patients lacking chronic constipation.

**Results.**—Seven of 8 specimens affected by colonic inertia harbored 1 to 4 massive ganglia, for a total of 11 massive ganglia. One specimen lacked massive ganglia but had limited sampling and nearly massive ganglia. Massive ganglia occupied both superficial and deep submucosal plexus. The patient with 4 massive ganglia also had 1 mitotically active giant ganglion. Only 1 massive ganglion occupied the entire set of 10 specimens from patients lacking chronic constipation.

**Conclusions.**—We performed the first, albeit distinctly small, study of massive submucosal ganglia and showed that massive ganglia may be linked to colonic inertia. Further, larger studies are necessary to determine whether massive ganglia are pathogenetic or secondary phenomena, and whether massive ganglia or mitotically active ganglia distinguish colonic inertia from other types of chronic constipation.

Chronic constipation is common and causes considerable morbidity and financial burden. Chronic constipation may be secondary to issues related to anatomy, diet, pharmacology, metabolism, or neurology.<sup>1</sup> Adult primary chronic constipation can be classified into 3 overlapping subtypes: colonic inertia, dyssynergic defecation, and constipation-predominant irritable bowel syndrome.<sup>1</sup> Colonic inertia is the most poorly defined subtype, characterized by long-standing intractable constipation, markedly prolonged transit time of stool, normal caliber of colorectum, and absence of aganglionosis.<sup>2</sup> Colonic inertia lacks established diagnostic criteria.<sup>1</sup> In contrast, dyssynergic defecation, characterized by uncoordinated abdominal and anorectal muscles, and constipation-predominant irritable bowel syndrome, characterized by pain, discomfort, and difficult defecation, are both more precisely defined subtypes. Dyssynergic defecation and constipation-predominant irritable bowel syndrome can be diagnosed in part on the basis of abnormal anorectal manometry findings, abnormal balloon expulsion test results,

abnormal defecography findings, and the Rome III criteria.<sup>1</sup> The terminology regarding chronic constipation in the literature is somewhat confusing. Colonic inertia is synonymous with the term slow-transit constipation. Some authors include cases of idiopathic chronic intestinal pseudoobstruction when studying colonic inertia.<sup>3</sup> However, chronic intestinal pseudo-obstruction encompasses enteric visceral myopathy, neuropathy, and mesenchymopathy, and it may be associated with well-established histopathology, including fibrotic or vacuolar degeneration of the muscularis propria, inclusions, hypoganglionosis, and inflammation.<sup>4</sup> Because chronic intestinal pseudo-obstruction can be considerably different from colonic inertia, for sake of clarity, we will avoid further use of the term chronic intestinal pseudo-obstruction.

Colonic inertia is idiopathic. Proposed etiologies include myopathy or neuropathy related to abnormally functioning smooth muscle, colocolonic reflexes, neurotransmitters, or interstitial cells of Cajal.<sup>1,2</sup> Patients with medically refractory colonic inertia usually respond symptomatically to colectomy with ileorectal anastomosis.<sup>1</sup> The pathology of colonic inertia has also yet to be well established. In fact, specimens from pancolectomy are typically histologically normal, and in particular have normal-appearing nerves, ganglia, and smooth muscle.<sup>2</sup> Giant ganglia, defined as enlarged ganglia containing large numbers of perikarya, have been previously described in the literature. Such giant ganglia are known to occupy presumably normal colonic submucosa as well as submucosa affected by colonic inertia.<sup>5-8</sup> We have occasionally observed massively enlarged submucosal ganglia with extremely large numbers of perikarya in specimens affected by colonic inertia, including ganglia with at least 20 perikarya. These ‘‘massive submucosal ganglia’’ have yet to be formally recognized. Our objective was to establish the link between such massive submucosal ganglia and colonic inertia.

## MATERIALS AND METHODS

The Institutional Review Board of the University of California, Irvine, approved the study as protocol HS No. 2008-6127 on January 24, 2008. We searched the electronic files of the University of California, Irvine, Department of Pathology and Laboratory Medicine, for all cases accessioned during the interval 1990–2008 involving pancolectomy and containing the term colonic inertia in the clinical history. Colonic inertia is the preferred term for this disease at our institution. We reviewed corresponding electronic clinical files to confirm clinical impression of colonic inertia, based on longstanding, medically refractive, chronic constipation; absence of metabolic, mechanical, or obstructive etiology; abnormal colonic transit diagnostic test results (SITZMARKS, Konsyl Pharmaceuticals, Easton, Maryland); and normal defecography or anorectal manometry findings. The controls consisted of 10 specimens accessioned during this same interval from colectomies of patients with nonobstructing colonic adenocarcinoma lacking history of chronic constipation. All material was routinely dissected and histologically processed. All histologic sections were stained only with hematoxylin-eosin, formalin-fixed, paraffin-embedded, and were 4- $\mu$ m thick. Microscopy consisted of initial review by 1 pathologist (K.N.) then confirmation by a second pathologist (M.L.W.) using a conventional optical microscope (BX45, Olympus America Inc, Melville, New York). Withheld were special techniques, including serial sectioning,

special histochemistry, and immunohistochemistry, owing to the retrospective nature of the study and financial restraints. We limited our study to sections taken from the colon for which submucosa was available for evaluation. Sections taken from colonic adenocarcinoma were eligible for review. For sake of simplicity, we considered sections from the rectosigmoid junction to be from the sigmoid colon proper and excluded sections from the terminal ileum, appendix, or rectum proper. We slightly modified previous definitions of perikarya and ganglia.<sup>5</sup> We defined a “perikaryon” as a large cell with extensive, finely granular amphophilic cytoplasm, and a large nucleus with dispersed chromatin with or without a prominent nucleolus, and with or without accompanying sustentacular cells. We tallied as perikarya objects that clearly partially represented perikarya. We defined a “ganglion” as a cluster of perikarya, which were not separated by submucosal connective tissue and which lacked the hamartomatous incorporation of other elements seen in ganglioneuromas.<sup>9</sup> We defined “giant submucosal ganglia” as submucosal ganglia containing greater than 8 perikarya in 1 histologic section.<sup>10</sup> We introduced the term massive submucosal ganglia to refer to submucosal ganglia containing at least 20 perikarya in 1 histologic section. This definition ensured that massive submucosal ganglia would be (1) easily distinguished from small giant ganglia; (2) potentially specific, since in our experience of daily sign-out ganglia of this size are rare; (3) of similar size to the largest reported nonneoplastic colorectal ganglia to our knowledge<sup>5,6</sup>; and (4) easily remembered owing to a convenient numerical criterion. We defined “enlarged submucosal ganglia” as submucosal ganglia that were either giant or massive. Excluded from our study were ganglia that (1) were intramucosal, as intramucosal giant ganglia are vanishingly rare<sup>11,12</sup>; (2) were in the Auerbach plexus, as ganglia in the Auerbach plexus are poorly circumscribed and difficult to accurately measure<sup>8</sup>; or (3) contained fewer than 9 perikarya, as these ganglia have poor interobserver reproducibility.<sup>5</sup> With these guidelines, we analyzed the numbers of submucosal giant, massive, and enlarged ganglia in both groups of patients.

We reviewed the slides with full knowledge of whether the slides were from patients with colonic inertia or adenocarcinoma. Review of slides blinded to the diagnosis was impractical, because we initially reviewed most of the specimens from both sets of patients during the course of daily sign-out and because slides with adenocarcinoma were eligible for review.

## RESULTS

Eight cases were accessioned in the relevant time interval with the term colonic inertia in the clinical history, and review of the corresponding electronic clinical files confirmed the clinical impression of colonic inertia for all of these 8 cases. Material from 8 patients with colonic inertia was therefore eligible for study. The 8 patients included 7 women (88%) and 1 man (12%), aged 33 to 68 years. The mean age was 43.9 years. All patients underwent pancolectomy with ileorectal anastomosis. All specimens lacked tissue from the rectum proper. The duration of chronic constipation ranged from approximately 1 year to several decades. The entire examined material from this set of patients consisted of 76 glass slides, with 1 to 2 histologic sections per slide. One hundred seventy-five enlarged submucosal ganglia were detected, including 164 giant submucosal ganglia (94%) and 11 massive submucosal ganglia (6%). Material from 7 of 8 patients had at

least 1 massive submucosal ganglion, with the most affected patient having 4 massive submucosal ganglia. Material from 1 woman had zero massive submucosal ganglia. However, for this patient, only 3 slides were available, and giant submucosal ganglia contained up to 17 perikarya. The massive submucosal ganglia contained 20 to 27 perikarya, with an average of 22.4 perikarya per massive submucosal ganglion. There were massive submucosal ganglia in both the Meissner and the Henle plexus as recently defined.<sup>13</sup> Although we reviewed the material 2-dimensionally, most massive submucosal ganglia appeared to be globular, and only 1 massive submucosal ganglion appeared to be disciform. The presumably disciform massive submucosal ganglion occupied the Henle plexus and appeared to be orthogonal to the mucosa. Figures 1 and 2 depict representative massive submucosal ganglia.

The set of 10 control patients that lacked chronic constipation consisted of 6 women and 4 men, aged 51 to 87 years. The mean age was 67.8 years. All patients underwent partial colectomy for colonic adenocarcinoma of either the right colon or left colon. All specimens lacked tissue from the rectum proper. The entire examined material from this set of patients consisted of 75 glass slides, with 1 to 2 histologic sections per slide. Thirty-four enlarged submucosal ganglia were detected, including 33 giant submucosal ganglia and only 1 massive submucosal ganglion. The massive submucosal ganglion contained 22 perikarya and was from a woman.

Interobserver agreement was achieved for all (209 of 209, 100%) enlarged submucosal ganglia. Although all massive submucosal ganglia lacked mitoses, interestingly, the specimen from the woman with colonic inertia that showed 4 massive submucosal ganglia also showed 1 mitotically active giant submucosal ganglion. The mitosis resembled a starburst (Figure 3). All enlarged submucosal ganglia in the set of controls lacked mitoses. All enlarged submucosal ganglia in the entire study lacked apoptotic bodies, showed no signs of plexitis, and were associated with nerve trunks of normal size. The average number of massive submucosal ganglia per slide was more than 10 times greater in patients with colonic inertia than in the control group (0.14 in colonic inertia, 0.01 in controls). The percentage of patients affected by massive submucosal ganglia was more than 8 times greater in the group with colonic inertia than in the control group (7 of 8 patients, 87.5%, in colonic inertia; 1 of 10 patients, 10%, in controls). The average number of enlarged submucosal ganglia per slide was more than 5 times greater in the group with colonic inertia than in the control group (2.3 in colonic inertia, 0.45 in controls). The average numbers of perikarya per enlarged submucosal ganglion (12.5 in colonic inertia, 11.2 in controls) were similar between groups and lacked practical significance. The Table summarizes key data.

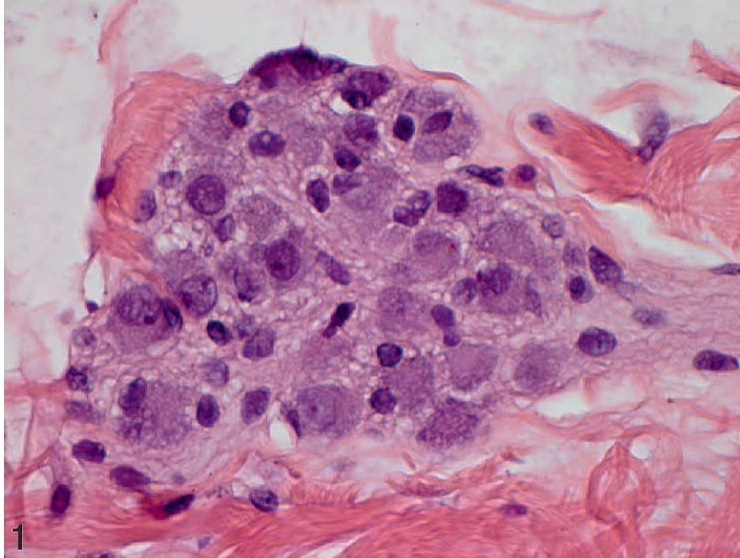


Figure 1. Globular massive ganglion in the Meissner plexus (hematoxylin-eosin, original magnification X600).

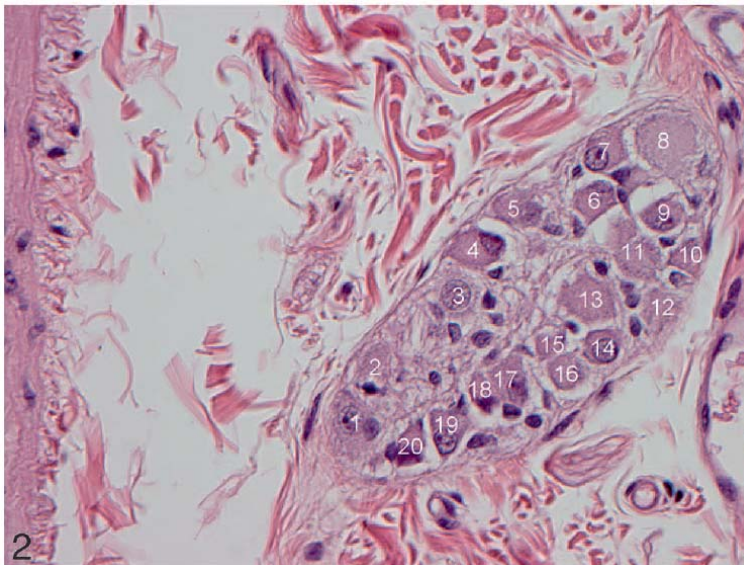


Figure 2. Disciform massive ganglion in the Henle plexus with perikarya numbered 1 to 20 (hematoxylin-eosin, original magnification 3600).

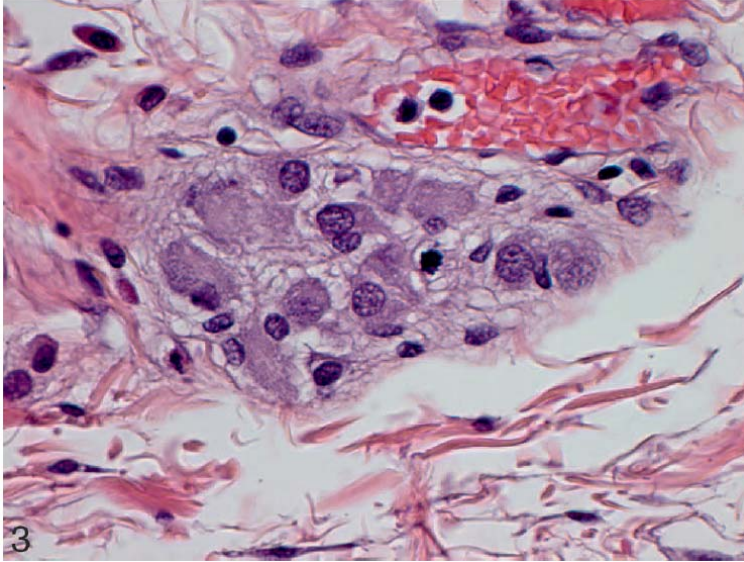


Figure 3. Giant ganglion with mitosis, right of center (hematoxylineosin, original magnification X600).

## DISCUSSION

Giant ganglia are currently defined as ganglia with greater than 8 perikarya,<sup>10</sup> though this threshold has ranged from 6 to 10 in various studies.<sup>12</sup> To our knowledge, all histologic studies of giant ganglia have used 2-dimensional analysis, with or without serial sections, and without digital 3-dimensional reconstruction. Giant ganglia were initially believed to be pathologic, and an important diagnostic criterion for neuronal intestinal dysplasia type B, a pediatric disease of chronic constipation. Subsequent studies showed that giant ganglia occasionally or commonly are seen in children and adults with presumably normal colorectal tissue, diverticulosis, or melanosis coli, as well as colonic inertia.<sup>5-8</sup> Giant ganglia are normal microanatomic variants.

Colonic inertia remains enigmatic in part because all elements of the specimens, including the neural tissue and smooth muscle, often appear histologically normal.<sup>2,3</sup> Furthermore, attempts to propose diagnostic histopathology suffer from low specificity, poor reproducibility, or impracticality. Prior studies have primarily focused on mast cells, histiocytes, smoothelin, interstitial cells of Cajal, and neural tissue. Colonic mast cells<sup>14</sup> and histiocytes<sup>15</sup> are increased in patients with colonic inertia. Unfortunately, colonic mast cells are also increased in patients with diarrhea or constipation associated with irritable bowel syndrome,<sup>16,17</sup> and melanosis coli often superimposes colonic inertia.<sup>2</sup> Specimens affected by colonic inertia may show decreased staining of smoothelin in the muscularis propria, confined to either the outer longitudinal layer or inner circular layer, or in both layers of the muscularis propria. However, the loss may affect only a minority of patients or be patchy.<sup>3,18</sup> As recently reviewed, conflicting data exist regarding whether colonic inertia causes a decrease in interstitial cells of Cajal.<sup>2</sup> Finally, the neural tissue, including nerve fibers and submucosal ganglia, may be decreased<sup>8,19,20</sup> or show giant ganglia and neuronal hypertrophy<sup>6,7</sup> in colonic inertia, but quantifying this volume may require immunofluorescence or immunohistochemistry.

Our anecdotal observation in our daily sign-out that submucosal ganglia with at least 20 perikarya occasionally occur in the setting of colonic inertia, and seldom occur outside this setting, prompted us to determine whether these ‘‘massive submucosal ganglia’’ might characterize colonic inertia. To our knowledge, only 2 previous studies have documented ganglia consistent with massive ganglia. One study of rectal biopsies from patients with colonic inertia depicted a ganglion detected by immunohistochemistry, containing approximately 24 perikarya, without any accompanying specific data or discussion.<sup>6</sup> The other study determined that patients lacking chronic constipation contained giant ganglia with 8 to 23 perikarya, without stating how many ganglia had numbers of perikarya toward the upper limit.<sup>5</sup>

Summary of Massive Submucosal Ganglia					
	Massive Ganglia	Slides	Average	Patients Affected, No. (%)	Mitoses
Colonic inertia	11	76	0.14	7 of 8 (87.5)	1
Controls	1	75	0.01	1 of 10 (10)	0

Although we studied a distinctly small number of patients, we showed that massive submucosal ganglia were over 10 times more common per slide in patients with colonic inertia than in controls; that massive submucosal ganglia occupied nearly all specimens from patients with colonic inertia, compared to only 1 patient from the controls; and that the average number of enlarged submucosal ganglia per slide was more than 5 times greater in patients with colonic inertia than in controls. The significantly lower prevalence of enlarged submucosal ganglia in the control population suggests a global upward shift in the likely continuous distribution of ganglion cells per ganglion, as opposed to a selective increase in massive ganglia. These data suggest that massive submucosal ganglia are characteristic of colonic inertia and potentially have diagnostic utility. If the findings of the current study are strengthened by subsequent studies, the presence of massive submucosal ganglia would be a convenient diagnostic criterion because massive submucosal ganglia are (1) positive findings, rather than negative findings; (2) highly visible by virtue of being large; (3) easily detected on hematoxylin-eosin-stained sections, obviating the need for immunostains; and (4) within the reach of biopsies, facilitating preoperative diagnosis. Some authors believe that normal ganglia are disciform and parallel to the mucosa.<sup>21</sup> In our study, 1 massive submucosal ganglion appeared to be disciform and orthogonal to the mucosa and others appeared to be globular, suggesting at least a subset of massive submucosal ganglia have abnormal microarchitecture.

The patient with the most massive submucosal ganglia also had a mitotically active giant submucosal ganglion. Given the large number of perikarya and the absence of plexitis, it is possible that the mitosis occupied a perikaryon or sustentacular cell and that the affected ganglion was transitioning from giant ganglion to massive ganglion, though further studies would be required to confirm the identity and significance of the mitotically active cell. Mitotically active ganglia in the setting of colonic inertia would support the notion that neurons, classically believed to be postmitotic, can divide during appropriate conditions,<sup>22</sup> or that cells with progenitor potential that give rise to neurons and glial cells persist in the adult colon.<sup>23,24</sup> Although quite rare, mitotically active ganglia might also have diagnostic utility.



The findings in the patients with colonic inertia share similarities with those of neuronal intestinal dysplasia type B, which may occur in adults. Diagnostic criteria for neuronal intestinal dysplasia type B include primarily submucosal neuronal hyperplasia, measured as the identification of at least 20% giant ganglia with at least 8 perikarya each, in 25 analyzed nerve ganglia, and other supportive findings.<sup>25</sup> In many respects, the data regarding neuronal intestinal dysplasia type B are consistent with the findings in this population of patients with colonic inertia and both potentially could be explained as a nonspecific submucosal neurogenesis in response to impaired motility. Indeed, a recent review of neuronal intestinal dysplasia type B depicts a giant ganglion that appears to have approximately 20 perikarya.<sup>25</sup>

Several factors limit our study. These factors include a distinctly small number of patients, retrospective unblinded review, relatively large difference in mean age (23.9 years) between patients with colonic inertia and the control group, and review of only routinely stained sections. Furthermore, we analyzed only submucosal ganglia and excluded from our study all ganglia in the Auerbach plexus, given that ganglia in the Auerbach plexus are more difficult to precisely measure.<sup>8</sup> Although massive submucosal ganglia were more common in patients with colonic inertia, if the prevalence of massive ganglia in patients without colonic inertia is even 1 of every 10 patients (10%), the finding cannot be relied upon diagnostically. Our study excluded the rectum, and the rectum would need to be studied to establish practical diagnostic utility given that rectal suction biopsies are often used in the diagnostic workup of chronic constipation, and suction or some other deep biopsy is required to reliably sample submucosa. Finally, the overall frequency of massive submucosal ganglia in the patients in this study suggests that many “biopsy-sized” samples would not contain massive submucosal ganglia. To establish the diagnostic utility of massive submucosal ganglia with respect to colonic inertia, we hope to confirm the findings in our descriptive pilot study by undertaking future studies with more comprehensive analysis. These future studies will include larger numbers of patients, standardized methods of grossing with thorough sampling for all specimens, prospective blinded review of slides, serial sectioning with 3-dimensional reconstruction, control sets with patients of similar age to that of patients with colonic inertia, and immunohistochemistry including Ki-67 or phosphohistone to further investigate mitotic activity.

We performed the first study of massive submucosal ganglia. Our study suggests that there may be a link between massive submucosal ganglia and colonic inertia. Further studies are necessary to determine whether massive submucosal ganglia are pathogenetic or secondary phenomena, and whether massive submucosal ganglia or mitotically active ganglia distinguish colonic inertia from other types of chronic constipation.

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