

# Histologic Study of Colonic Mucosa in Patients With Chronic Diarrhea and Normal Colonoscopic Findings

José Guilherme Nogueira da Silva, MD,\* Thales De Brito, MD,†  
Aderson Omar Mourão Cintra Damião, MD,\* Antônio Atilio Laudanna, MD,\*  
and Aytan Miranda Sipahi, MD\*‡

**Background:** There are controversies about the importance of biopsies of normal colon mucosa in the investigation of patients with chronic diarrhea.

**Study:** Colonic and terminal ileum biopsies of 167 patients were reviewed. In 5 patients, used as controls, colonoscopy was done due to family history of colon cancer.

**Results:** The 5 patients without symptoms had no histologic abnormalities. The histologic findings in 162 patients with chronic diarrhea were as follows: 110 patients (67.9%) with normal histology, microscopic colitis not otherwise specified, and isolated small granulomas; 17 (10.5%) patients had findings of borderline diagnostic significance, including possible collagenous colitis, some features of lymphocytic colitis and melanosis coli; and 35 (21.6%) patients, with diagnostic significant histologic findings as collagenous colitis, lymphocytic colitis, minimal change microscopic colitis, eosinophilic colitis, pericrypt eosinophilic enterocolitis, intestinal spirochetosis, schistosomiasis, and Crohn's disease. Of the 52 patients with either borderline or significant diagnostic abnormalities, in 8 (15.4%) the diagnosis was done only with a proximal study (ascending, transverse, or descending colons).

**Conclusions:** Histologic lesions of possible diagnostic value could exist in 32.1% of chronic diarrhea patients with normal colonoscopy, which can justify, in certain cases, mucosa biopsies, which might contribute for a more precise etiologic diagnosis; also, the distribution of these histologic changes has pointed out the importance of having all colon segments biopsied.

**Key Words:** biopsy, colitis, colonic diseases, colonoscopy, diarrhea

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From the \*Department of Gastroenterology and ‡Medical Investigation Laboratory of Gastroenterology (LIM 07), University of São Paulo Medical School, São Paulo, Brazil; and †Laboratory of Immunopathology, Institute of Tropical Medicine, Division of Pathology, "Hospital das Clínicas," University of São Paulo, São Paulo, Brazil.

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Reprints: José Guilherme Nogueira da Silva, MD, Disciplina de Gastroenterologia, Clínica da FMUSP, Av. Dr. Enéas Carvalho de Aguiar, 255/9 andar - sala 9159, São Paulo, SP Brazil (e-mail: jgnogueirasilva@uol.com.br).

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Colonoscopy has increasingly been used in the investigation of patients with chronic diarrhea.<sup>1</sup> This procedure enables biopsies to be used for pathologic study as a means of confirming diagnosis.<sup>2</sup> However, the majority of colonoscopic screenings have disclosed a macroscopically normal mucosa.

The contribution to diagnosis of histologic studies of macroscopically normal colonic mucosa has already been verified, as in the case of Crohn's disease,<sup>3,4</sup> collagenous and lymphocytic colitis, eosinophilic colitis, intestinal spirochetosis, melanosis coli, and colitis caused by cytomegalovirus.<sup>5–9</sup> However, there is still no consensus among gastroenterologists on whether obtaining biopsies of an apparently normal mucosa during colonoscopy do provide a significant increase in the diagnostic elucidation rates.<sup>3,5,6,10–13</sup>

The present study aims, therefore, to contribute to the elucidation of these controversies, using uniform inclusion criteria for a population exposed to environmental agents that might lead to chronic diarrhea.

## PATIENTS AND METHODS

Histologic slides of the terminal ileum, colon, and rectum from 167 outpatients with normal ileocolonoscopy referred by the Department of Gastroenterology of the Hospital das Clínicas of the Medical School of the University of São Paulo, between 1996 and 2000, were reviewed. A total of 162 patients presented with chronic diarrhea and 5 were asymptomatic. Colonoscopy, for the latter, was justified because of a family history of malignant neoplasia of the large bowel. The histologic characteristics of the colonic mucosa and ileum of these 5 patients were used as the basis for analysis of those with chronic diarrhea. Chronic diarrhea was defined for those patients who presented with three or more daily evacuations, with soft or liquid stools, for a period of at least 4 weeks.<sup>7,9,11,12</sup> The patients with chronic diarrhea ranged in age from 16 to 79 years, with an average of 44.2 years. Sixty-six patients (40.7%) were male and 96 (59.3%) were female. Patients who had any macroscopic alteration of the colon or ileal mucosa were excluded, except for those with inflammatory or adenomatous small polyps, vascular ectasias, and uncomplicated colonic diverticular disease.

The same endoscopist (J.G.N.S.) did all the ileocolonoscopies. The examinations reached as far as terminal ileum in all cases. Four biopsy fragments were collected randomly from each segment, ie, the terminal ileum, the ascending, transverse, descending and sigmoid colons, and the rectum. A single



pathologist (T.D.B.) reviewed three times, together with the endoscopist, all histologic slides.

Special stains, such as periodic acid-Schiff, Masson's trichrome, and the immunohistochemical reaction to tenascin, were used to better characterize the cases of collagenous colitis.<sup>14,15</sup> Intestinal spirochetosis immunohistochemical reaction was performed as previously described.<sup>8</sup>

The presence of a low-grade inflammatory infiltration, with plasma cells, lymphocytes, and rare eosinophils, distributed over the superficial colonic mucosa is normal and should not be interpreted as colitis.<sup>2-16</sup> Nevertheless, the presence of lymphocytes and plasma cell infiltration down to the muscularis mucosae represents a loss of the normal gradient of chronic inflammatory cells. In this study, the term "microscopic colitis not otherwise specified" was used to designate such chronic inflammatory processes of the colonic mucosa, predominantly with lymphocytes and plasma cells, for which an etiology cannot be determined.<sup>2,16</sup>

Collagenous and lymphocytic colitis, minimal change microscopic colitis, eosinophilic colitis, pericrypt eosinophilic enterocolitis, intestinal spirochetosis, Crohn's colitis, and melanosis coli have previously been shown to have characteristic and well-established histologic features.<sup>2,4,8,16-25</sup>

The granulomas were diagnosed according to three types: 1) the epithelioid, fully developed, noncaseating, found in the deep mucosa and submucosa, composed of epithelioid macrophages, lymphocytes, foreign body and/or Langhans type giant cells; 2) the mature granuloma, without giant cells, found in the lower third of the mucosa, with epithelioid macrophages and lymphocytes; and 3) the microgranuloma, found in the upper third of the mucosa, composed of macrophages, without giant cells, lymphocytes, and an array less compact than mature granulomas.<sup>4,23,26</sup> It may be interpreted as a late phase of a persistent chronic inflammation evolving to an early phase of a granulomatous inflammation.

With the objective of verifying the utility of rectosigmoidoscopy as an initial procedure to investigate chronic diarrhea in these patients, the histologic findings that allowed for diagnosis were studied separately at the distal and proximal colon. The rectum and sigmoid colon, which could be evaluated by rectosigmoidoscopy, were considered to be distal. The rest of the colon and the terminal ileum, which can only be reached by colonoscopy, were considered to be proximal.

This study was approved by the Ethical Scientific Committee of the Department of Gastroenterology of the Medical School of the University of São Paulo and by the Commission on Ethics for the Analysis of Research Projects of the Hospital das Clínicas of the Medical School of the University of São Paulo.

## RESULTS

The 5 asymptomatic patients had histologic aspects of the mucosa of the colon and ileum within normal limits. Of the 162 patients with chronic diarrhea, 51 (31.5%) presented normal histology. The other 111 patients (68.5%) had some histologic alterations that are listed in Table 1.

Microscopic colitis not otherwise specified was found in 37 patients (22.8%). The isolated granulomas represented

TABLE 1. Histologic Findings in Patients With Chronic Diarrhea

Histologic Finding	N	%
Normal histology	51	31.5
Histologic abnormalities	111	68.5
Microscopic colitis, not otherwise specified	37	22.8
Collagenous colitis*	19	11.7
Lymphocytic colitis†	12	7.4
Minimal change microscopic colitis	12	7.4
Isolated granulomas	22	13.6
Eosinophilic colitis	02	1.2
Pericrypt eosinophilic enterocolitis	02	1.2
Intestinal spirochetosis	01	0.6
Schistosomiasis	01	0.6
Crohn's disease	01	0.6
Melanosis coli	02	1.2
Total no. of patients	162	100

\*Ten patients with histology of possible collagenous colitis.

†Five patients with some features of lymphocytic colitis.

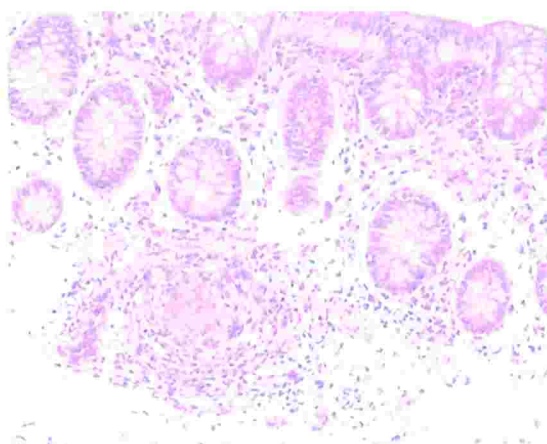
the predominant histologic finding, occurring in 22 (13.6%) patients (Fig. 1). Collagenous colitis (Fig. 2) and lymphocytic colitis (Fig. 3) were found in 19 (11.7%) and 12 (7.4%) patients, respectively. Another frequently encountered diagnosis was minimal change microscopic colitis, found in 12 patients (7.4%) (Fig. 4). Less frequent findings were eosinophilic colitis in 2 (1.2%) patients, pericrypt eosinophilic enterocolitis in 2 (1.2%) patients, intestinal spirochetosis in 1 (0.6%) patient (Figs. 5, 6), Crohn's disease in 1 patient (0.6%), and schistosomiasis in 1 patient (0.6%). Melanosis coli was found in 2 (1.2%) patients.

Collagenous colitis, with the use of only the routine tests hematoxylin and eosin, periodic acid-Schiff, and Masson's trichrome, was detected in 9 of 19 (47.4%) patients. However, by using the immunohistochemical reaction for tenascin, this number increased in 10 (52.6%) patients (Fig. 2). The first 9 patients had typical histologic features, with inflammatory infiltration and thickening of the subepithelial collagen band equal to or greater than 10  $\mu$ m. Of the 10 patients for whom this diagnosis was considered only after a positive reaction to tenascin, the thickening of the subepithelial collagen band was focal and/or measured less than 10  $\mu$ m.

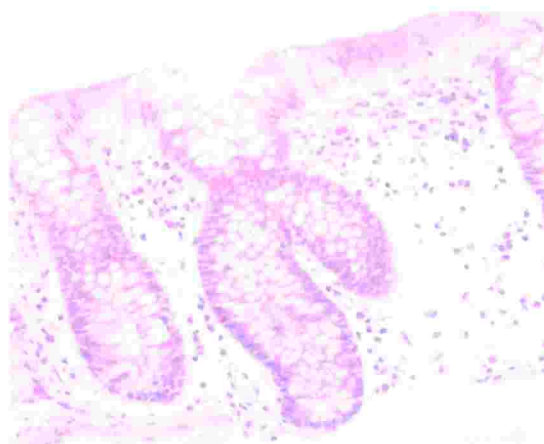
Of the 12 patients with lymphocytic colitis, 7 (58.3%) presented typical histologic features and the remaining 5 (41.7%) showed "some features of lymphocytic colitis," according to criteria proposed by Lazenby et al<sup>18</sup> (Fig. 3).

Minimal changes microscopic colitis was found in 12 patients. The "minimal changes" were represented by ramification of the crypts in 9 (75%) patients (Fig. 4), abscesses of the crypts in 2 (16.7%) patients, and the presence of these two alterations in 1 (8.3%) of the 12 patients. Microgranulomas located in the mucosa were found in 3 patients.

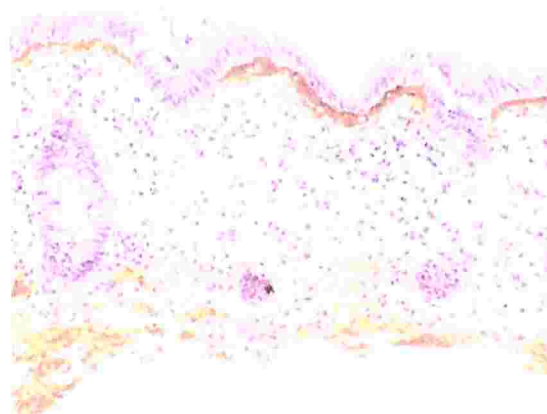
Of the 22 patients with isolated granulomas, microgranulomas were found in 11 (50%), mature granulomas in 9 (40.9%), epithelioid granulomas in 1 (4.5%) (Fig. 1) and epithelioid granulomas and microgranulomas in 1 (4.5%). Mature granulomas with the presence of eosinophils were found in two



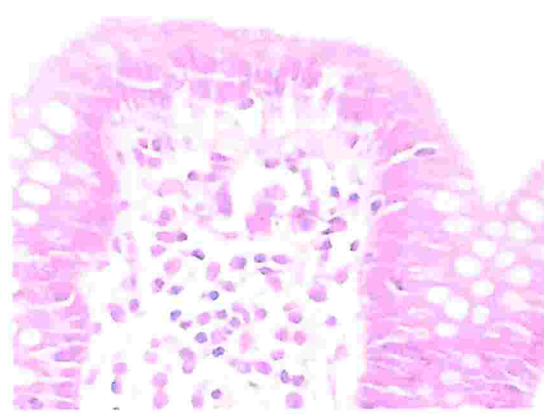
**FIGURE 1.** Colonic mucosa (hematoxylin and eosin, original magnification  $\times 200$ ). Noncaseating epithelioid granuloma in the submucosa.



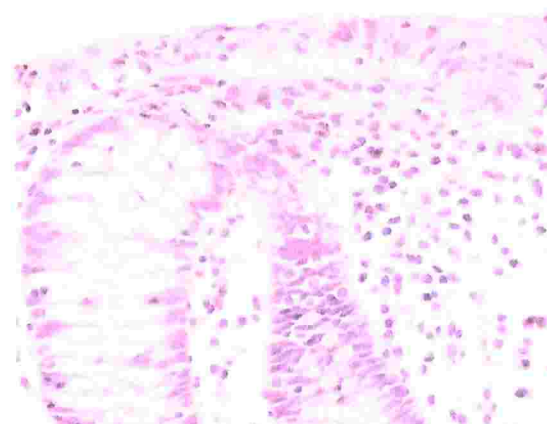
**FIGURE 4.** Minimal changes microscopic colitis (hematoxylin and eosin, original magnification  $\times 200$ ). See the crypt bifurcation.



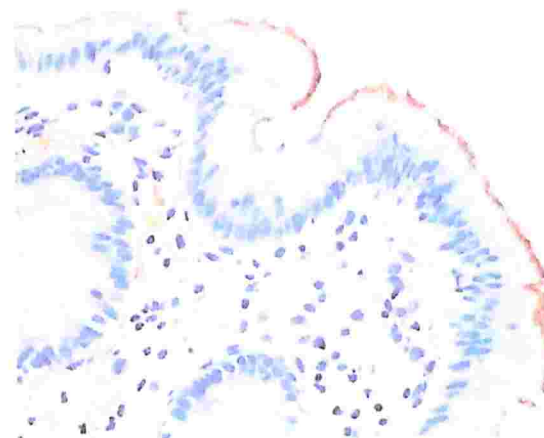
**FIGURE 2.** Collagenous colitis (immunohistochemical reaction to tenascin, original magnification  $\times 200$ ). See the thickening of the subepithelial collagen band after a positive reaction to tenascin.



**FIGURE 5.** Intestinal spirochetosis (hematoxylin and eosin, original magnification  $\times 400$ ). See the thick hematoxyphilic fringe on the brush border of the surface epithelium.



**FIGURE 3.** Lymphocytic colitis (hematoxylin and eosin, original magnification  $\times 400$ ). See the intraepithelial lymphocytes, epithelial damage, and increase in lamina propria chronic inflammation.



**FIGURE 6.** Intestinal spirochetosis immunohistochemical reaction, original magnification  $\times 400$ . See the marked contrast of the fringe over the colonic epithelium.



patients with parasites upon parasitologic fecal study (*Ancylostoma duodenale* and *Strongyloides stercoralis*, respectively).

After the analysis of the histologic findings, the 162 patients with chronic diarrhea were divided into three groups, according to their importance in the etiology of chronic diarrhea (Table 2).

Of the 52 patients (32.1%) with histologic alterations of some diagnostic importance, in 44 (84.6%) the diagnosis was possible using only an evaluation of the rectum and sigmoid colon. Nevertheless, if only the distal examination had been done, the diagnosis would not have been made in 8 patients (15.4%). The diagnosis would not have been made in 16.7% of lymphocytic colitis, 25% colitis with minimal change microscopic colitis, and in the cases of schistosomiasis and pericrypt eosinophilic enterocolitis. The histologic study of the terminal ileum failed to contribute to diagnosis in 100% of cases.

Of the 22 patients with histologic findings of isolated granulomas, it was possible to establish a final diagnosis by follow-up in 15 (68.2%). In 9 cases (40.9%), with any other indication of a specific disease, irritable bowel syndrome was finally diagnosed. In the others, ulcerative colitis was found in 2 (9.1%), intestinal parasitoses were found in 2 (9.1%) and Crohn's disease was found in 2 patients (9.1%). The 2 patients with diagnosis of ulcerative colitis had microgranulomas. A later diagnosis of Crohn's disease in the small intestine was made in 2 patients: 1 with epithelioid granulomas in the submucosa and another with mature granulomas of the mucosa.

## DISCUSSION

In the 162 patients who had chronic diarrhea, in this study, histologic aspects of unquestionable diagnostic importance were found in 35 patients (21.6%) with minimal changes microscopic colitis,<sup>16,20</sup> collagenous and lymphocytic colitis with typical histologic features, eosinophilic colitis, pericrypt

eosinophilic enterocolitis, intestinal spirochetosis,<sup>5,8,18,27</sup> schistosomiasis, and Crohn's disease. The findings in 17 patients (10.5%), 10 of whom with possible collagenous colitis, 5 with some features of lymphocytic colitis and 2 patients with melanosis coli, could generate some discussion. With regard to collagenous colitis, authors such as Lazenby et al<sup>18,19</sup> consider the thickening of less than 10  $\mu$ m of the subepithelial collagen band in making a diagnosis in the presence of a clinical picture and characteristic inflammatory infiltration. They need follow-up with periodic colonoscopy with biopsies to detect possible evolution toward classic cases of colitis.<sup>9</sup> With regard to melanosis coli, which cannot be considered a disease and much less be directly related to the diarrhea presented by the patients, this finding might suggest the abusive use of laxatives, which has an undeniable effect on medical decisions.<sup>12,25</sup>

Isolated granulomas, found in 22 patients, were a frequent finding in this study (13.6%). Nevertheless, it cannot be definitely stated that they have diagnostic significance for the elucidation of the etiology of the chronic diarrhea. Similar studies do not mention findings of isolated granulomas in the histologic study.

Crohn's disease is the main differential diagnosis of granulomatous disease of the gut.<sup>4,24</sup> No other alterations were found in any of the 22 patients, which would allow for a histologic diagnosis of Crohn's disease. Nevertheless, follow-up permitted a final diagnosis in 6 patients. Two patients, 1 with an epithelioid granuloma and another with a mature granuloma were diagnosed as Crohn's disease, detected on the radiologic contrast examination of the small intestine. Two other patients, with microgranulomas, evolved to a diagnosis of ulcerative colitis, made with a new colonoscopy with biopsies. The microgranulomas are nonspecific and can also occur in ulcerative colitis.<sup>23</sup> Two other patients with isolated granulomas presented intestinal parasitosis, 1 with strongyloidiasis and another with ancylostomiasis. There are reports in the literature of the formation of granulomas in the large bowel wall in cases of infestation with *Strongyloides stercoralis* but not with *Ancylostoma duodenale*.<sup>28,29</sup>

The frequency of histologic alterations, etiologically related to chronic diarrhea in 32.1% of patients, proved to be a little higher than the 14.7% to 27.2% described by other studies.<sup>3,5-7,9-12</sup> However, a critical review of these studies has showed a great deal of heterogeneity, with a small number of patients,<sup>3</sup> or the inclusion of patients with anemia or hematochezia or constipation,<sup>5,6</sup> or patients with macroscopic abnormalities at colonoscopy,<sup>11,12</sup> or having their evaluations restricted to a rectosigmoidoscopy.<sup>7,10</sup> The validity of the biopsies, taken only from the rectum and sigmoid colon for diagnosis of lymphocytic and collagenous colitis, might be questionable. Some authors have suggested that thickening of the subepithelial collagen band and an increase in intraepithelial lymphocytes become less evident from the cecum to the rectum, and consequently, the biopsies by rectosigmoidoscopy can fail to elucidate a diagnosis.<sup>17</sup> Lee et al<sup>9</sup> also presented a set of cases similar to those in this article, with collagenous colitis in 1.7%, lymphocytic colitis in 0.8%, eosinophilic colitis in 0.8%, alterations suggestive of ulcerative colitis in 0.8%, melanosis coli in 3.4%, and alterations

TABLE 2. Importance of the Histologic Findings for the Diagnosis of Chronic Diarrhea Etiology

Histologic Findings	N	%
With no importance	110	67.9
Normal histology	51	31.5
Microscopic colitis, not otherwise specified	37	22.8
Isolated granulomas	22	13.6
With borderline importance	17	10.5
Possible collagenous colitis	10	6.2
Some features of lymphocytic colitis	05	3.1
Melanosis coli	02	1.2
With diagnostic importance	35	21.6
Minimal change microscopic colitis	12	7.4
Collagenous colitis	09	5.6
Lymphocytic colitis	07	4.3
Eosinophilic colitis	02	1.2
Pericrypt eosinophilic enterocolitis	02	1.2
Intestinal spirochetosis	01	0.6
Schistosomiasis	01	0.6
Crohn's disease	01	0.6
Total no. of patients	162	100

suggestive of collagenous and lymphocytic colitis in 6.8%. They also concluded in favor to the routine biopsy in this kind of patient.

The high frequency of histologic alterations in this study can be explained, at least in part, by the uniform protocol, by the criteria for histologic diagnosis, as well as by the type of population studied, not observed in other publications.<sup>10-12,18,19</sup> Another explanation could lie in the broader criteria for diagnosis of the two types of colitis adopted in this study, which is, the inclusion of patients "with some features of lymphocytic colitis" and also those with focal or borderline thickening of the subepithelial collagen band. Finally, in our country, a large amount of the population is exposed to a variety of pathogens and antigenic stimuli such as parasitosis, bacterial and viral colitis, and contamination by xenobiotics (food additives, pesticides).<sup>30</sup> This is suggested by the incidence of parasitosis and by the large number of patients with isolated granulomas.

With regard to the need of macroscopic study with biopsies of the entire colon in patients with chronic diarrhea, authors who defend just the study of the distal colon<sup>12</sup> affirm that the alterations found in the rectum and sigmoid are representative of the rest of the colon, ruling out the need of colonoscopy. Fine et al<sup>12</sup> showed that the study of the rectum and sigmoid colon would provide a diagnosis in 99.5% of their patients. On the other hand, Prior et al<sup>5</sup> recommended proximal biopsies, given that in 13.6% of cases the diagnosis could not be made merely with the distal histology. The results of the present study, where the histologic findings only in the proximal colon in 15.4% of the 52 patients with alterations related to diarrhea, emphasize the importance of studying the entire colon in cases of chronic diarrhea.

In summary, the analysis of the results of this study reveals that taking random biopsies of the macroscopically normal colon mucosa might contribute for the etiologic investigation of patients with chronic diarrhea.

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