Pattern of Epithelial Cell Proliferation in Colorectal Mucosa of Normal Subjects and of Patients with Adenomatous Polyps or Cancer of the Large Bowel

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ABSTRACT

Microautoradiography has been largely used to characterize the proliferative activity of colorectal mucosa. We used this technique in a large series of patients with polyps or cancer of the large bowel and in normal controls with the following objectives: (a) to define the normal pattern of cell replication in different tracts of the large bowel; (b) to compare the proliferative activity of colonic crypts in patients with colorectal cancer or polyps with that of controls; (c) to evaluate replicative activity of colorectal mucosa in the close vicinity and at distance from a neoplastic mass. Observations on colorectal mucosa were taken during endoscopy (controls and polyps) or at surgery (cancer). During histological examination each intestinal hemicyrst was divided into five equal longitudinal compartments from the base to the surface and the labeled cells in each compartment were counted. In controls, total labeling index (ratio of labeled to total cells) and labeling index per crypt compartment showed only minor differences between the various large bowel tracts. Total labeling index tended to be higher in patients with polyps or cancer than in controls (13.5 ± 0.4 and 12.5 ± 0.4, respectively, versus 11.3 ± 0.5). Labeling index per crypt compartment in the most superficial portions of the crypt ( compartments 3 to 5) was significantly higher in the two groups of patients with tumors than in controls. This was particularly evident in the fifth compartment (the most superficial), in which labeled cells were observed in 15.8% (three subjects out of 19) of controls but in 71% (15 out of 16) of polyp and cancer patients, respectively. In patients with colorectal cancer there were not significant differences of cell proliferation between mucosal samples taken at various distances from the tumor margin; however, increased cell replication, especially in the most superficial portions of the crypt, has been observed. In conclusion, a significant upwards expansion of the proliferative zone of intestinal glands has been observed in patients with either polyps or cancer of the large bowel. In particular, labeling of the fifth compartment seems to possess the highest discriminatory power between subjects with or without intestinal neoplasms. Hyperproliferation of the entire colonic mucosa seems to be a common feature in patients with colorectal cancer.

INTRODUCTION

Despite the most recent technological advances in early diagnosis, screening procedures, and identification of individuals at risk, the incidence and the mortality of colorectal cancer have remained virtually unchanged (1, 2). There are, however, many biological markers whose critical evaluation might be of help in controlling this common malignancy. Among these markers, one of the most widely accepted is the autoradiographic evaluation of the proliferative pattern of colorectal mucosa after incubation of small biopsies with tritiated thymidine (3). Using this technique, Deschner, Lipkin, and coworkers (4–7) found significant differences of epithelial cell kinetics between populations at increased risk of colorectal cancer and other individuals at low risk of cancer. More in particular, they found that the proliferative zone of normal colorectal mucosa is confined to the lower two-thirds of the colonic crypts, whereas in conditions of high risk of cancer proliferating cells are observed throughout the whole length of the gland. They also described two stages of alteration; in the first ( Stage 1 abnormality) proliferative cells are observed in the whole crypt but the area of higher epithelial cell proliferation is still confined to the lower two thirds of the gland; in the second ( Stage 2 abnormality) the zone of maximal kinetic activity is shifted to the upper portions of the crypts. This abnormal pattern of cell proliferation has been characterized in members of families with inherited colonic tumors (6–8) and in patients with adenomatous polyps (9–11) or cancer (3, 5, 12).

Despite the numerous studies on this topic there are still many aspects which need to be investigated in more detail. For example, in most of the above-mentioned studies, cell proliferation has been evaluated in samples of rectal mucosa, simply because this segment is by far the most easily accessible; little is known on cytoproliferation in the various tracts of the large bowel and, consequently, if the rectal epithelial cell kinetics may appear as representative of the proliferative activity of the entire colorectal tract of humans. In addition, although normal subjects tend to show a proliferative pattern limited to the lower two-thirds of the colonic crypt and high risk (or cancer) patients tend to show Stage 1 or 2 abnormalities, the difference is not clear-cut. There are studies in which a sizable proportion of normal individuals shows a clear expansion of the proliferative compartment to the upper portion of the crypt (4, 10); by contrast, a normal cytoproliferative pattern has been reported in some subjects undoubtedly at risk of colorectal cancer (9, 13). It follows that despite the application of new analytical methods of greater precision in measuring cell kinetics (7, 14), the predictive value of colonic cell proliferation pattern in individual subjects is still unclear. Finally, preliminary studies have shown the existence of a hyperproliferative state throughout the entire colon in patients with adenomatous polyps or with large bowel cancer (15), and an increase in the amount of DNA in the proliferative cells close to the tumor as compared to more distal areas (16).

The purpose of the present study was threefold: Firstly, to characterize, in normal subjects, the pattern of epithelial cell proliferation in different tracts of the large bowel (cecum, ascending, transverse and descending colon, sigmoid, and rectum). Secondly, to investigate the cytoproliferative pattern of rectal mucosa in patients with adenomatous polyps of various size or with large bowel cancer and to compare the observed
CELL PROLIFERATION IN COLORECTAL MUCOSA

findings to those of normals. Thirdly, to find out if cytoproliferation of colorectal mucosa in the close vicinity of a tumoral mass is higher than that observed more distally. Finally, the more general objective of this as well as other studies from our group (17-19) remains to establish the predictive and discriminatory value of the microautoradiographic technique in the definition and follow-up of individuals at risk of colorectal cancer.

MATERIALS AND METHODS

Patients. Three groups of subjects entered the study. The first group was represented by 19 individuals (10 male, nine female, age range, 33-88; mean ± SD, 57 ± 15) with a negative panendoscopy and no personal or familial history of colorectal neoplasms. The second group consisted of 21 patients (16 male, five female; age range, 27-76; mean ± SD, 56 ± 16) with adenomatous polyps measuring <20 mm of diameter. 13 patients had single polyps, eight multiple polyps. Although found in all the large bowel segments, the polyps were more frequent in the rectosigmoid region. All polyps were removed during endoscopy.

Panendoscopy was executed usually late in the morning or in the early afternoon. The patients were prepared for the investigation with a mixture of O2 (95%) and CO2 (5%) was bubbled through the medium for 1 h. transferred to ethanolic solutions and embedded in paraffin. The entire block was cut into 3-μm thick sections (usually not less than 20) which were placed on a slide; these were rehydrated and counterstained with hematoxylin and eosin. Microscopic examination was usually performed at x 400 or x 1000 magnification under oil immersion. Only longitudinally oriented crypts with a single cell layer were considered for analysis. For each hemicyrst (or "column," i.e., each side of the length of a crypt), the total number and the position of labeled cells were determined. A cell was considered "labeled" (i.e., in S-phase of the replication cycle during the incubation period) when at least six grains were observed over the nucleus (against a clear background). In order to study the height distribution of labeled cells and to compare crypts of different size, each column was divided in five equal longitudinal compartments, from the base (compartment 1) to the mouth of the gland (compartment 5). Total LI* is the percentage of labeled cells for each column (i.e., the ratio of labeled to total cells). Labeling index for crypt compartment is the ratio between labeled and total cells in each compartment.

Statistical Analysis. When the results were "normally" distributed (as in the case of total LI or LI for crypt compartments 1 to 2) the statistical significance of differences between means was evaluated with Student's t test for paired or unpaired analysis. When the distribution of data was not normal (as in computing the data of compartments 4 and 5, in which many zeros were observed) the results were also evaluated with nonparametric methods (Wilcoxon test). When relevant, analysis of variance and χ² tests have been used.

RESULTS

Epithelial Cell Proliferation in Different Segments of the Large Bowel. Table 1 summarizes the investigated parameters in the 19 subjects with a normal endoscopy. All subjects had biopsies taken from the rectum; in ten, samples were also taken from sigmoid and descending colon; in 12, from the transverse colon, and in seven from the ascending colon and the cecum. The number of columns assayed for each patient ranged from 23.4 (rectum) to 45.3 (descending colon). The number of epithelial cells per crypt column showed only minor differences between each segment and, on average, was in the order of 45-50, a value similar to those reported in other studies (9, 13, 21) but lower than that observed in other investigations (5, 19, 22). The mean total LI was 10-11% in all the segments with the exception of cecum, whose mean value (8.3 ± 0.3%) was significantly lower than those found in all the other tracts. LI per crypt compartment showed the same trend in each of the investigated segments: proliferative activity was maximal in the first and in the second compartment and gradually decreasing in the most superficial portions of the crypts.

Table 2 shows, for each segment and compartment, the total number of crypts with at least one labeled cell; the large majority (72-85%) of investigated crypts had labeled cells in the first two compartments without any appreciable difference between segments. Approximately half of the crypt had labeled cells in compartment 3, whereas the proportion was reduced to 13-20% in compartment 4, again without any relevant difference between the various large bowel tracts. As for the fifth compartment, labeled cells were found in a few crypts only (0.5-3.0%); in the rectum, however, the absolute number of proliferative cells was significantly (p < 0.01 by χ² test) higher than in descending and transverse colon (15 out of 445, three out of 453, and three out of 386, respectively).

Proliferative Pattern in Patients with Adenomatous Polyps or Cancer. The epithelial cell proliferation parameters in patients with colorectal neoplasms are shown in Table 3. Total LI did not show any significant difference between groups, as can be inferred by the wide range of observed values. In the polyps group, LI per crypt compartment showed maximal proliferative activity in the first and second compartment; however, as compared to the control group, a significant increase of labeled nuclei in compartments 3, 4, and 5 was observed, indicating an upwards expansion of the proliferative zone. These features were even more marked in the cancer group, in which LI in compartment 1 was significantly lower than in the other two groups; the further expansion of the proliferative zone towards the surface of the gland was indicated by the significant increase of labeled nuclei in the most superficial compartments. Considering compartments 4 and 5 together [the "high-crypt region"

* The abbreviation used is: LI, labeling index.

4122

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CELL PROLIFERATION IN COLORECTAL MUCOSA

Table 1 Pattern of epithelial cell proliferation in different segments of the large bowel in normal individuals

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Rectum</th>
<th>Sigmoid</th>
<th>Descending</th>
<th>Transverse</th>
<th>Ascending</th>
<th>Cecum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells/compartment (mean ± SE)</td>
<td>43.2 ± 0.4</td>
<td>47.5 ± 0.4</td>
<td>49.4 ± 0.3</td>
<td>48.5 ± 0.4</td>
<td>46.8 ± 0.5</td>
<td>49.5 ± 0.7</td>
</tr>
<tr>
<td>Cells counted</td>
<td>19,258</td>
<td>13,306</td>
<td>22,296</td>
<td>18,653</td>
<td>13,802</td>
<td>8,578</td>
</tr>
<tr>
<td>Labeled cells</td>
<td>2,193</td>
<td>2,168</td>
<td>2,116</td>
<td>2,116</td>
<td>2,116</td>
<td>2,116</td>
</tr>
<tr>
<td>LI (mean ± SE)</td>
<td>11.3 ± 0.3</td>
<td>10.1 ± 0.3</td>
<td>9.9 ± 0.2</td>
<td>11.2 ± 0.4</td>
<td>10.4 ± 0.3</td>
<td>8.3 ± 0.3a</td>
</tr>
<tr>
<td>(Range per crypt)</td>
<td>(2-39)</td>
<td>(2-26)</td>
<td>(2-30)</td>
<td>(2-40)</td>
<td>(2-32)</td>
<td>(2-20)</td>
</tr>
</tbody>
</table>

LI per crypt compartment (mean ± SE)
- Compartment 1: 0.22 ± 0.02
- Compartment 2: 0.20 ± 0.01
- Compartment 3: 0.11 ± 0.00
- Compartment 4 + 5: 0.02 ± 0.00

*p < 0.01 at least versus controls.

Table 2 Absolute number of crypts with at least one labeled cell (labeled crypts) for each of the investigated segments of normal controls, and in each of the five compartments in which the column has been divided

<table>
<thead>
<tr>
<th>Compartment no.</th>
<th>Rectum (445)*</th>
<th>Sigmoid (282)</th>
<th>Descending (453)</th>
<th>Transverse (386)</th>
<th>Ascending (292)</th>
<th>Cecum (173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labeled crypts</td>
<td>% of total</td>
<td>Labeled crypts</td>
<td>% of total</td>
<td>Labeled crypts</td>
<td>% of total</td>
<td>Labeled crypts</td>
</tr>
<tr>
<td>1</td>
<td>379</td>
<td>85</td>
<td>227</td>
<td>80</td>
<td>377</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>76</td>
<td>228</td>
<td>80</td>
<td>334</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>227</td>
<td>51</td>
<td>138</td>
<td>49</td>
<td>250</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>85</td>
<td>19</td>
<td>43</td>
<td>15</td>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3*</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*p < 0.01 vs. respective controls.

Table 3 Pattern of epithelial cell proliferation in the three groups investigated

In controls and in the polyps group, samples of flat mucosa were taken at 10-15 cm from the anus. In patients with cancer mucosal specimens were taken at 2 cm from the tumor margin.

<table>
<thead>
<tr>
<th>Compartment no.</th>
<th>Controls</th>
<th>Polyps</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>445</td>
<td>445</td>
<td>445</td>
</tr>
<tr>
<td>Cells counted</td>
<td>19,258</td>
<td>19,731</td>
<td>18,445</td>
</tr>
<tr>
<td>Labeled cells</td>
<td>2,193</td>
<td>2,168</td>
<td>2,116</td>
</tr>
<tr>
<td>LI (mean ± SE)</td>
<td>11.3 ± 0.3</td>
<td>13.5 ± 0.4</td>
<td>12.5 ± 0.4</td>
</tr>
<tr>
<td>(Range per crypt)</td>
<td>(2-39)</td>
<td>(2-30)</td>
<td>(2-32)</td>
</tr>
</tbody>
</table>

*p < 0.05 difference between sample variation of compartments 4 + 5 but not for the more proximal compartments (1, 2, and 3).

Table 4 shows, for each group and compartment, the absolute number of crypts with at least one labeled cell. Most of the investigated columns had labeled cells in the first and in the second compartment; however, in the cancer group there were 268 labeled crypts in the first compartment (out of 403) versus 379 (out of 445) in controls and 344 (out of 442) in patients with polyps (p < 0.001 versus both groups). The total number of labeled crypts in the third compartment was significantly higher in both polyps and cancer patients versus controls. This trend was even more marked in the fourth compartment, where the percentage of labeled crypts was 36 and 49 in the two patient groups versus 19% in controls (p < 0.001). As for the fifth compartment, in patients with cancer 105 out of 403 (i.e., 26%) columns showed labeled cells. This value was significantly higher than that observed either in the polyp (60 out of 442, 13%) or in the control group (15 out of 445, 3%). Considering individual patients instead of crypts, all cancer patients had labeled cells in the first four compartments and 14 out of 16 (87.5%) had proliferating cells in the fifth compartment. The same trend was seen in the polyp group, in which 15 out of 21 (71%) had proliferating cells in the fifth compartment; in contrast, in three controls only, out of 19, we found labeled cells in the most superficial compartment.

Table 5 shows the epithelial cell proliferation kinetics in normal appearing colorectal mucosa taken at various distances from the tumor. The absolute number of hemicyclons assayed for each patient and the average number of cells per column were similar for each distance from the neoplastic mass. The various kinetic parameters showed only minor differences between samples taken at 2, 4, 8, and more than 10 cm; more in particular, total LI ranged between 11 and 14%, whereas LI (7%), it is interesting to note that the mean values of LI per crypt compartment rose almost linearly from 0.02 in controls, to 0.04 in patients with polyps, to 0.07 in the cancer group. Further details are given in Fig. 1, which shows LI per crypt compartment in the "high-crypt region" (compartments 4 and 5, separately analyzed). Individual points represent the ratio between labeled and total cells in each investigated column; values of zero (no labeled cells) were not reported. The figure shows an extension of the proliferative zone to the fourth compartment in all three groups (although less marked in controls); in contrast, labeling of the fifth compartment is evident in a consistent proportion of patients with adenomatous polyps or, even more, colorectal cancer, but it was negligible in controls (only 15 labeling values out of 445 investigated crypts). Analysis of variance showed a significant (F = 4.66, p < 0.05) difference between sample variation of compartments 4 + 5 but not for the more proximal compartments (1, 2, and 3).

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per crypt compartment showed an evident upwards expansion of the proliferative zone at all sites.

**DISCUSSION**

The main findings of the present study can be summarized as follows: (a) In normal subjects, the different segments of the large bowel show basically the same proliferative pattern. This is characterized by a high kinetic activity in the lower two thirds of the gland and by a gradually decreasing proliferation in the most superficial portions. (b) In rectal mucosa of patients with adenomatous polyps or large bowel cancer there is a significant increase of the mean cytoproliferative activity in the most superficial portions of the crypt. (c) We did not observe appreciable differences of cell proliferation between samples of intestinal mucosa taken in the close vicinity of colorectal cancer and samples excised more distally; however, most of the samples taken from cancer patients showed an increased cell replicative activity, especially in the high-crypt region. Compared to previous observations the results of this study are largely confirmatory. A novel finding is, however, represented by the discriminatory power of the fifth compartment in separating individuals with or without colorectal tumors. As shown in Fig. 1 and Table 4, in normal subjects only few crypts (15 out of 445) showed proliferating cells in the upper one-fifth of the columns and in three individuals only. In contrast, labeling of the fifth compartment was much more frequent and consistent in the two groups of patients with colorectal neoplasms.

In the present study the number of total cells for hemycrypt was, on average, between 40 and 50 in the various groups. Although these values are in agreement with most of the previous observations (9, 13, 21), there are studies in which a higher number of cells per crypt has been reported (19, 22); since the conditions of the assay and the population studied were similar, we are unable to provide any obvious explanation for such differences. Total LI in our controls was, on average, 11.3% in rectal mucosa and showed only minor changes in the other large bowel tracts; these values are similar to those reported in other investigations (11-13), but consistently higher than those observed by Lehy et al. (22) and by other authors (5,
It is possible that the different preparation of patients for colonoscopy may account for the observed differences. In our study all the investigated subjects received two doses of a saline laxative plus two to four enemas before colonoscopy to ensure a good visualization of the entire large bowel; in most of the above-mentioned studies mucosal samples were taken during rectosigmoidoscopy (which usually requires only a tap water enema prior to the investigation) or at surgery. Lehy and coworkers (23) recently showed that warm Normacol enemas prior to proctoscopic investigation induce a significant shortening of the crypts in normal rectal mucosa (62.0 ± 1.4 cells per crypts versus 70.7 ± 2.4 in subjects not receiving any preparation) a significant increase of total LI (10.9 ± 1.1 versus 6.6 ± 0.6) and, thus, an artificial expansion of the proliferative zone towards the surface. Although our subjects were not prepared with Normacol enemas, we cannot exclude that the rather energetic preparation for endoscopy might have influenced the results of the study. It should be noted, however, that all the investigated subjects had the same standard preparation. It is therefore much more likely that the observed pattern of cytoproliferation and the differences between groups have biological rather than methodological explanations.

Terpstra and colleagues recently studied a large group of patients with colorectal neoplasms (adenomatous polyps of various size or cancer) and a suitable control group (15). An increased proliferative activity was found along the entire colon in patients with either polyps or cancer (versus controls), however, within each group the difference between proximal and distal segments of the large bowel was negligible and did not reach the statistical significance. The present study shows a rather homogeneous pattern of epithelial cell proliferation in the six investigated segments, but with two interesting exceptions. First, in the cecum total LI slightly, though significantly, lower than in the other tracts has been found. The relevance of this observation is unclear, but it might also be due to the lower number of columns assayed in this area. Second, as shown in Table 2, the number of labeled cells in the fifth compartment was higher in the rectum as compared to the other segments, although the difference reached the statistical significance only in descending and transverse colon. Despite these two points it seems to us that the data shown in Tables 1 and 2 suggest that the overall epithelial cell proliferation in the rectal mucosa is roughly comparable to the replicative activity observed in the rest of the colon; it follows that the rectum, the most accessible part of the large bowel, is presumably representative of the entire colon.

Deschner and Lipkin (6) proposed that in the early stage of colorectal tumorigenesis, colonic epithelial cells become unable to repress DNA synthesis during migration from the base to the surface and develop an enhanced capacity to proliferate; this leads to an expansion (Stage 1) or to a shift (Stage 2) of the proliferative compartment towards the upper portions of the crypt. Many lines of evidence support this view; thus, a significant upwards shift of the proliferative cell compartment has been reported in patients with colorectal cancer (5, 11). Furthermore, a similar kinetic abnormality has been reported in patients with adenomatous polyps (4, 11), ulcerative colitis (19, 22), and adenomatosis coli (6-9, 24-26), conditions associated with an increased risk of colorectal cancer. Other authors, however, were unable to report significant differences of cell replication between normal subjects and individuals with colorectal tumors. Thus, Maskens and Deschner (5) found an abnormal pattern of proliferation (i.e., upwards expansion of the proliferative zone) only in some (six out of 17) of the cancer patients studied. In another study the same authors observed much more frequently Stage 1 or 2 abnormalities in colorectal cancer patients than in controls, especially in the subgroup with a high LI; however, among the 13 control subjects, some extension of the proliferative compartment to the upper third of the crypt was also observed (10). Similarly, two out of ten biopsy specimens of normal mucosa of a patient with multiple polyps showed a normal pattern of cytoproliferation. Furthermore, in a recent paper Markowitz et al. (13) did not observe any significant abnormality of epithelial cell proliferation in 15 members of families with adenomatosis coli (although the investigated subjects were, on average, younger than those of previous studies) (13).

In the present study significant differences of many of the investigated parameters have been observed between controls and either patients with adenomatous polyps or cancer. As shown in Fig. 1 and in Tables 3 and 4, all three groups showed a zone of major proliferative activity in the lower two-fifths of the gland. In the two groups of patients with neoplasms the replicative activity in compartments 3, 4, and 5 was significantly higher than in controls, indicating an upwards expansion of the proliferative zone (Stage 1 abnormality). Shift of the zone of major replicative activity, however, was rare and has been observed in a minority only of the crypts (21 out of 422 columns in polypl patients and 34 out of 403 columns assayed in cancer patients). The two upper compartments deserve more comment. As shown in Table 4, the fourth compartment showed labeled cells in a consistent proportion of the crypts (in all three groups) and in almost all the investigated subjects, it follows that this compartment has a poor discriminatory value. In contrast, the fifth compartment showed labeled cells in 13-26% of the crypt of patients with either polyps or cancer but only in a few crypts.
of normal controls (15 out of 445, or 3%); consequently the analysis of this compartment should provide the most valuable information in discriminating individuals or populations at high risk of colorectal cancer.

Matthews and Cooke (16) recently studied the DNA content of colonic mucosa in patients with colorectal carcinoma; they reported a significant increase of the amount of DNA in the proliferative cells adjacent to the neoplasms compared to more distal areas. In the present study we were unable to detect any significant difference of epithelial cell proliferation between samples taken at different distances from the tumoral mass. However, the proliferative activity of the most superficial compartments, at all distances, was significantly higher than that observed in normal controls and in patients with polyps. These findings are in close agreement with the results of Terpstra and coworkers (15). If we assume that the hyperproliferative state precedes the development of tumors, then one might hypothesize that the extension of the proliferative zone to the surface of the colonic crypts, as the present study and many other previous observations have shown, brings a larger fraction of the replicative cells to be exposed to the action of fecal carcinogens, an event which might ultimately lead to the development of cancer.

REFERENCES

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