Somatostatin in the Idiopathic Inflammatory Bowel Diseases

TIMOTHY R. KOCH, M.D.,* J. AIDAN CARNEY, M.D., PH.D.,† VICKIE A. MORRIS, B.S.,* VAY LIANG W. GO, M.D.*

Koch TR, Carney JA, Morris VA, Go VLW. Somatostatin in the idiopathic inflammatory bowel diseases. Dis Colon Rectum 1988;31: 198-203.

To study the effect of mucosal inflammation on tissue concentrations of somatostatin, the distribution and concentration of somatostatin in specimens of normal and abnormal (ulcerative colitis and Crohn's disease) ileum and colon were determined by a specific radioimmunoassay. Each tissue specimen obtained at surgery was separated by microdissection into the mucosa-submucosa and the muscularis externa. Immunoreactive somatostatin was acid-extracted from each layer before measurement. Gel chromatography was used to characterize immunoreactive somatostatin measured by radioimmunoassay; somatostatin-28 was the major immunoreactive species measured in human intestine. In normal colon, concentrations of somatostatin were not related to patient age. Concentrations of immunoreactive somatostatin in the mucosa-submucosa of the descending colon were significantly decreased in ulcerative colitis and in Crohn's colitis, compared with normal colon. There was no apparent relationship between concentrations of somatostatin and the duration of inflammatory bowel disease. However, somatostatin concentrations appeared to be lower in patients with severe colitis than in patients with minimal colitis. The decrease in mucosal-submucosal concentrations of somatostatin is in agreement with previous morphologic studies, which have suggested diminished populations of endocrine cells in ulcerative colitis. The possible role of somatostatin in the colon suggests that further studies of the alteration of this gut peptide may be useful in understanding a component of the pathophysiology of idiopathic inflammatory bowel disease. [Key words: Human colon; Crohn's disease; Ulcerative colitis; Somatostatin]

Received for publication August 11, 1987.

Dr. Koch is a recipient of a Career Development Award from the National Foundation for Ileitis and Colitis.

Address reprint requests to Dr. Koch: Gastrointestinal Section, III-C, Zablocki VA Medical Center, 5000 West National Avenue, Milwaukee, Wisconsin 53295.

From the Gastroenterology Research Unit and Department of Pathology,† Mayo Clinic and Foundation, Rochester, Minnesota*

SINCE EARLY IN THIS century, it has been known that endocrine cells are present in human intestine scattered throughout the epithelial layer.[1] Immunoreactive somatostatin (SRIF) has been localized by immunocytochemistry within mucosal D-cells possessing cell processes in human small intestine and colon.[2,3] The morphology of SRIF-containing cells suggested a paracrine role for SRIF, affecting neighboring mucosal cells. In addition, immunoreactive somatostatin has been measured by radioimmunoassay in guinea pig intestine within the external musculature and the mucosa-submucosa, and localized by immunohistochemistry within nerve cell bodies and axons of the submucosal and myenteric plexuses.[4]

There have been few studies of the possible alteration of intestinal endocrine cells in idiopathic inflammatory bowel diseases (IBD). In early morphologic studies, diminished colonic populations of argentaffin cells[5] and enterochromaffin cells[6,7] were described in patients with ulcerative colitis. In one immunocytochemical examination of peptide-containing intestinal endocrine cells, there appeared to be no alteration of SRIF-containing cells in ulcerative colitis and Crohn's disease.[8]

To determine whether tissue concentrations of SRIF might be abnormal in IBD, immunoreactive SRIF in the mucosa-submucosa and in the muscularis externa of

normal and abnormal (ulcerative colitis and Crohn's disease) ileum and colon was measured. Radioimmunoassay (RIA) was used in this study because it is currently the most accurate method for quantitation of gut regulatory peptides. The possible relationship between the tissue concentrations of SRIF in IBD and selected clinical and pathologic features in these diseases was examined.

Materials and Methods

Tissue Samples: Specimens of normal and diseased intestine were obtained from the antimesenteric border of intestine within 30 minutes of removal at surgery, and transported to the laboratory on ice. Permission for human studies was granted by the Mayo Clinic Institutional Review Board on December 6, 1984.

As controls, grossly and microscopically normal areas of ileum and colon were obtained from patients undergoing surgery for colonic angiodysplasia, solitary colonic polyps, rectal prolapse, and nonobstructing colonic cancer (N = 48: 21 male; 27 female). The mean age of the control patients was 62 years (age range, 19 to 87 years). Diseased bowel specimens were obtained from patients with Crohn's disease (N = 23: 10 male; 13 female) undergoing surgery for treatment of intractable symptoms, and from patients with ulcerative colitis (N = 27: 18 male; 9 female) undergoing surgery for treatment of intractable symptoms or dysplasia. In the group of 23 patients with Crohn's disease, 11 patients were receiving both oral corticosteroid and sulfasalazine treatment, three patients were receiving only oral corticosteroid treatment, two patients were receiving only oral sulfasalazine treatment, and seven patients were receiving no drug treatment before surgery.

In the group of 27 patients with ulcerative colitis, 14 patients were receiving both oral corticosteroid and sulfasalazine treatment, four patients were receiving oral corticosteroid treatment only, five patients were receiving oral sulfasalazine treatment only, and four patients were receiving no drug treatment before surgery. The mean age of the patients with Crohn's disease was 37 years (age range, 17 to 74 years), and the mean age of the patients with ulcerative colitis was 32 years (age range, 14 to 57 years). In patients with IBD, no specimens were obtained from regions of diseased colon in which there were visible ulcers.

Tissue Processing: In a pilot RIA study using canine colon and duodenum, the concentrations of SRIF extracted into water, 0.05 M acetic acid and 0.1 M hydrochloric acid were compared. Somatostatin in canine gut was measured in highest concentrations following extraction into 0.1 M HCl.

In this study, each tissue specimen was immediately separated by microdissection into the muscularis externa and the mucosa-submucosa.[9] The layers were weighed, immersed in 0.1 M HCl (1:20, M/V), and plunged into a boiling water bath for ten minutes. The tissue samples were then homogenized using a Brinkman Polytron, and centrifuged at low speed for 30 minutes at 4° C. Supernatant liquid was removed, frozen at −20° C, and stored for later neutralization and radioimmunoassay for SRIF.

Histology: A transmural section from each intestinal specimen was fixed for 20 hours in Carson's fixative,[10] and then processed for routine histology. Duplicate sections stained by the hematoxylin and eosin method were examined (blinded) to confirm the presence of histologically normal gut, or the histopathologic diagnosis of Crohn's disease or ulcerative colitis. The severity of inflammation present in specimens from patients with IBD was estimated by one author (JAC) as minimal (or inactive) colitis (1+), moderate colitis (2+), or severe colitis (3+). To estimate the severity of inflammation in Crohn's disease, histologic sections were examined to determine the depth of inflammation, the density of inflammatory cells, the depth of ulcers, and the extent of serosal inflammation. Ulcerative colitis tissue sections were examined to estimate the frequency of crypt abscesses, the density of inflammatory cells in the mucosa-submucosa, and the frequency of lamina propria lymphoid follicles.

Clinical Diagnosis: Patient histories were obtained to confirm the radiologic and clinical diagnosis of IBD using accepted criteria. A diagnosis of Crohn's disease or ulcerative colitis required either consistent clinical symptoms for a duration of at least two years or, if the disease duration was less than two years, negative stool cultures for Salmonella, Shigella, Yersinia, and Campylobacter, negative stool examinations for ova and parasites, and negative stool neutralization assay for *Clostridium difficile* toxin.

Radioimmunoassays: Unless otherwise indicated, all peptides were synthetic porcine peptides obtained from Peninsula Laboratories, Belmont, CA.

Somatostatin: The RIA of SRIF was a modification of the method of Gerich *et al.*[11] Synthetic Tyr-O-somatostatin was iodinated by the Chloramine-T method.[12] Sheep antiserum 479 (provided by Dr. J. Gerich, Mayo Foundation, Rochester, MN) was used at a dilution of 1:18000, and the assay was sensitive to 15 pg/tube using a 50 μl sample. The assay was carried out in dysequilibrium conditions. Antiserum 479 did not cross-react with gastrin, secretin, vasoactive intestinal peptide, cholecystokinin-33, pancreatic glucagon, motilin, gastric inhibitory peptide, neurotensin, or peptide YY, but did recognize somatostatin-14 and somatostatin-28 equally well. In dilutions of human intestinal tissues extracted into 0.1 M HCl, parallelism as compared with the standard curve was demonstrated. The intra-assay variation was 7 percent, and the interassay variation was 15 percent.

Statistical Analysis: In a previous lyophilization study

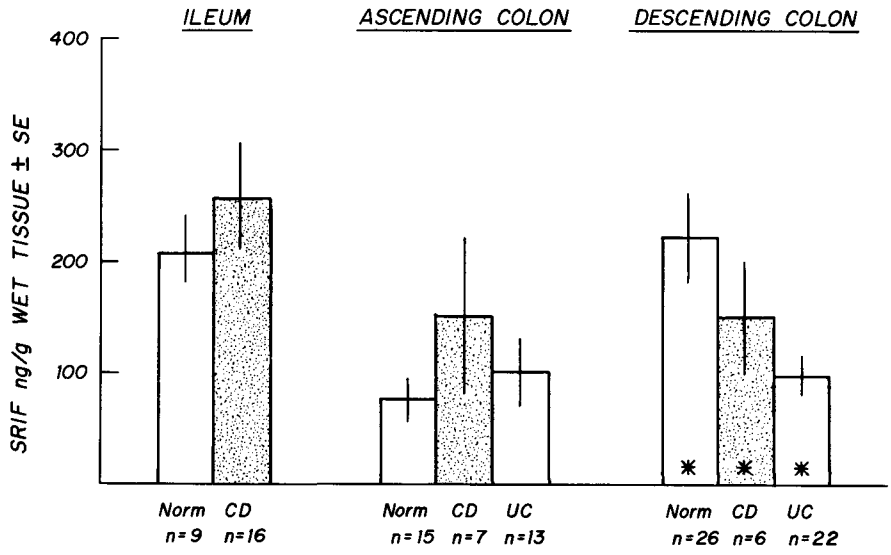

FIG. 1. Concentrations (mean ± SE) of immunoreactive somatostatin (SRIF) in mucosa-submucosa of normal intestine (Norm), Crohn's disease (CD), and ulcerative colitis (UC) measured by radioimmunoassay. One-way analysis of variance (ANOVA) confirmed that there were significantly decreased concentrations of SRIF in the mucosa-submucosa from the inflammatory bowel diseases ($P < .05$). Decreased concentrations of SRIF were more pronounced in descending colon from patients with ulcerative colitis than in Crohn's colitis.

using normal and IBD colon, it was found that the water content of both groups of samples was not significantly different (range, 79 to 81 percent of wet tissue weight).[13] In this study, the authors chose to express the results as nanograms of immunoreactive SRIF per gram wet tissue. Population mean values and standard error of the mean were calculated for ileum, ascending colon, and descending colon. Statistical differences in mean values among normal intestine and disease groups for each region of the gut were tested by one-way analysis of variance. The possible relationship between patient age and concentrations of SRIF in normal intestine, and the possible relationship between duration of IBD (estimated by the duration of clinical symptoms) and SRIF concentrations in IBD colon were examined using linear correlation analysis.

Chromatographic Studies: The gel chromatography column was calibrated with blue dextran to determine Vo (0 percent elution), and NaI125 to determine V_s (100 percent elution). Samples of bovine somatostatin-14 (SRIF-14) and somatostatin-28 (SRIF-28) were then applied separately on a 1 × 100 cm G-50 superfine Sephadex column (Pharmacia) equilibrated with 0.01 M phosphate-buffered saline, *p*H 7.6, with 0.5 percent bovine serum albumin. At 4° C, fractions of 1 ml were collected at a flow rate of 6 ml/hr, and then assayed by RIA to determine the respective characteristic elution volume for each peptide.

Tissue extracts of the mucosa-submucosa of normal intestine were then applied on this column to separate immunoreactive somatostatin. Fractions of 1 ml were collected and then assayed by RIA.

Results

Concentrations of Somatostatin in the Mucosa-Submucosa: Similar concentrations of immunoreactive SRIF were measured in the mucosa-submucosa of normal ileum and normal descending colon (Fig. 1). In the descending colon, significantly decreased concentrations of immunoreactive SRIF were present in both Crohn's colitis and ulcerative colitis, with the decrease being greater in ulcerative colitis (Fig. 1). There was no significant difference between the mean concentrations of SRIF in normal ileum and Crohn's ileitis.

Among the patients with ulcerative colitis, the mean [SE] concentration of SRIF in descending colon was 120 [19] ng/g in patients receiving oral corticosteroid treatment before surgery, 98 [16] ng/g in patients receiving oral sulfasalazine treatment before surgery, and 80 [10] ng/g in patients receiving no medical treatment before surgery. There was no statistical difference in the mean concentrations of SRIF among these three groups (one-way-analysis of variance: $P > .05$).

Concentrations of Somatostatin in the Muscularis Externa: In normal intestine, concentrations of immunoreactive SRIF measured in the muscularis externa were much lower than those in the mucosa-submucosa (Fig. 2). The mean concentrations of SRIF in normal intestine and IBD were not significantly different (Fig. 2).

Effect of Aging Upon Concentrations of Somatostatin: Linear correlation analysis demonstrated no significant relationship in the mucosa-submucosa of normal descending colon, normal ascending colon, and normal ileum between concentrations of SRIF and patient age

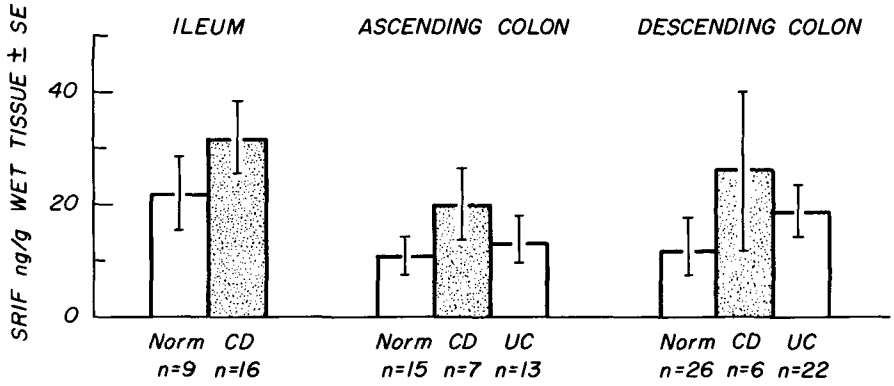

FIG. 2. Concentrations (mean ± SE) of immunoreactive somatostatin (SRIF) in muscularis externa of normal intestine (Norm), Crohn's disease (CD), and ulcerative colitis (UC) measured by radioimmunoassay. One-way analysis of variance showed no significant differences ($P > .05$) in the mean concentrations of SRIF in normal intestine, Crohn's disease, and ulcerative colitis.

(the absolute value of each correlation coefficient was less than 0.50).

Effect of Disease Duration Upon Concentrations of Somatostatin: Concentrations of SRIF in the mucosa-submucosa of descending colon were decreased in patients with both recent onset of ulcerative colitis and with long duration of symptoms. The correlation coefficient ($r = -0.10$) suggested no significant relationship between disease duration and concentrations of SRIF in these patients with ulcerative colitis. Similarly, there appeared to be no effect of disease duration upon concentrations of SRIF in ulcerative colitis ascending colon ($r = 0.16$), and in ascending colon ($r = 0.03$) and descending colon ($r = 0.07$) obtained from patients with Crohn's colitis.

Effect of Tissue Inflammation Upon Concentrations of Somatostatin: The severity of tissue inflammation in specimens obtained from patients with Crohn's colitis and ulcerative colitis ranged from minimal colitis to severe colitis. In descending colon obtained from patients with ulcerative colitis, there was a trend toward decreased colonic SRIF in tissues with increased severity of inflammation (Fig. 3). In these colonic specimens from patients with ulcerative colitis, mucosal atrophy was noted histologically in one specimen (4 percent), and mucosal ulceration was noted histologically in three specimens (14 percent). Due to the small number of specimens obtained from patients with Crohn's colitis, it was not possible to determine whether colonic inflammation might affect tissue concentrations of SRIF.

Column Chromatography: Following separation of extracts of human intestine by gel chromatography, RIA for somatostatin revealed two separate immunoreactive peaks which appeared to coelute with somatostatin-14 and somatostatin-28, respectively (Fig. 4). The major immunoreactive species measured in extracts of human intestine appeared to coelute with somatostatin-28 (Fig. 4).

Discussion

This RIA study measures significantly decreased mucosal-submucosal concentrations of SRIF in both ulcerative colitis and Crohn's colitis, while there was no significant change in concentrations of SRIF in Crohn's ileitis. The results in diseased colon conflict with the

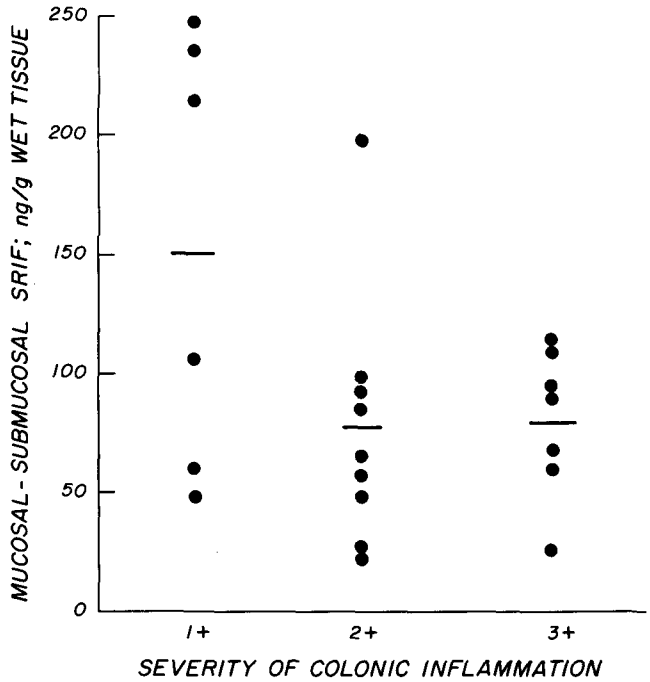

FIG. 3. The effect of the severity of colonic inflammation in ulcerative colitis was compared with concentrations of somatostatin in the mucosa-submucosa from descending colon. The severity of tissue inflammation was estimated as inactive colitis (1+), moderate colitis (2+), or severe colitis (3+). The horizontal bars indicate the mean concentrations in each group. There appeared to be a trend toward decreased concentrations of somatostatin in more severely involved colonic specimens.

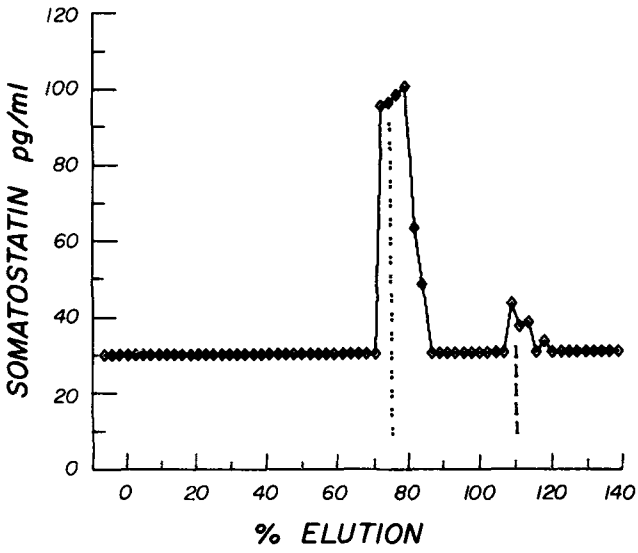

FIG. 4. Characterization of immunoreactive somatostatin in an extract of normal human intestine by separation on a Sephadex G-50 superfine column, followed by radioimmunoassay. Calibration of this column with somatostatin-28 is indicated by a dotted line, and calibration with somatostatin-14 is indicated by a dashed line. Somatostatin-28 appeared to be the major immunoreactive species measured in extracts of human intestine.

results of a previous immunohistochemical examination of somatostatin-containing cells in IBD.[8] The authors believe that this study provides a more accurate assessment of SRIF concentrations because of the increased sensitivity of radioimmunoassay.

The mechanism of decreased colonic concentrations of SRIF in patients with IBD is presently unknown. Murine studies have suggested that enteroendocrine cells proliferate from progenitor cells located at the base of crypts.[14] Crypt abscesses, which may be seen in both ulcerative colitis and Crohn's disease, have been previously suggested to be an early histopathologic lesion in ulcerative colitis.[15] It, therefore, is reasonable to speculate that during pathologic damage of the colon in patients with IBD, crypt abscesses might be one abnormality which could affect the proliferation of or survival of SRIF-containing cells.

There were two observations that were consistent with this hypothesis. First, in descending colon obtained from patients with ulcerative colitis, a trend toward diminished concentrations of SRIF in more severely involved colon was found. Second, the decreased concentrations of SRIF in the inflammatory bowel diseases were limited to the descending colon. Review of the gross pathology of the colonic specimens showed that eight of the 27 patients with ulcerative colitis had primarily left-sided colitis. The authors believe that these results are consistent with a trend toward decreased concentrations of SRIF in colon in which there was more pronounced inflammatory infiltration.

Other possible explanations for decreased colonic concentrations of SRIF that were excluded include age-related changes and disease duration-related changes. Although control intestine was obtained from patients who had a higher mean age than that of IBD patients, the absence of a significant correlation between SRIF concentrations and patient age suggests that decreased concentrations of SRIF in colon from IBD patients was not related to patient age. In addition, no apparent relationship between concentrations of SRIF and the duration of symptoms of IBD was found. Decreased SRIF was found both in patients with recent onset of IBD and in patients with a long duration of symptoms. At this time, the authors are not aware of a mechanism by which concentrations of SRIF could be decreased in Crohn's colitis, but unchanged in Crohn's ileitis.

The major immunoreactive species present in human intestine appeared to coelute with somatostatin-28. The chromatographic data are consistent with previous chromatographic studies of somatostatin in human gut which reported high concentrations of a somatostatin-28-like peptide in intestinal mucosa, while a somatostatin-14-like peptide was found within nerves, the pancreas, and the antrum.[16] Based on these results, the decreased concentrations of SRIF in IBD most likely resulted from loss of SRIF within colonic mucosal D-cells.

In the intestine, SRIF has been proposed as an inhibitory gut peptide. For example, colonic mucosal and submucosal blood flow in man appears to be decreased by somatostatin.[17] Somatostatin in the intestine of different animals decreases fluid secretion[18] and stimulates sodium and chloride absorption.[19] In animal models, somatostatin has been shown both *in vivo* and *in vitro* to inhibit the proliferation of gut epithelial cells.[20-22] Following intestinal resection in rats, somatostatin treatment has been shown to inhibit the normal proliferative activity in ileal crypts.[22] The proliferation of and immunoglobulin synthesis by lymphocytes isolated from murine Peyer's patches are inhibited by the addition of somatostatin.[23]

These results permit speculation that the abnormalities of colonic crypt cell proliferation previously reported in patients with ulcerative colitis[24,25] might result from the loss of a gut peptide necessary for the inhibition of colonic mucosal cell proliferation. Further studies are needed to examine the possibility that alteration of SRIF could support this hypothesis.

Somatostatin has been used previously for medical therapy in several intestinal disorders. Patients with ileostomy diarrhea who have undergone proctocolectomy,[26] patients with intestinal fistulas,[27,28] and patients with

secretory diarrhea secondary to the pancreatic cholera syndrome[29,30] appear to be clinically improved while receiving somatostatin. The recent availability of a long-acting derivative of somatostatin (SMS 201-995)[31] has permitted clinical trials for treatment of selected intestinal disorders.

In summary, decreased colonic concentrations of SRIF in IBD colon are consistent with the hypothesis that SRIF might be involved in the pathophysiology of IBD. Further studies are needed to delineate the possible role of SRIF in the alteration of colonic functions in patients with IBD. This area of research is especially interesting because of the recent availability of a new long-acting somatostatin analogue, SMS 201-995.

References

1. Masson MP. La glande endocrinaire de l'intestine chez l'homme. C R Acad Sci 1914;158:59-61.
2. Lehy T, Peranzi G, Cristina ML. Correlative immunocytochemical and electron microscopic studies: identification of (entero)-glucagon-somatostatin- and pancreatic polypeptide-like-containing cells in the human colon. Histochemistry 1981;71:67-80.
3. Grube D. Die endokrinen zellen des verdauungsapparats. Klin Wochenschr 1982;60:213-7.
4. Costa M, Patel Y, Furness JB, Arimura A. Evidence that some intrinsic neurons of the intestine contain somatostatin. Neurosci Lett 1977;6:215-22.
5. Verity MA, Mellinkoff SM, Frankland M, Greipel M. Serotonin content and argentaffin and paneth cell changes in ulcerative colitis. Gastroenterology 1962;43:24-31.
6. Ahonen A, Kyösola K, Penttilä O. Enterochromaffin cells and macrophages in ulcerative colitis and irritable colon. Ann Clin Res 1976;8:1-7.
7. Kyösola K, Pentillä O, Salaspuro M. Rectal mucosal adrenergic innervation and enterochromaffin cells in ulcerative colitis and irritable colon. Scand J Gastroenterol 1977;12:363-7.
8. Bishop AE, Polak JM, Bryant MG, Bloom SR, Hamilton S. Abnormalities of vasoactive intestinal polypeptide-containing nerves in Crohn's disease. Gastroenterology 1980;79:853-60.
9. Angel F, Schmalz PF, Morgan KG, Go VL, Szurszewski JH. Innervation of the muscularis mucosa in the canine stomach and colon. Scand J Gastroenterol (suppl) 1982;71:71-5.
10. Robinson G, Dawson I. A formalin fixative for immunochemical and ultrastructural studies on gastrointestinal *endocrine* cells. J Clin Pathol 1979;32:40-5.
11. Gerich J, Greene K, Hara M, Rizza R, Patton G. Radioimmunoassay of somatostatin and its application in the study of pancreatic somatostatin secretion *in vitro*. J Lab Clin Med 1979;93:1009-17.
12. Greenwood FC, Hunter WM, Glover JS. The preparation of ^{131}I-labelled human growth hormone of high specific radioactivity. Biochem J 1963;89:114-23.
13. Koch TR, Carney JA, Go VL. Distribution and quantitation of gut neuropeptides in normal intestine and the inflammatory bowel diseases. Dig Dis Sci 1987;32:369-76.
14. Ponder BA, Schmidt GH, Wilkinson MM, Wood MJ, Monk M, Reid A. Derivation of mouse intestinal crypts from single progenitor cells. Nature 1985;313:689-91.
15. Lumb G, Protheroe RH. Biopsy of the rectum in ulcerative colitis. Lancet 1955;2:1208-15.
16. Baldissera FG, Holst JJ, Jensen SL, Krarup T. Distribution and molecular forms of peptides containing somatostatin immunodeterminants in extracts from the entire gastrointestinal tract of man and pig. Biochim Biophys Acta 1985;838:132-43.
17. Agerskov K, Bousfield R, Mortensen PE, Olsen J, Christiansen J. Effect of somatostatin on ^{133}Xe clearance from colonic mucosa before and after local nervous blockade in unanaesthetized man. Scand J Gastroenterol 1986;21:951-4.
18. Dharmsathaphorn K, Sherwin RS, Dobbins JW. Somatostatin inhibits fluid secretion in the rat jejunum. Gastroenterology 1980;78:1554-8.
19. Dharmsathaphorn K, Binder HJ, Dobbins JW, Leo L. Somatostatin stimulates sodium and chloride absorption in the rabbit ileum. Gastroenterology 1980;78:1559-65.
20. Lehy T, Dubrasquet M, Bonfils S. Effect of somatostatin on normal and gastric-stimulated cell proliferation in the gastric and intestinal mucosae of the rat. Digestion 1979;99:99-109.
21. Stange EF, Schneider A, Schusdziarra V, Ditschuneit H. Inhibitory effects of somatostatin on growth and differentiation in cultured intestinal mucosa. Horm Metab Res 1984;16:74-8.
22. Holmes SJ, Jaspan JB, Moossa AR. The effect of somatostatin on postresectional ileal hyperplasia. Endocrinology 1982;111:1397-9.
23. Stanisz AM, Befus D, Bienenstock J. Differential effects of vasoactive intestinal peptide, substance P, and somatostatin on immunoglobulin synthesis and proliferations by lymphocytes from Peyer's patches, mesenteric lymph nodes, and spleen. J Immunol 1986;136:152-6.
24. Allan A, Bristol JB, Williamson RC. Crypt cell production rate in ulcerative proctocolitis: differential increments in remission and relapse. Gut 1985;26:999-1003.
25. Kanemitsu T, Koike A, Yamamoto S. Study of the cell proliferation kinetics in ulcerative colitis, adenomatous polyps, and cancer. Cancer 1985;56:1094-8.
26. Cooper JC, Williams NS, King RF, Barker MC. Effects of a long-acting somatostatin analogue in patients with severe ileostomy diarrhoea. Br J Surg 1986;73:128-31.
27. Reasbeck PG. Somatostatin treatment of gastrointestinal fistulas: evidence for a rebound effect on withdrawal. Aust NZ J Surg 1984;54:465-7.
28. Geerdsen JP, Pedersen VM, Kjaergard HK. Small bowel fistulas treated with somatostatin: preliminary results. Surgery 1986;100: 811-4.
29. Maton PN, O'Dorisio TM, Howe BA, et al. Effect of a long-acting somatostatin analogue (SMS 201-995) *in* a patient with pancreatic cholera. N Engl J Med 1985;312:17-21.
30. Edwards C, Cann PA, Read NW, Holdsworth CD. Effect of two new antisecretory drugs on fluid and electrolyte transport in a patient with secretory diarrhoea. Gut 1986;27:581-6.
31. Bauer W, Briner U, Doepfner W, et al. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982;31:1133-40.