Calcium and colorectal epithelial cell proliferation

EDITOR.—There is still much debate whether calcium can prevent colorectal cancer in patients with an increased risk of the development of such tumours. Calcium intervention studies, using epithelial cell proliferation as an intermediate endpoint, have produced inconsistent results. Most studies have focused only on the effect of calcium on the rectal epithelium. Several open uncontrolled studies have shown a reduction of rectal epithelial cell proliferation during calcium supplementation, but small placebo controlled studies are not as uniform in their conclusions. Recently Weisberger et al (Gut 1996; 38: 396–402) considered this aspect of sample size, as well as the fact that studies were performed with biopsy specimens from the rectum. With respect to the small size of patient populations, two recent studies included a large number of subjects. Bostick et al, performed a randomised, double blinded study in sporadic adenoma patients.9 Patients received placebo (n=66), 1 g calcium/day (n=64) or 2 g calcium/day (n=63) for six months. Rectal biopsy specimens were obtained at baseline, and at one, two, and six months. In this study no difference in proliferation was observed between the three groups. However, calcium normalised the proliferative activity of epithelial cells in the crypts, which is supposedly beneficial with respect to cancer risk. Rothstein et al10 published a preliminary report on a very large study in adenoma patients who were randomised to receive 1-2 calcium (n=173) or placebo (n=160). Before and after six months supplementation rectal biopsy specimens were taken. Calcium had no effect on proliferation and, in contrast with the previous study, no effect on the distribution of proliferating cells either. With respect to the effect of calcium on proliferation of colonic mucosa, Weisberger et al12 suggested in their recent paper that, apart from one open uncontrolled study,13 this had not been studied before. In another open uncontrolled study we unexpectedly observed an increase of proliferation in the sigmoid of adenoma patients after 12 weeks 1.5 g calcium/day.14 Weisberger et al15 performed a randomised, double blinded study and did not find any effect of longterm calcium supplementation on sigmoidal cell proliferation. This study agrees to a great extent with our recently reported findings in a randomised, double blinded study in 30 first degree relatives of patients with hereditary non-polyposis colorectal cancer.13 These subjects proved to have an increased epithelial cell proliferation rate,15 which responded to calcium in two open studies.13 The subjects received 1.5 g calcium/day or placebo. To elucidate the potential site specific effects of calcium in the colorectum, biopsy specimens were obtained from the sigmoid colon before and after three months. In none of the three parts of the colorectum was a significant effect of calcium on proliferation observed compared with placebo. The only noticeable difference between the two groups was a decrease of proliferation rate in the luminal crypt compartment in the rectum compared with placebo, a finding similar to that of Bostick et al.9 In summary, from the calcium suppsed, double blinded studies reported, the following conclusions can be drawn: (1) in the rectum calcium supplementation may normalise the abnormal distribution of proliferating cells in the crypt without affecting overall proliferation rate; (2) no appreciable effect of calcium supplementation on proliferation in the sigmoid can be observed, and the same seems to be true for the ascending colon. Based on these conclusions our doubt should arise on the value of calcium supplementation for the prevention of colorectal cancer in people with an increased risk of this disease.

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12 O’Sullivan KR, Mathias PM, Beantie S, O’Morain C. Effect of oral calcium supplement-


13 Kleibeuker JH, Welberg PW, Mulders NH, van der Meer R, Cats A, Limburg AJ, et al. Epithelial cell proliferation in the human sigmoid colon of patients with adenomatous polyps increases during oral calcium supple-


controlled intervention study with supple-


Reply

EDITOR,—We thank Kleibeuker et al for their supportive comments about our recent paper (Gut 1996; 38: 396-402). They highlight the latest evidence with regard to the effect of calcium on rectal and colonic cell prolifera-

tion in different patient groups. We very much agree with their concluding suggestion and wish to add some additional points. The value of calcium supplementation in the prevention of colorectal cancer seems questionable on conditions of adequate calcium intake, accompanied by impaired calcium absorption as typically observed in elderly people.

Furthermore, if there is indeed some beneficial effect in the rectum but not in the colon, then this seems rather incompatible with an intraluminal effect of calcium such as binding and precipitating bile acids and fatty acids for the following reasons: (1) The rectal mucosa is in far less direct contact with intestinal digesta than the colon and is therefore comparatively unlikely to benefit from a lower concentration of potential carcinogens in the intestinal lumens; (2) chelation by calcium of long chain fatty acids (there is no direct evidence that calcium chelates bile acids in vivo) at least, seems to occur at the favourable alkaline pH of the upper small intestine1 and therefore should have a beneficial effect along the whole of the large bowel in terms of cell proliferation.

Unfortunately the calcium bile acid hypo-

thesis has until now relied too heavily on inappropriate assumptions made from in vitro experiments, animal models, and short-term uncontrolled human studies.

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Emergency endoscopy

EDITOR,—I read with interest the paper by Dr Bowling et al showing the apparently narrow relations between collagen and lymphocytic colitis, and describing the possibility of severe clinical episodes in the colitis patients (Gut 1996; 38: 788-91). I wonder however whether a total colectomy was necessary in this patient. Indeed, the pathological finding of the usual features of lymphocytic colitis, without any sign of severe alteration of the colonic wall, led the authors to consider whether continuing conservative treatment in similar circumstances, despite failing of medical treatment, could be successful.

In this case, may I ask if a new colonicoscopy performed in emergency before considering a colectomy would have 'refrained' the surgeon’s arm? For many years, we have advocated emergency colonicoscopy, in severe episodes of inflammatory colitis.1 Provided the endoscopist has the necessary experience, this procedure is safe in patients with severe clinical symptoms for distinguishing those with true anastomotic leaks from those with merely acute mucosal colonic inflammation, but without deep and extensive ulcerations.

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Reply

EDITOR,—Professor Rambaud wonders whether a total colectomy was necessary in this patient and whether 'continuing conserva-

tive treatment in similar circumstances, despite failing of medical treatment could be appropriate'. He asks if a new colonicoscopy was performed as an emergency before making the final decision about colectomy.

As outlined in our paper, two colonoscopies were performed. On her last admission she failed to respond to medical treatment. She remained acutely unwell with profuse diarrhoea, persistent fever, abdominal tender-

ness, and leucocytosis. Her plain abdominal x ray showed evidence of a total colitis with mucosal oedema. From the clinical stand-

point this was clearly a serious situation and indeed life threatening and on clinical grounds an emergency subtotal colectomy was advised and carried out. There was no question in this case of needing to refrain 'the surgeon’s arm'. The advantages of working in a combined medical and surgical gastro-

enterology unit is that decisions about surgery in acute inflammatory bowel disease can be made jointly between the physicians and surgeons concerned and that was the case here.

One of the reasons for presenting the case report was that this patient had to come to surgery and as outlined in the paper she made an excellent recovery and has remained well for years later.

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BOOK REVIEWS


It is perhaps a rather arbitrary matter to define when a trainee endoscopist can be considered to have completed their training. At a time when trainees’ programmes are being examined more closely than ever before, there are obvious limitations in defining proficiency in terms of numbers of procedures performed. Any gastroenterologist who has had the privi-

lege of helping junior colleagues to acquire endoscopic skills will know that they may show considerable variation in the gradient of the learning curve. To some extent, the shape of this curve depends on the teacher’s skills as much as anything. Their ability to pass on the trainee’s expertise. Furthermore, there are few of us so endowed with natural endoscopic talent that we have reached a stage when there is nothing more to learn ourselves.

All practising gastroenterologists – whether they know which end of the instrument to introduce into the patient or whether they have carried out ‘tens of thousands of procedures’ – will learn something from the latest edition of Cotton and Williams. These two titans of the endoscopic firmament have updated a book that is packed end to end with practical advice. I have no idea how many hundreds of endoscopies this pair has performed but their students are fortunate indeed. The rest of us can just share in the experience from their book.

This is a practical manual that is illustrated by superb line drawings, which have become one of the hallmarks of this excellent publishing house. It would be entirely appropriate for every gastroenterologist to have studied the first four chapters before wording a scope for the first time. The incredibly helpful des-

criptions of how to perform ERCP and colonoscopy are most unlikely ever to be bettered. Maybe we feel we know how to cope with common problems of retained splenic flexure, but it can seem difficult to explain to a trainee quite what to do. Somehow, with the skilled teacher’s instinctive gifts, Cotton and Williams articulate just what to do and why – in terms of the anatomy of the gut and the manoeuvrability of the endoscope. Obviously, one cannot learn a practical skill from a book but it would be a very fine teacher indeed who could not use a book of this quality.

As upper and lower gastrointestinal endoscopy is dealt with so comprehensively, it does come as rather a disappointment that small bowel endoscopy is covered so superficially in just four pages. There is much more to be said about push and sonde enteroscopy than is described here in just two pages. In our experience, passage of the sonde scope to the distal ileum may require a little more attention than the endoscopist can give, especially in the very young patient. For example, the technique of enteroscope withdrawal jus-

ifies more than eight lines of text.

This, however, is the book’s only weakness. I found myself nodding in agreement with much of what these fictitious heroes have to say. It is good to know they recognise and recommend patience as a key virtue in a