pharmacokinetics and pharmacodynamic effects. Pain 1989;37:193–202.
6. Sandler AN, Baxter AD, Norman P, *et al.* A double blind, placebo-controlled trial of transdermal fentanyl for post-hysterectomy pain relief. II: respiratory effects. Can J Anaesth 1991;38:A114.

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Therapy of Anal Fissure Using Botulin Toxin

We have been practicing this new method (Therapy of Anal Fissure Using Botulin Toxin, Dis Colon Rectum 1994;37:1321–4) since mid 1992. A lecture on this subject was held for the first time by a member of our Department (WHJ) on December 2, 1992. The first English publication of our results with this new therapy appeared in *Diseases of the Colon and Rectum* in 1993.[1] The underlying study was handed in on December 30, 1993. In March 1994, we were already able to present the long-term results of 24 patients.[1] Both of the manufacturers of the toxin have been informed of our work and have supported it; Pharm-Allergan informed its representatives and customers of the study in December of 1993.

It is regrettable that an article on this subject by Gui *et al.*[3] appeared in the October issue of *The Lancet* (data gathered in May 1994) without pointing out that we were the first to describe this method.

REFERENCES

1. Jost WH, Schimrigk K. Use of Botulinum toxin in anal fissure [letter]. Dis Colon Rectum 1993;36:974.
2. Jost WH, Mlitz H, Schimrigk K. Therapie der analfissur mit botulinumtoxin. In: Hager T, ed. Aktuelle koloproktologie. Vol. 11. München: Urban & Vogel, 1994:208–12.
3. Gui D, Caesseta E. Anastasio G, Bentivoglio AR, Maria G, Albanese A. Botulinum toxin for chronic anal fissure. Lancet 1994;344:1127–8.

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Folate Supplementation and Adenomatous Colonic Polyps

To the Editor—Diminished red blood cell folate levels have been associated with an increased risk of various human precancerous changes.[1–3] A recent study has reported that high dietary folate intake was inversely associated with the risk of colonic adenomas.[4] Previous studies have suggested that folate supplementation may provide some protection against the risk of premalignant changes.[5, 6] A double-blind, randomized, prospective, controlled clinical trial was designed to test whether folate supplementation had any influence on the rate of colonic adenoma recurrence.

Sixty consecutive patients, who were having colonic adenomas removed by endoscopic polypectomy (index colonoscopy), were randomized to receive either folate (1 mg/day) or placebo. Thirty-one patients (15 males, 16 females; mean age, 60 years) were randomized to folate and 29 patients (14 males, 15 females; mean age, 64 years) to placebo. None had ever been previously diagnosed as having colonic adenomas. All patients underwent total colonoscopy three months after the index colonoscopy to look for possible missed polyps. Surveillance total colonoscopy in all patients was performed at 12 months (first surveillance) and at 24 months (second surveillance) after the index colonoscopy. All individuals continued their usual diet during the study.

In the first surveillance colonoscopy, the percentages of adenoma recurrence were 23 percent (7/31) and 38 percent (11/29) in the folate and placebo groups, respectively. In the second surveillance colonoscopy, the percentages of adenoma recurrence were 13 percent (4/31) and 28 percent (8/29) in the folate and placebo groups, respectively. The differences do not reach statistical significance (Fisher's exact test).

Folate is an important coenzyme used for DNA methylation and DNA synthesis. It has been suggested that low folate status may act as a cocarcinogen.[7] The exact mechanism by which folate deficiency might be associated with carcinogenesis is not yet known. Folate deficiency has been associated with reduced DNA methylation. Reduced DNA methylation has been observed in human colonic cancers as well as in colonic