This pilot experience warrants a further formal study of ondansetron compared with standard agents. The 5-HT3 receptor axis might play a part in the pathogenesis of some syndromes of central vertigo.

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Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome)

Sir—Hereditary non-polyposis colorectal cancer (HNPPC) is an autosomal dominantly inherited disease caused by loss of function of a mismatch repair gene. It is characterised by the development of colorectal cancer at an early age, a predilection for tumours in the proximal colon, an excess of multiple colorectal cancers, and an association with various extracolonic cancers including endometrial cancer.1 Periodic examination of high-risk family members may prevent development of disease and death from cancer. Because of the high frequency of the HNPPC gene in the population (between 1 in 200 and 1 in 2000) and the fact that young people are involved, surveillance programmes in high-risk families should be an important goal of national health-care programmes. Identification of gene carriers within these families is of great importance because surveillance may be restricted to these relatives, and the relatives who do not carry the gene may refrain from examination. The recommended surveillance protocol for HNPPC (colonoscopy at 2–3 year intervals from age 20–25) is based on the hypothesis that the adenoma-carcinoma sequence, which is generally accepted in sporadic colorectal cancer, is also applicable in HNPPC. Observations from the US National Polyp Study indicate that it takes a mean of 10–12 years for a polyp to develop and degenerate into a gross cancer,3 which suggests that an interval of 2–3 years is adequate. In the Netherlands one of the largest series of HNPPC families (51 families including 394 first-degree relatives, mean follow-up 5 years) participates in a nationwide surveillance programme that is financially supported by the government. An unexpectedly high occurrence of advanced cancers was detected within 3–5 years after a negative screening examination (table). Another unexpected finding was that most of the adenomas (about 60%) detected in patients under surveillance were located in the distal part of the colon and the rectum, an observation that does not correspond with the anatomical distribution of carcinomas in HNPPC.

A possible explanation for the high frequency of interval cancers in our screening programme is that adenomas were missed during the previous screening examination. However, another explanation, which ties in with the discrepancy in location of adenomas and cancers in the colon, is that the HNPPC gene accelerates the processes of initiation and progression of cancer even in very small adenomas which are reported to be evenly distributed along the large intestine.4 This explanation is also in agreement with a study5 that revealed that adenomas in HNPPC more often show a villous growth pattern and a high degree of dysplasia than adenomas in a necropsy series, though there was no difference in size of the adenomas. A third explanation is that gene carriers develop "de novo" cancers.

On the basis of these findings we recommend a shortening of the interval between examinations to 1–2 years in proven gene carriers who have a risk of about 85% of developing colorectal cancer. A barium enema should be done when the colon is not completely visualised during endoscopy. Prophylactic subtotal colectomy may be considered in patients with (recurrent) polyps with a high degree of dysplasia or with a villous growth pattern. On the other hand prophylactic surgery in gene carriers without any colonic abnormalities should probably be avoided because of the

<table>
<thead>
<tr>
<th>Age at diagnosis (yr)</th>
<th>Location of tumour</th>
<th>Stage (Dukes)</th>
<th>Previous negative examination</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>46</td>
<td>R</td>
<td>C</td>
<td>Colorectal 2 yr, 7 mo</td>
</tr>
<tr>
<td>2/F</td>
<td>46</td>
<td>R</td>
<td>B</td>
<td>Colorectal 2 yr</td>
</tr>
<tr>
<td>2/H</td>
<td>41</td>
<td>R</td>
<td>C</td>
<td>Barium enema 2 yr, 6 mo</td>
</tr>
<tr>
<td>2/M</td>
<td>40</td>
<td>R</td>
<td>B</td>
<td>Colorectal 3 yr, 6 mo</td>
</tr>
<tr>
<td>2/F</td>
<td>53</td>
<td>R</td>
<td>B</td>
<td>Colorectal 3 yr</td>
</tr>
<tr>
<td>2/H</td>
<td>51</td>
<td>R</td>
<td>C</td>
<td>Colorectal 2 yr, 2 mo</td>
</tr>
</tbody>
</table>

*3 patients were symptomatic and 3 symptom free.
†Died from colorectal cancer.
‡Located from ascending or transverse colon.

Table: Patients with colorectal cancer detected after negative screening examination
morbidity that would be associated with this operation and because of the chance that individuals (10–20%) will never develop colorectal cancer. Reluctancy to undertake prophylactic surgery seems to be justified because HNPCC patients are at risk for development of cancer in various organs.

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Adjuvant intraperitoneal chemotherapy for colorectal cancer
Sir—The Swiss Group for Clinical Cancer Research (SAKK) report perioperative intraperitoneal mitomycin and fluorouracil for colorectal cancer (Feb 11, p 349). This study shows a modest, though statistically significant, survival advantage for patients randomised to chemotherapy when compared with those receiving no adjuvant treatment.

The Swiss group investigators state in their concluding paragraph that they now accept perioperative adjuvant chemotherapy as the standard treatment for further clinical trials in colorectal cancer. Although most would agree that treatment for node-positive colorectal cancers should now include some form of adjuvant therapy, we cannot find any justification for treating Dukes' B (T3–4,N0,M0) cases in a similar manner. This group of patients, constituting over a third of all colorectal cancer cases, has a 5-year survival in excess of 70% without adjuvant treatment, and there are few published data or data in the SAKK study to suggest that this survival rate is improved by conventional chemotherapeutic regimens.

The data provided by SAKK do not include an overall or disease-free survival curve for node-negative patients stratified by treatment. However, the percentage of tumour recurrences was almost identical in treated and untreated groups (27% vs 29%), and the small difference in cancer-related 5-year survival (5%) with extensively overlapping 95% CIs in the two groups suggests that any survival advantage attributable to chemotherapy is marginal in these node-negative cases. In addition, the hypothesis that portal chemotherapy might reduce the frequency of liver metastases in node-negative patients has clearly not been validated, since there were 60% fewer cases of isolated liver metastasis in the control group. Indeed, locally recurrent disease accounted for over 50% of all recurrences in the untreated group, suggesting that improved surgical techniques rather than adjuvant therapy might be of greater benefit to these node-negative patients.

The inclination to administer conventional adjuvant therapies to virtually all patients with colorectal cancer may be compelling, but we believe that the temptation should be resisted in non-metastatic cases in the absence of any supporting data. An alternative policy of enrolling Dukes' B patients into controlled trials of new agents, while giving conventional regimens to selected high-risk cases, might greatly improve survival in the node-negative group while sparing most such cases unnecessary and potentially toxic treatments.

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Authors' reply
Sir—Mulcahy and Farthing's comment allows us the opportunity to emphasise the fact that we regard our perioperative regimen as standard treatment only for further clinical research in colon cancer. We are certain that our results do not justify the routine use of this regimen for patients outside clinical trials.

Perioperative adjuvant treatments could be tested in a patient population before the full histopathological staging took place. The overall results of the study show an estimated 21% reduction of the chance of relapse and 26% reduction of the likelihood of death for patients given perioperative treatment compared with controls. The magnitude of the effect and the reasonably small degree of statistical uncertainty (range of 95% CIs and p values) allowed us to formulate the conclusions. Retrospective subgroup analysis, as in the one that led to defining treatment results by nodal status, are mainly useful for the generation of new research, rather than to justify a policy for routine patient care.

The estimated 14% reduction in the risk of relapse in the subpopulation without lymph-node metastases, although statistically uncertain, indicates that some patients with such disease presentation might benefit from the treatment. On the other hand, the 5-year estimated baseline disease-free survival was 63% (SD 4%), which indicates an important opportunity for improvement. This treatment is, therefore, the strategy chosen by SAKK to further investigate whether the addition of a prolonged treatment might lead to improved outcome, even for patients without lymph-node metastases.

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Leprosy
Sir—The grand round on leprosy (March 18, p 697) was an eye opener for physicians in the developed world. In the present immigrant era, no nation is shielded from this crippling disease of the developing world, where the associated social stigmata parallels that of AIDS in western countries. The training that physicians receive for leprosy in developed nations is so grossly inadequate that there might be a danger of failing to recognise and manage the disease appropriately. However, with the low case load and the abundant financial resources in developed countries leprosy is unlikely to affect western populations with the same tenacity as is seen in the third world.

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