Screening for colorectal cancer
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wonder if the authors of the two studies published in The Lancet might be able to report the all-cause mortality rates of their trials, since they were based on biennial screening. The trials used a biennial screening strategy, which will also affect the cost-effectiveness ratio in a negative way. Most important, both assume an effect of screening on the totally mortality, by contrast with the results of the trials. The results of existing cost-effective analyses cannot simply be combined with the findings of the recent trials to advocate screening for colorectal cancer. A new cost-effectiveness analysis based on the data of the recently published trials is necessary before a national screening programme for colorectal cancer can be recommended.

Brian Budenholzer
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Sir—The investigators in the two large randomised trials of screening for colorectal cancer conclude that it is time to consider screening for colorectal cancer. In their commentary Lieberman and Siegnsinger wrote that the time has come to encourage colon screening. We believe that these recommendations are premature. The investigators base their conclusions on the reduction of the colorectal mortality recorded (disease specific rate ratio 0.85 and 0.82)—the addition of Alb and CEA further improved sensitivity. By contrast, Hardcastle and Kronborg do not provide any data on gastric cancer findings after a positive FOBT. Our new combined quantitative immunological faecal occult-blood/ protein test offers some advantages, which the 1995 International Union Against Cancer Colorectal Cancer Workshop set as specific goals for future FOBTs: improved sensitivity, fewer difficulties with specificity, and automated method for batch processing. In addition to measurement of haemoglobin (Hb) we tested faecal albumin (Alb) and carcinoembryonic antigen (CEA) with chemiluminescent CEA bead assays (method unpublished). Hb-Alb-CEA 53·3

<table>
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<th>Sensitivity (%)</th>
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<td>Colorectal cancer (n=9)</td>
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<tr>
<td>Hb-Alb-CEA</td>
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<td>Hb-Alb</td>
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<td>Alb</td>
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Polyps (n=20)
Hb-Alb-CEA | 90 |
Hb-Alb | 70 |
Hb | 60 |
Alb | 60 |
CEA | 60 |

Gastric cancer (n=15)
Hb-Alb-CEA | 53 3 |
Hb-Alb | 46 6 |
Hb | 33 3 |
Alb | 33 3 |
CEA | 26 6 |

*Two to six faecal samples were obtained from each patient.

Sensitivity of immunological single and combination faecal occult-blood tests

The immunological tests do not need the patient to follow a special diet. Patients were instructed to take two samples from three consecutive bowel movements with special air-tight stool sample collection vials, providing a more representative amount of faeces (about 1 g) than paper smears. In the laboratory the samples were weighed, diluted and thoroughly mixed before analysis.

In early studies with diagnosed but untreated patients we evaluated the faecal Hb-Alb and a Hb-Alb-CEA combination test to determine sensitivity. Threshold values and specificity were defined in screening 80 healthy controls (age 6–81; mean 40, SD 23) with six faecal samples each, by taking the highest value of this series. Patients were regarded as positive if one result of the immunological tests was positive. The specificity of each test was set at 97.5% (table). Our test for faecal Hb has high sensitivity and specificity for colorectal cancer. For polyps (χ2 test, p<0.05)—as in gastric cancer (p<0.05)—the addition of Alb and CEA further improved sensitivity. By contrast, Hardcastle and Kronborg do not provide any data on gastric cancer findings after a positive FOBT. Comparing our results with published data for chemical faecal peroxidase testing, we conclude that the immunological test of Hb with proper specimens increases sensitivity, specificity, and patient compliance since no diet is necessary. The results may be further improved by combination testing. Our findings add to Lieberman’s conclusion that a faecal occult blood alone programme is more cost-effective than other screening programmes. We plan to examine the reliability of our combination test (Hb-Alb) by
obtaining faecal samples from 1000 patients before scheduled colonoscopy, as well as from those in a screening study on 5000 healthy persons above 45 years of age.

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Author’s reply

Sir—Your correspondents mistakenly assume that we were looking for a difference in all cause mortality as an endpoint of this trial. The purpose of showing all cause mortality was to demonstrate that the randomisation process had resulted in study and control groups of comparable health status. It would be impractical to attempt to show a significant reduction in all cause mortality because of the small size of our study sample.

Colorectal cancer accounts for only 3% of all deaths; a 15% reduction in deaths from disease would then be expected to reduce all cause mortality by only 0.5% which is included in the 95% CI of the observed risk. The same argument applies to all preventive interventions aimed at a single disease.

Gøtzsche combines the results of the UK and Danish studies, although the risk difference for colorectal cancer is one death prevented per 1000 invited, not screened as he suggests. Our own combined analysis shows a relative risk of 0.84 (95% CI: 0.75-0.94) in the group offered screening. He also raises the issue of psychological side-effects; this has been studied and we were pleased to find that a false-positive finding did not result in long-term psychiatric morbidity. Those data will be published shortly.

John and colleagues are right that it is important to improve the performance of FOBTs. However, improving test sensitivity may result in a reduction in specificity, thereby increasing costs. This was demonstrated by our comparison of Hemoccult with a more sensitive immunological FOBt in population screening.

J D Hardcastle

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Author’s reply

SIR—It has never been shown that an offer of screening turns the world’s healthy citizens into fearful patients-to-be—on the contrary, there is no substantial evidence from other screening programmes to support Gøtzsche’s idea. Whether the benefits obtained justify the costs is a political matter. Long-term randomised studies including screening for many diseases have been done, and others are underway.

Budenholzer is right that no reduction in overall mortality was documented in our study, but it was not our intention to identify such an effect. The slight reduction in mortality could mean a substantial reduction in disease progression, or their combinations for those receiving either two-drug combination therapy, zidovudine and didanosine or zidovudine and zalitabine, compared with those receiving only zidovudine, when analysed separately or in aggregate. The Delta 2 trial result for the treatment effect of zidovudine and didanosine in experienced zidovudine users presented in figure 1 and given in the text (p 287), cited by Sherer, is one of multiple comparisons, and, therefore, with p=0.05 is of doubtful statistical significance.

The complete results of the ACTG 175 trial, published on Oct 10, 1996, were not available when I submitted my letter. The data of the ACTG 175 trial for individuals with CD4 cell counts of 200-500 per µL presented in table 4 (p 1085), indicates a modest effect from zidovudine and didanosine compared with zidovudine alone for experienced zidovudine users, and similarly for the endpoint of death alone. However, the modest effect is questionable. Multiple comparisons of this nature could mean that the results of the ACTG 175 trial finding indicated no significant benefit from zidovudine and zalitabine therapy compared with zidovudine alone in experienced zidovudine users in terms of progression to AIDS or death.

ACTG 175 report on effects of combination therapy on individuals with AIDS or CD4 cell counts less than 200 per µL indicates no benefit from combination therapy with either zidovudine and didanosine or zidovudine plus zalitabine compared with zidovudine alone in terms of disease progression or death for those with more than 12 months of previous zidovudine treatment (table 4, p 1104).

For those with such experience of less than or equal to 12 months of zidovudine or a slight benefit in terms of disease progression or death resulted from...