The benefit of colorectal cancer screening using a test for blood in stool (Hemoccult) was established in 1993 (1). Subsequently, this result was corroborated in two other randomized controlled trials, leading to recommendations in many countries for colorectal cancer screening (2,3). In the United States, the current recommendations include a number of screening tests in addition to Hemoccult, but other than Hemoccult none of the tests have been proven to be effective through a randomized controlled trial. However, it can be assumed that all are effective to some extent, given what is known about these tests and the biology of the disease.

Although the Hemoccult test is effective in reducing colorectal cancer mortality and incidence, it is not optimal, and developing a simple and relatively inexpensive test for blood in stool that performs better would be beneficial. Immunochemical tests, which have not been evaluated in a randomized controlled trial, have performed at least as well and in some cases better and with generally higher compliance rates than Hemoccult or other guaiac-based tests (4–8). Quantitative immunochemical tests have the advantage of calibration of positivity to adjust the screening program according to the resources available. Applying an immunochemical test to patients scheduled for colonoscopy, Levi et al. (9) showed the advantages of a quantitative test to determine the cutoff for positivity. These kinds of screening tests warrant more attention.

Screening with a 1-day immunochemical hemagglutination test (Immuida-Hem Sp or HemSelect; Fujirebio, Tokyo, Japan) was introduced in Japan in 1986 and evaluated by case–control studies (10–12) that showed colorectal cancer mortality reductions of up to 80%. In Japan, more than 6 million people have been screened with immunochemical tests, with a positivity rate of 7.1% (13). With 60% of test positives complying with the diagnostic protocol, the colorectal cancer detection rate was 1.6 per 1000. More than 70% of the cancers were classified as Duke’s A or Duke’s B, suggesting that the program worked well in detecting cancer early. In a cohort study of more than 40,000 men and women in Japan who were screened with an immunochemical test and compared with unscreened control subjects, colorectal cancer mortality and incidence were reduced by 72% and 59%, respectively (14).

Which immunochemical test is best is yet to be determined, but evidence is rapidly mounting that immunochemical is superior to guaiac. It offers some advantages such as not requiring a restricted diet before and during sample collection, the potential to automate the test, the ability to quantify the cutoff, and the need for two rather than three samples.

The study by Allison et al. (15) in this issue of the Journal of two types of fecal occult blood tests, guaiac and immunochemical, is an important contribution to the evolving literature on colorectal cancer screening. The authors attempt to improve on a previous study from Allison et al. (16) by using a flexible sigmoidoscopy examination for those with a negative test result rather than relying solely on a 2-year clinical follow-up to ascertain false-negatives. However, colonoscopy of all participants would have eliminated speculation about right-sided lesions. In the current study (15), both guaiac and immunochemical tests were administered, and initially, the immunochemical test was processed only if the guaiac test was positive or inconclusive. Subsequently, the protocol was changed so that all tests were processed. The only restriction imposed on participants was avoiding vitamin C for 3 days before and during the stool collection period. The guaiac test, which is not specific for human blood, has generally been administered with recommended dietary restrictions, particularly the avoidance of red meat, and it is unclear if using the test without dietary restrictions can be justified, given the properties of the test. However, the investigators added dietary restrictions, compliance might have been reduced.

In the study, a positive test on any one of the fecal occult blood tests led to a colonoscopy examination. Those with a negative screening test were encouraged to have a flexible sigmoidoscopy, and those with inconclusive results were asked to redo the tests. Participants with advanced neoplasms on flexible sigmoidoscopy were referred for colonoscopy. Those with a negative test or a negative examination were encouraged to repeat screening in 1 year. Follow-up was for 2 years and was complete for 93% of the study participants.

This study evaluated the performance of the screening tests, which were administered one or two times, in detecting primarily distal lesions. The authors conclude that the immunochemical test could replace the guaiac test because the sensitivity for cancer was greater (81.8% versus 64.3%, based on 14 and 11 total cancers). Somewhat puzzling was the fact that guaiac was more sensitive than immunochemical for advanced adenomas (41.3% versus 29.5%, based on 126 and 112 cases). The authors speculate that this could result from the peroxidase sensitivity of the guaiac test being set so high that it detects lower levels of bleeding than the immunochemical test. However, other explanations must also be considered.

There are some things that cannot be definitively concluded from this study. One cannot conclude that FlexSure OBT is the immunochemical test of choice, that an immunochemical test such as FlexSure OBT could result in the same benefit as colonoscopy screening, that any fecal occult blood test combined with flexible sigmoidoscopy would result in a mortality reduction of a certain magnitude, or that results from this study can necessarily be generalized to right-sided lesions.

The study does illustrate the utility of comparing different fecal occult blood tests rather than conducting long-term and expensive randomized controlled trials to evaluate each new fecal occult
blood test. There are considerable data on Hemoccult, so comparing performance, outcome, compliance, and cost with new fecal occult blood tests, as was done in this study, should be sufficient. More studies of this type would be helpful in deciding on the most cost-effective fecal occult blood test. The study does show that an immunochemical test is probably better than a guaiac test for screening for colorectal cancers, but the specific immunochemical test of choice is still unclear.

References