

Colorectal Cancer Screening

Scientific Review

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COLORECTAL CANCER IS THE second leading cause of cancer death in the United States. In women, it ranks third after lung and breast cancer, and in men, it ranks third after lung and prostate cancer. Incidence and mortality from colorectal cancer are similar in both men and women. In 2001, an estimated 135 400 cases were diagnosed and an estimated 56 700 deaths occurred in the United States.¹

Death from colorectal cancer is preventable. Effective, safe, and relatively inexpensive methods for screening for the disease have been available for decades, and screening is championed by a large number of public, private, and professional organizations (Multidisciplinary Expert Panel,² US Preventive Services Task Force,³ the American College of Gastroenterology,⁴ and the American Cancer Society⁵). This article provides practicing physicians with an evidence-based review of the literature of the current status of colorectal cancer screening, including the methods of screening that are likely to be widely available within the next several years.

METHODS

In addition to reviewing published systematic reviews, we conducted a literature search using PubMed for English-language articles from January 1966 through August 2002. For the search, we combined search terms *colorectal neoplasm* or *occult blood* or *sigmoidoscopy* or

See also p 1297 and Patient Page.

Context Screening for colorectal cancer clearly reduces colorectal cancer mortality, yet many eligible adults remain unscreened. Several screening tests are available, and various professional organizations have differing recommendations on which screening test to use. Clinicians are challenged to ensure that eligible patients undergo colorectal cancer screening and to guide patients in choosing what tests to receive.

Objective To critically assess the evidence for use of the available colorectal cancer screening tests, including fecal occult blood tests, sigmoidoscopy, colonoscopy, double-contrast barium enema, and newer tests, such as virtual colonoscopy and stool-based molecular screening.

Data Sources All relevant English-language articles were identified using PubMed (January 1966-August 2002), published meta-analyses, reference lists of key articles, and expert consultation.

Data Extraction Studies that evaluated colorectal cancer screening in healthy individuals and assessed clinical outcomes were included. Evidence from randomized controlled trials was considered to be of highest quality, followed by observational evidence. Diagnostic accuracy studies were evaluated when randomized controlled trials and observational studies were not available or did not provide adequate evidence. Studies were excluded if they did not evaluate colorectal screening tests and if they did not evaluate average-risk individuals.

Data Synthesis Randomized controlled trials have shown that fecal occult blood testing can reduce colorectal cancer incidence and mortality. Case-control studies have shown that sigmoidoscopy is associated with a reduction in mortality, and observational studies suggest colonoscopy is effective as well. Combining fecal occult blood testing and sigmoidoscopy may decrease mortality and can increase diagnostic yield.

Conclusion The recommendation that all men and women aged 50 years or older undergo screening for colorectal cancer is supported by a large body of direct and indirect evidence. At present, the available evidence does not currently support choosing one test over another.

JAMA. 2003;289:1288-1296

www.jama.com

barium enema or *colonoscopy* with the term *screening*. To supplement the search, we reviewed published meta-analyses and personal files and bibliographies from published articles, conducted hand searches, including the proceedings of recent national professional organization meetings, and consulted with experts on colorectal cancer screening. Eligibility criteria for articles that evaluated colorectal screening tests, such as fecal occult blood tests (FOBTs), sigmoidoscopy, colonoscopy, and double-contrast barium en-

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Financial Disclosure: Dr Terdiman is on the scientific advisory board at Exact Laboratories, Maynard, Mass. **Scientific Review and Clinical Applications Section Editor:** Wendy Levinson, MD, Contributing Editor. We encourage authors to submit papers to "Scientific Review and Clinical Applications." Please contact Wendy Levinson, MD, Contributing Editor, JAMA; phone: 312-464-5204; fax: 312-464-5824; e-mail: wendy.levinson@utoronto.ca.

ema, were that they include asymptomatic subjects (hence, screening) who were at average-risk and that information be provided on clinical outcomes. The clinical outcomes included mortality, cancer incidence, and identification of adenomas. Studies to be of the highest quality were randomized controlled trials (RCTs), which assessed morbidity and/or mortality, followed by observational studies. Diagnostic accuracy studies were evaluated when RCTs and observational studies were not available or did not provide adequate evidence. The highest quality evidence available was included for each topic: for FOBT, RCTs; for sigmoidoscopy, RCTs and observational studies; for FOBT plus sigmoidoscopy, controlled trials, observational studies, and diagnostic accuracy studies; for double-contrast barium enema, diagnostic accuracy studies; and for colonoscopy, observational studies and diagnostic accuracy studies. This review included additional literature to provide background material on the performance, interpretation, and safety of colorectal cancer screening tests and to provide preliminary data on new, emerging methods for colorectal cancer screening, such as computed tomography (CT) colonography and stool-based molecular testing.

EVIDENCE FOR COLORECTAL CANCER SCREENING

Death from colorectal cancer can be prevented by the detection of early-stage disease that has not metastasized. The disease itself can be prevented by the detection and removal of colorectal adenomas, from which greater than 95%

of cancers arise.⁶⁻⁹ The majority of these adenomas are polypoid growths. But as many as 20% to 30% of adenomas are flat or depressed, which make them more difficult to detect and remove.^{10,11}

The optimal means to prevent colorectal cancer remain uncertain. Evidence for the efficacy of the commonly practiced colorectal cancer screening tests are reviewed.

Fecal occult blood testing had 3 RCTs and sigmoidoscopy had 1 randomized trial and 3 case-control studies that assessed mortality. No RCTs were found for colonoscopy, but 4 observational studies were identified in which asymptomatic individuals underwent colonoscopy and in which adenoma and cancer incidences were assessed. Combined FOBT and sigmoidoscopy screening had 5 trials that assessed clinical outcomes: 1 trial assessed mortality, and the other trials assessed incidence of polyps and/or cancer. Finally, for double-contrast barium enema, no RCTs or observational studies were identified that assessed clinical effectiveness and 4 diagnostic accuracy studies were identified and evaluated.

Fecal Occult Blood Testing

Evidence of Clinical Efficacy. Results from 3 large RCTs of serial FOBTs conducted in Minnesota,^{12,13} United Kingdom,^{14,15} and Denmark,^{16,17} involving more than 250 000 subjects followed for up to 18 years, have consistently demonstrated that serial FOBT reduces colorectal cancer mortality (TABLE 1). Screening with FOBT reduced colorectal cancer mortality from 15% to 33%,¹²⁻¹⁴ with the absolute risk reduc-

tion for colorectal cancer death ranging from a low of 0.8 per 1000 person-years with biennial screening in the UK study to a high of 4.6 per 1000 person-years with annual screening in the Minnesota trial. Recent 18-year follow-up data from the Minnesota trial demonstrate that annual and biennial serial FOBT screening reduces colorectal cancer incidence by 17% to 20% as well.¹⁸

How the Test Is Performed. The FOBT detects blood loss in the stool. It can detect blood loss caused by colorectal neoplasms, which tend to bleed more than normal colonic mucosa. A variety of FOBTs are available,^{19,20} but the Hemoccult II is most widely used in the United States (Beckman-Coulter, Palo Alto, Calif). This test detects the pseudoperoxidase activity found in hemoglobin when it interacts with a guaiac-impregnated card in the presence of a hydrogen peroxide developer. A positive result is indicated by the immediate appearance of a blue color on addition of the hydrogen peroxide developer. The testing process requires that the patient apply 2 distinct samples of 3 different stools to 6 test card windows. Because the test detects peroxidase or pseudoperoxidase activity in stool, it is not specific for human hemoglobin. Dietary substances can result in false positive (eg, rare red meat, turnips, horseradish) or false negative (eg, vitamin C) results. However, a recent systematic review found that a restricted diet does not reduce the positivity rate but it may reduce patient compliance.²¹

A rehydration procedure that enhances the sensitivity of the Hemoc-

Table 1. Summary of Clinical Trials for Fecal Occult Blood Testing

Study Characteristics	Mandel et al ^{12,13} (United States)	Hardcastle et al ¹⁴ (United Kingdom)	Kronborg et al ^{16,17} (Denmark)
No. of study participants	46 551	150 251	61 933
Follow-up, y	18	7.8	13
Relative risk mortality with annual FOBT (95% CI)	.67 (0.51-0.83)	Not studied	Not studied
Relative risk mortality with biennial FOBT (95% CI)	.79 (0.62-0.97)	.85 (0.74-0.98)	.82 (0.69-0.97)
Absolute risk reduction for CRC death per 1000 subjects	4.6 (annual) 2.9 (biennial)	0.8	1.8
No. of subjects needed to screen to prevent CRC death	217 (annual) 344 (biennial)	1250	555

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FOBT, fetal occult blood testing; RR, relative risk.

cult test, at the expense of specificity, can be performed by adding a few drops of water to the stool samples before adding the hydrogen peroxide to the test windows.¹² This procedure reduces the positive predictive values of the test by more than 50%. In the Minnesota Colon Cancer Control Society trial, of the guaiac-impregnated cards, 83% were screened using this procedure, and as a result, colonoscopy was performed on 38% of the participants in the annually screened group and 28% of the participants in the biennially screened group during the first 13 years of the study.¹² By comparison, only 4% to 5% of subjects in the UK and Denmark studies underwent colonoscopy.^{14,16,17}

No direct comparison has been made with respect to the efficacy of the rehydrated and nonrehydrated procedures for FOBT,^{12,14,16,17} and any incremental benefit of rehydration with respect to mortality reduction may be small in light of the increased costs due to a much higher false positive rate. In the Minnesota Colon Cancer Control Society trial, use of the rehydration procedure reduced the 13-year cumulative mortality rate by 33% for colorectal cancer.¹² It has been argued that some of the mortality reduction in this trial was simply a consequence of the high rate of colonoscopy performed (ie, a similar benefit would have been demonstrated in the population if the number of colonoscopies performed in the study population had been randomly allocated).²² The degree of the reduction in the rate of mortality has been clarified by additional data from the Minnesota trial and additional mathematical modeling.²³

At the present time, professional organizations, such as the World Health Organization,²⁰ US Preventive Services Task Force,³ and American College of Physicians,²⁴ do not recommend the rehydration FOBT procedure because of the uncertainties regarding effectiveness and cost, compared with the nonrehydrated FOBT procedure. Guaiac-based tests other than the Hemoccult II also are available, but they are not often used. Recently, the World Health Organization endorsed the He-

moccult Sensa (Beckman Coulter, Palo Alto, Calif) as the test of choice because of its greater sensitivity than the Hemoccult II and its greater specificity than the rehydrated Hemoccult.²⁰ Immunochemical FOBTs have the advantage of not requiring dietary or drug restrictions, but these tests are more expensive, and published data on effectiveness are limited.²⁰

Based on evidence from large RCTs, FOBT should be repeated at least every other year to be clinically beneficial.^{12-14,16,17} An annual FOBT may offer greater reductions in mortality than a biennial screening, but at an increased cost.^{3,13,25}

Fecal occult blood testing itself is safe, but false positive results can lead to unnecessary further invasive tests, such as colonoscopy, that have a measurable complication rate.^{26,27}

How to Interpret the Test Results. The greater the number of test windows that are positive, the higher the positive predictive value of the test.¹⁸ However, even if only 1 of the 6 test windows is positive, the overall test should be considered positive, and these individuals should be referred for complete colonoscopy.²⁸ This was the approach used by the Minnesota and Denmark FOBT studies.^{13,17}

Performance Characteristics. Fecal occult blood testing performed on a single occasion for the detection of colorectal cancer and adenomas shows poor sensitivity. However, the key to the success of FOBT lies in serial testing.²⁹⁻³¹ In the UK and Denmark studies, FOBT screening detected 27% of the patients in the intervention group who developed cancer.^{14,16} In the Minnesota trial, after 13 years, 39% of patients in the biennial group and 49% of patients in the annual group who developed colorectal cancer were identified through FOBT screening.¹²

Flexible Sigmoidoscopy

Evidence of Clinical Effectiveness. No completed large RCTs have demonstrated the effectiveness of sigmoidoscopy in the prevention of colorectal cancer death. The National Cancer Institute

is funding the Prostate, Lung, Colorectal, and Ovarian screening trial, which is evaluating 60-cm flexible sigmoidoscopy,³² and the UK FlexiScope Trial is being conducted to study one-time screening sigmoidoscopy in subjects between ages 55 years and 64 years.³³⁻³⁵ These 2 large studies ultimately will enroll more than 250 000 subjects, but no outcome data are yet available.

The Telemark Polyp Study, a small randomized trial, demonstrated that one-time flexible sigmoidoscopy screening could reduce colorectal cancer incidence. However, no reduction in colorectal cancer mortality was observed in the screened group.^{36,37}

The major evidence supporting the effectiveness of sigmoidoscopy comes from well-designed, retrospective case-control studies.³⁸⁻⁴⁰ The landmark study by Selby et al³⁸ found that rigid sigmoidoscopy screening was associated with a 59% reduction in colorectal cancer mortality (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.25-0.69). The reduction in mortality from cancers within the reach of the sigmoidoscope was 70% (OR, 0.30; 95% CI, 0.19-0.48), while there was no significant reduction in mortality seen from cancers proximal to the reach of the sigmoidoscope (OR, 0.80; 95% CI, 0.54-1.19).³⁸ These results have been confirmed by 2 other well-designed case-control studies by Newcomb et al³⁹ and Muller and Sonnenberg,^{40,41} which have expanded the findings to include flexible sigmoidoscopy (TABLE 2). In addition, 2 case-control studies have demonstrated a reduction in incidence of colorectal cancer using flexible sigmoidoscopy.^{40,42}

How the Test Is Performed. Flexible sigmoidoscopy generally is performed using a 60-cm flexible endoscope.⁴² Preparation for the procedure requires that at least 1 to 2 saline enemas are administered to the patient the morning of the examination.

The examination can be performed in a physician's office or in the hospital. Special training is required to perform the procedure, but a variety of practitioners (physician's assistants, nurses, primary

care physicians, gastroenterologists) routinely perform the procedure.⁴⁴⁻⁴⁸ The procedure takes about 10 minutes to perform. The patient often experiences some tolerable abdominal pain. Sedation is not administered, and the patient may drive alone to the physician's office or hospital and return to work immediately following the procedure.

The flexible sigmoidoscopy procedure is safe when performed by experts. In a retrospective review of 49 501 flexible sigmoidoscopy procedures performed during a 10-year period, only 2 perforations occurred (0.004%).²⁶ Similar low complication rates have been reported from large population-based flexible sigmoidoscopy screening programs in the United States and the United Kingdom.^{34,35,49,50}

How to Interpret the Test Results. An important question is which lesions identified by sigmoidoscopy should prompt evaluation of the entire colon. Guidelines published by the 3 major US organizations specializing in the gastrointestinal tract state that the finding of an adenomatous polyp 1 cm or larger in diameter, or one with advanced histologic findings (eg, villous changes or high-grade dysplasia), or multiple polyps, at sigmoidoscopy examination requires follow-up with complete colonoscopy, even if the lesions were removed at the initial examination.⁹

However, controversy remains regarding the appropriate follow-up for the finding of 1 or 2 small tubular adenomas. Some experts recommend

complete colonoscopy if any adenoma is found at sigmoidoscopy examination, while others feel that no additional procedure is required if only 1 or 2 small adenomas are detected and removed at sigmoidoscopy examination.^{9,25} These recommendations are based on a large number of studies that correlate the findings in the distal region of the colon and rectum, with the likelihood of finding a cancer or an advanced polyp in the proximal region of the colon at complete colonoscopy examination (TABLE 3).^{31,51-56}

After a negative sigmoidoscopy result in which no adenoma is found, the standard recommendation is to repeat the screening examination in 5 years. This recommendation is based on case-control studies that have demonstrated that the protective effects of sigmoidoscopy appear to last at least 6 years³⁸ and a prospective follow-up sigmoidoscopy study in which the likelihood of finding an advanced adenoma or cancer was 0 in the 3 to 4 years following a negative sigmoidoscopy result.⁵⁷ However, preliminary data from the large-scale

Prostate, Lung, Colorectal, and Ovarian sigmoidoscopy screening trial indicated that the risk of advanced adenoma in the distal region of the colon 3 years after an initial negative sigmoidoscopy result was 0.8%, although the incidence of cancer in this region of the colon was less than 0.1%.⁵⁸ Longer term follow-up of this study will further clarify the importance of this finding.

Performance Characteristics. Flexible sigmoidoscopy only examines a portion of the colon, and therefore important colonic lesions will be missed even if the finding of any adenoma on sigmoidoscopy examination indicates a complete colonoscopy. Only 20% to 30% of colorectal cancers in the proximal region are associated with an adenoma in the distal region that might be detected at flexible sigmoidoscopy examination.⁵⁹ Furthermore, recent observational studies on colonoscopy screening suggest that one half of all advanced adenomas and cancers in the proximal region would be missed on sigmoidoscopy examination.^{56,60} However, sigmoidoscopy screening followed by com-

Table 2. Case-Control Studies of Mortality Reduction Associated With Sigmoidoscopy Screening

Study Characteristics	Selby et al ³⁸	Newcomb et al ³⁹	Muller and Sonnenberg ^{40,41}
No. of cases of colorectal cancer	261	66	4411
Type of sigmoidoscope	Rigid	Rigid and flexible	Rigid and flexible
Odds ratio (95% CI) for colorectal cancer death	0.41 (0.25-0.69)	0.21 (0.08-0.52)	0.41 (0.33-0.5)
Interval of apparent protective effect, y	9-10	Not specified	6

Abbreviation: CI, confidence interval.

Table 3. Rate of Advanced Proximal Neoplasm* According to Colorectal Findings in the Distal Colon

Source	Findings in Distal Colon, % (No./Total)				
	Normal	Hyperplastic Polyp	Tubular Adenoma <1 cm	Multiple Tubular Adenomas <1 cm†	Advanced Neoplasm
Lieberman et al ³¹	2.7 (48/1765)	2.8 (13/464)	6.4 (35/543)	9.1 (4/44)	11.7 (32/274)
Zarchy and Ershoff ⁵¹	Not reported	Not reported	0.8 (1/124)	Not reported	11.8 (12/102)
Read et al ⁵²	Not reported	Not reported	6.9 (13/189)‡	Not reported	28.6 (4/14)
Schoen et al ⁵³	Not reported	Not reported	2.9 (15/521)	2.4 (2/85)	5.9 (27/460)
Wallace et al ⁵⁴	Not reported	Not reported	1.6 (3/190)	10.4 (5/48)	7.4 (5/63)
Levin et al ⁵⁵	5.3 (29/544)	Not reported	5.0 (22/444)	6.3 (20/319)	8.8 (147/1665)
Imperiale et al ⁵⁶	1.5 (23/1564)	4.0 (8/201)	7.1 (12/168)	Not reported	11.5 (7/61)§

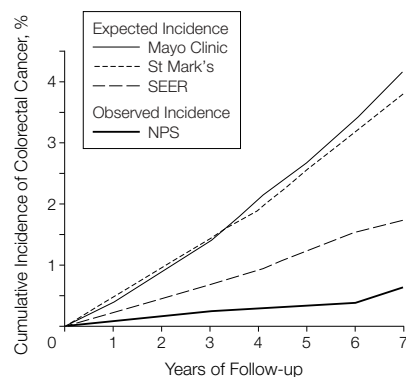
*Defined as invasive cancer or adenoma 1 cm or larger in diameter or with villous features or high-grade dysplasia.

†Defined as 3 or more adenomas.

‡Includes adenomas with villous features.

§Does not include adenomas 1 cm or larger.

Figure. Cumulative Incidence of Colorectal Cancer in the National Polyp Study Cohort (NPS)



The observed incidence is compared with the expected incidence based on data from 3 reference groups: the Mayo Clinic cohort, the St Mark's cohort, and the US Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute. Reprinted with permission from Winawer et al.⁶²

plete colonoscopy for the finding of any adenoma most likely will have detected 70% or 80%, respectively, of all the advanced neoplasms.⁶⁰

Colonoscopy Screening

Evidence of Clinical Efficacy. The efficacy of colonoscopy screening for the prevention of colorectal cancer and colorectal cancer death has not been studied to date in RCTs. The National Cancer Institute is now sponsoring a pilot/feasibility study of colonoscopy screening,⁶¹ but results from a large RCT, if undertaken, are not expected to be available for many years. However, indirect evidence suggests that colonoscopy is almost certainly a highly effective screening test.

First, the reduction in mortality demonstrated in the FOBT screening studies is attributable to the performance of follow-up colonoscopy.^{12,14,16} Second, a reduction in colorectal cancer incidence has been demonstrated in the US National Polyp Study and the Italian Multicenter Study,^{62,63} 2 large cohort studies of individuals who had adenomatous polyps removed at colonoscopy. These studies were not about colonoscopy screening, and they used historical controls, so the results must

be interpreted with some caution. In the US National Polyp Study,⁶² only 5 colorectal cancers were detected in the study population for an incidence of 0.6 cancers per 1000 years of subject follow-up, and all the patients were asymptomatic and the cancers were in early stages (4 in stage I and 1 in stage II). This low incidence of metachronous cancer represented a 76% to 90% reduction in cancer incidence compared with 3 reference populations, the Mayo Clinic cohort, the St Mark's cohort, and the US Surveillance, Epidemiology, and End Results Program cohort (FIGURE).⁶² Third, recent cross-sectional colonoscopy screening studies indicate that colonoscopy is more sensitive than flexible sigmoidoscopy or sigmoidoscopy plus FOBT for the detection of large adenomas and cancers.^{56,60} It has not been shown but it can be assumed that increased sensitivity would translate into increased effectiveness.

How the Test Is Performed. Colonoscopy generally is performed by a gastroenterologist or a surgeon using a 160-cm flexible endoscope. Extensive training is required to perform the procedure safely and effectively.⁶⁴ The day prior to the procedure the patient must only have consumed clear liquids and then consume some form of purgative (low-volume sodium phosphate purge or high-volume polyethylene glycol purge). Sedation is administered and patients cannot drive so they must be accompanied by another individual to escort them home. The patient should not experience pain during the examination and often the patient cannot recall the procedure. In a recent large study of colonoscopy screening, a complete examination was possible in 98% of patients, with a mean procedure time of 30 minutes.^{60,65} Recovery time for the patient is approximately 2 to 3 hours.

Flexible sigmoidoscopy has been shown to be a safer procedure than colonoscopy, but colonoscopy is considered safe.^{26,27} For instance, in a large study on colonoscopy screening, no deaths were directly attributable to colonoscopy and no colonic perforations occurred.^{60,65} Major morbidity did occur in

0.3% of subjects, including gastrointestinal tract bleeding, myocardial infarction, and stroke, and 3 subjects died within 1 month of the screening examination.^{60,65}

How to Interpret the Test Results. Colonoscopy is considered the criterion standard for detecting colorectal cancers and adenomas. If an adenoma is detected, a repeat surveillance examination is generally recommended in 3 or 5 years, depending on the number, size, and histologic findings of the adenomas removed.⁹ The recommendations for the appropriate surveillance interval after a positive finding at colonoscopy examination are based on data from the US National Polyp Study.^{66,67} If no adenomas are detected, the test result is negative. The recommendation for the 10-year repeat screening interval is based on indirect evidence. Case-control studies of sigmoidoscopy screening suggest that the protective effect of endoscopy screening lasts about 10 years.³⁸ In addition, in the US National Polyp Study, low rates of metachronous adenomas or cancer were seen after colonoscopic polypectomy during extended follow-up.^{62,67} Finally, 2 small prospective studies have found that the incidence of cancer is less than 1% within 5 years after a negative colonoscopy screening result.^{68,69}

Performance Characteristics. Colonoscopy screening can detect advanced polyps and cancers that would otherwise be missed by sigmoidoscopy and/or FOBT.^{31,56,60} Although considered highly sensitive and specific for the detection of colonic neoplasia, colonoscopy is not a perfect test, and lesions can be missed.⁷⁰⁻⁷² In one study in which tandem colonoscopies were performed by 2 expert examiners, the miss rates were 6% for adenomas 1 cm and larger in diameter, 13% for adenomas 6 to 9 mm in diameter, and 27% for adenomas 5 mm and smaller in diameter.⁷¹

Combined FOBT and Sigmoidoscopy Screening

Evidence of Clinical Effectiveness. The limitations of using FOBT and sigmoidoscopy separately may be overcome

by performing the 2 tests in concert. These are widely practiced procedures and little evidence in the published literature supports combination testing. In the study most commonly cited to support combination testing, the investigators nonrandomly allocated 12 479 individuals either to annual screening with FOBT combined with rigid sigmoidoscopy or to rigid sigmoidoscopy alone.⁷³ Patient adherence to the protocol in both groups was poor. Colorectal cancer mortality was lower in the combined testing group after 5 to 11 years of follow-up (0.36 deaths per 1000 per year vs 0.63 deaths per 1000 per year), showing only a borderline statistical significance ($P=.053$).⁷³ Given that the results are marginal, the use of yearly rigid sigmoidoscopy in the protocol and the poor compliance rates, generalizability of this study is tenuous.

How the Test Is Performed. The standard recommendation for patients who are undergoing colorectal cancer screening is to have an FOBT performed every year and to have sigmoidoscopy performed every 5 years. In a year in which both tests are to be performed, the FOBT should be completed first because a positive FOBT result would then require a complete colonoscopy to be performed and therefore eliminate the need for sigmoidoscopy.

How to Interpret the Test Results. If either the FOBT or the sigmoidoscopy procedure has an abnormal result, then complete colonoscopy is indicated.

Performance Characteristics. Two large RCTs have demonstrated that combination testing will detect 4 to 5 times more large polyps and cancers than FOBT alone.^{74,75} However, in another large randomized study, more polyps and cancers were not detected among patients undergoing FOBT and sigmoidoscopy compared with patients who underwent sigmoidoscopy alone.⁷⁶ These studies involved a single application of FOBT and not serial testing, so the applicability of these findings to clinical practice is unclear. In a study recently completed in a large

population from a health maintenance organization, the addition of an immunochemical FOBT did detect advanced adenomas and cancers in the proximal region of the colon that otherwise would have been missed by screening with flexible sigmoidoscopy alone. However, more than 600 individuals would need to be screened by the immunochemical FOBT to detect 1 additional advanced adenoma or cancer that otherwise would have been missed.⁷⁷ Finally, in the Veterans Affairs Cooperative Study of colonoscopy screening, the addition of FOBT to sigmoidoscopy would have increased the percentage of patients identified with advanced neoplasia from 70.3% to 75.8%.³¹

Double-Contrast Barium Enema

Evidence of Effectiveness. Double-contrast (air-contrast) barium enema has been advocated as a screening method for colorectal cancer, but to date no published evidence from controlled studies is available examining the effectiveness of this method.

How the Test Is Performed. Patient preparation for double-contrast barium enema is similar to that for colonoscopy. Sedation is not required, although patients often complain of pain and embarrassment.⁷⁸ A trained radiologist must be present to perform the procedure. Barium, followed by air, is instilled into the colon under gentle pressure. The patient is then moved to different positions on an examination table while radiographs are obtained. The procedure takes 30 to 60 minutes to complete. This procedure has been shown to be safe; perforation of the colon is extremely rare, and serious complications of any type occurring have been reported in approximately 1 in 10 000 examinations.^{79,80}

How to Interpret the Test Results. Polypoid lesions and masses detected at double-contrast barium enema examination would indicate follow-up complete colonoscopy to verify the presence of the lesions, to obtain a biopsy sample, and to remove the lesions if possible. The standard recom-

mendation is to perform screening by double-contrast barium enema every 5 to 10 years.

Performance Characteristics. The double-contrast barium enema examination is not as sensitive as the endoscopy examination in the detection of polyps. It does appear that double-contrast barium enema will detect a majority of advanced adenomas and cancers.⁸¹⁻⁸⁴ In the US National Polyp Study, 862 paired double-contrast barium enema and colonoscopy examinations were compared in a surveillance population.⁸⁵ In a large percentage of cases, the results of the double-contrast barium enema examination were false negatives, especially when the largest polyp found at colonoscopy was small. Even for polyps larger than 1 cm in diameter, the sensitivity of double-contrast barium enema was approximately 50%.⁸⁵ However, many of the small polyps missed by double-contrast barium enema examination may be not be clinically important, and therefore, a decreased sensitivity for detecting adenomas, especially those of small or medium size, does not necessarily mean that double-contrast barium enema is not an effective screening test.

FUTURE DIRECTIONS OF COLORECTAL CANCER SCREENING

Two new promising screening technologies are CT-assisted colonography, also termed *virtual colonoscopy*, and stool-based molecular testing. Before any new screening methods are routinely adopted, they should be assessed in clinical studies among average-risk patients that compare sensitivity and specificity for the detection of advanced polyps and cancers, cost, safety, and acceptability to patients with currently recommended screening tests. Ideally, clinical trials that assess the impact of these new screening tests on colorectal cancer incidence and mortality should be undertaken, but this may be impractical.

Computed Tomography Colonography Screening

Virtual colonoscopy is a technique that uses data generated from CT or mag-

netic resonance imaging to generate 2-dimensional and 3-dimensional images of the colon.⁸⁶⁻⁹⁵ Usually, the colon is scanned while the patient is in the prone and supine position, and the time it takes to acquire the images is less than 5 minutes. Patients must undergo a colonic preparation, as with double-contrast barium enema or colonoscopy. Research is ongoing that may eventually eliminate the need for colonic preparation.⁹⁶ Following colonic preparation, air or another gas, such as carbon dioxide, must be insufflated through a rectal tube to distend the colon to enhance imaging. The patient may experience some slight discomfort from the air insufflation, and no sedation is required. After the images are reformatted, they are reviewed by a radiologist, a process that takes 20 to 40 minutes. Patients who have a suspected polyp or mass lesion are referred for follow-up colonoscopy.

In the largest study published to date comparing virtual colonoscopy to conventional colonoscopy, polyp detection using virtual colonoscopy was positive in 90% of cases in which conventional colonoscopy found 1 polyp and was negative in 72% of cases in which conventional colonoscopy found no polyp.⁹¹ Good sensitivity for the detection of large polyps and cancers using virtual colonoscopy has been reported by several other investigators,⁸⁸⁻⁹⁰ but not by all investigators.⁹²⁻⁹⁵

Virtual colonoscopy is a promising technology for colorectal cancer screening, but practical barriers and additional clinical studies are required before it can be embraced as a screening option.⁹⁷ The cost of virtual colonoscopy is high, and radiologists will need to undergo extensive training to interpret the test results. Furthermore, it is not clear whether virtual colonoscopy will be better tolerated and more acceptable to the general population than conventional colonoscopy.⁹⁸ A recent cost-effectiveness analysis found that virtual colonoscopy, even if 100% sensitive and specific for colorectal neoplasia, would only be as cost-effective as conventional colonoscopy for colo-

rectal cancer screening if it costs approximately 50% less than conventional colonoscopy, or was associated with an initial compliance rate 15% to 20% better than colonoscopy.⁹⁹

Stool-Based Molecular Screening

Genomic alterations drive the adenoma to carcinoma DNA sequence, and alterations in the neoplasm-specific DNA in colorectal adenomas and carcinomas have been well-characterized.¹⁰⁰ Colorectal epithelial DNA can be extracted from stool samples and amplified, allowing for the detection of mutations indicative of colorectal neoplasia.¹⁰¹ Such stool-based testing is appealing because it is non-invasive, requires no special colonic preparation, and has the capability of detecting neoplasia throughout the entire length of the colon. A recent study reported that mutations in the adenomatous polyposis coli (*APC*) gene could be detected in fecal DNA using a novel method, digital protein truncation, among 26 (57%) of 46 patients with known colonic cancers or large polyps (95% CI, 41%-71%), but in none of 28 control patients without colonic neoplasms (95% CI, 0%-12%).¹⁰² However, because the DNA alterations in colorectal cancer are heterogeneous, future assays will need to detect mutations in a number of genes typically mutated in colorectal cancer in addition to *APC*, such as Kirsten-ras (*K-ras*) and *p53*.¹⁰³⁻¹⁰⁵ A small pilot study of a proprietary assay that looks for mutations in a number of genes was more than 80% sensitive for the detection of large adenomas or cancer and was 93% specific.¹⁰³ Large-scale prospective studies comparing the sensitivity and specificity of this assay with FOBT and colonoscopy in a colorectal cancer screening population are under way (David Ahlquist, MD, and Michael Ross, MD, oral communication, September 2002).

COMMENT

Colorectal cancer mortality can be reduced by screening all men and women aged 50 years or older for colorectal

cancer. Several tests are available for colon cancer screening, including FOBT, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy. Direct and indirect evidence indicates that all the tests are effective, but they differ in their sensitivity, specificity, cost, and safety. The available evidence does not currently support choosing one test over another. In addition, other colorectal cancer tests, such as virtual colonoscopy or stool-based molecular testing, have the potential to become important screening tests in the future.

Funding/Support: Dr Walsh was supported by an American Cancer Society Cancer Control Career Development Award for Primary Care Physicians.

Acknowledgment: We would like to thank Hai Emily Huang for her assistance with manuscript preparation.

REFERENCES

- Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin*. 2001;51:15-36.
- Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology*. 1997;112:594-642.
- United States Preventive Services Task Force. Clinical guidelines: screening for colorectal cancer: recommendation and rationale. *Ann Intern Med*. 2002;137:129-131.
- Rex DK, Johnson DA, Lieberman DA, Burt DW, Sonnenberg A. Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. *Am J Gastroenterol*. 2000;95:868-877.
- Smith RA, von Eschernbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers; also update 2000—testing for early lung cancer detection. *CA Cancer J Clin*. 2001;51:38-75, quiz, 77-80.
- Morson B. President's address: the polyp-cancer sequence in the large bowel. *Proc R Soc Med*. 1974;67:451-457.
- Morson BC. The evolution of colorectal carcinoma. *Clin Radiol*. 1984;35:425-431.
- Bond JH. Clinical evidence for the adenoma-carcinoma sequence, and the management of patients with colorectal adenomas. *Semin Gastrointest Dis*. 2000;11:176-184.
- Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps: Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol*. 2000;95:3053-3063.
- Rembacken BJ, Fujii T, Cairns A, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet*. 2000;355:1211-1214.
- Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology*. 2001;120:1657-1665.
- Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood: Minnesota Colon Cancer Control Study. *N Engl J Med*. 1993;328:1365-1371.

13. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst.* 1999; 91:434-437.
14. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet.* 1996; 348:1472-1477.
15. Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut.* 2002;50:840-844.
16. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet.* 1996;348:1467-1471.
17. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut.* 2002;50: 29-32.
18. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med.* 2000;343:1603-1607.
19. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med.* 1996;334:155-159.
20. Young GP, St John DJ, Winawer SJ, Rozen P. Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. *Am J Gastroenterol.* 2002;97:2499-2507.
21. Pignone M, Campbell MK, Carr C, Phillips C. Meta-analysis of dietary restriction during fecal occult blood testing. *Eff Clin Pract.* 2001;4:150-156.
22. Lang CA, Ransohoff DF. Fecal occult blood screening for colorectal cancer: is mortality reduced by chance selection for screening colonoscopy? *JAMA.* 1994; 271:1011-1013.
23. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. *J Natl Cancer Inst.* 1997;89:1440-1448.
24. Ransohoff DF, Lang CA. Screening for colorectal cancer with the fecal occult blood test: a background paper: American College of Physicians. *Ann Intern Med.* 1997;126:811-822.
25. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology.* 1997;112:594-642.
26. Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: lessons for a 10-year study. *Am J Gastroenterol.* 2000;95:3418-3422.
27. Zubarik R, Fleischer DE, Mastropietro C, et al. Prospective analysis of complications 30 days after outpatient colonoscopy. *Gastrointest Endosc.* 1999;50: 322-328.
28. American College of Physicians. Suggested technique for fecal occult blood testing and interpretation in colorectal cancer screening. *Ann Intern Med.* 1997;126:808-810.
29. Allison JE, Feldman R, Tekawa IS. Hemoccult screening in detecting colorectal neoplasm: sensitivity, specificity, and predictive value: long-term follow-up in a large group practice setting. *Ann Intern Med.* 1990;112:328-333.
30. Ahlquist DA, Wieand HS, Moertel CG, et al. Accuracy of fecal occult blood screening for colorectal neoplasia: a prospective study using Hemoccult and HemoQuant tests. *JAMA.* 1993;269:1262-1267.
31. Lieberman DA, Weiss DG. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med.* 2001;345:555-560.
32. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. *Control Clin Trials.* 2000; 21(6 suppl):2735-3095.
33. Atkin WS, Cuzick J, Northover JM, Whynes DK. Prevention of colorectal cancer by once-only sigmoidoscopy. *Lancet.* 1993;341:736-740.
34. Atkin WS, Hart A, Edwards R, et al. Uptake, yield of neoplasia, and adverse effects of flexible sigmoidoscopy screening. *Gut.* 1998;42:560-565.
35. UK Flexible Sigmoidoscopy Screening Trials Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet.* 2002;359:1291-1300.
36. Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer: Telemark Polyp Study I. *Scand J Gastroenterol.* 1999;34:414-420.
37. Hoff G, Thiis-Evensen E, Grotmol T, Sauar J, Vatn MH, Moen IE. Do undesirable effects of screening affect all-cause mortality in flexible sigmoidoscopy programmes? experience from the Telemark Polyp Study 1983-1996. *Eur J Cancer Prev.* 2001;10:131-137.
38. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med.* 1992;326:653-657.
39. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst.* 1992;84: 1572-1575.
40. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy: a case-control study of 32,702 veterans. *Ann Intern Med.* 1995;123:904-910.
41. Muller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer: a case-control study among veterans. *Arch Intern Med.* 1995; 155:1741-1748.
42. Kavanagh AM, Giovannucci EL, Fuchs CS, Colditz GA. Screening endoscopy and risk of colorectal cancer in United States men. *Cancer Causes Control.* 1998; 9:455-462.
43. Rex DK, Lehman GA, Hawes RH, O'Connor KW, Smith JJ. Performing screening flexible sigmoidoscopy using colonoscopes: experience in 500 subjects. *Gastrointest Endosc.* 1990;36:486-488.
44. Schertz RD, Baskin WN, Frakes JT. Flexible fiberoptic sigmoidoscopy training for primary care physicians: results of a 5-year experience. *Gastrointest Endosc.* 1989;35:316-320.
45. Cash BD, Schoenfeld PS, Ransohoff DF. Licensure, use, and training of paramedical personnel to perform screening flexible sigmoidoscopy. *Gastrointest Endosc.* 1999;49:163-169.
46. American Society for Gastrointestinal Endoscopy. Guidelines for training non-specialists in screening flexible sigmoidoscopy. *Gastrointest Endosc.* 2000; 51:783-785.
47. Wallace MB, Kemp JA, Meyer F, et al. Screening for colorectal cancer with flexible sigmoidoscopy by non-physician endoscopists. *Am J Med.* 1999;107:214-218.
48. Schoenfeld P, Lipscomb S, Crook J, et al. Accuracy of polyp detection by gastroenterologists and nurse endoscopists during flexible sigmoidoscopy: a randomized trial. *Gastroenterology.* 1999;117:312-318.
49. Levin TR, Conell C, Shapiro JA, Chazan SG, Nadel M, Selby JV. Complications of screening sigmoidoscopy. *Gastroenterology.* 2002;123:1786-1792.
50. Atkin WS, Edwards R, Wardle J, Northover JM, Cuzick J. UK flexible sigmoidoscopy screening trial: compliance, yield and adverse events [abstract]. *Gastroenterology.* 2000;118:A187.
51. Zarchy TM, Ershoff D. Do characteristics of adenomas on flexible sigmoidoscopy predict advanced lesions on baseline colonoscopy? *Gastroenterology.* 1994;106:1501-1504.
52. Read TE, Read JD, Butterly LF. Importance of adenomas 5 mm or less in diameter that are detected by sigmoidoscopy. *N Engl J Med.* 1997;336:8-12.
53. Schoen RE, Corle D, Cranston L, et al. Is colonoscopy needed for the nonadvanced adenoma found on sigmoidoscopy? the Polyp Prevention Trial. *Gastroenterology.* 1998;115:533-541.
54. Wallace MB, Kemp JA, Trnka YM, Donovan JM, Farraye FA. Is colonoscopy indicated for small adenomas found by screening flexible sigmoidoscopy? *Ann Intern Med.* 1998;129:273-278.
55. Levin TR, Palitz A, Grossman S, et al. Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy. *JAMA.* 1999;281:1611-1617.
56. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med.* 2000;343:169-174.
57. Rex DK, Lehman GA, Ulbright TM, Smith JJ, Hawes RH. The yield of a second screening flexible sigmoidoscopy in average-risk persons after one negative examination. *Gastroenterology.* 1994;106:593-595.
58. Schoen RE, Wissfeld J, Bresalier R, et al. The yield of repeat flexible sigmoidoscopy three years after a negative exam: results from the PLCO cancer screening trial [abstract]. *Gastroenterology.* 2002;122:A355.
59. Lemmel GT, Haseman JH, Rex DK, Rahmani E. Neoplasia distal to the splenic flexure in patients with proximal colon cancer. *Gastrointest Endosc.* 1996;44: 109-111.
60. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer: Veterans Affairs Cooperative Study 380. *N Engl J Med.* 2000; 343:162-168.
61. Winawer SJ, Zauber AG, Church T, et al. National colonoscopy study preliminary results: a controlled trial of general population screening colonoscopy. *Gastroenterology.* 2002;122:T1560.
62. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy: the National Polyp Study Workgroup. *N Engl J Med.* 1993;329:1977-1981.
63. Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. *Gut.* 2001;48:812-815.
64. Marshall JB. Technical proficiency of trainees performing colonoscopy: a learning curve. *Gastrointest Endosc.* 1995;42:287-291.
65. Nelson DB, McQuaid KR, Bond JH, Lieberman DA, Weiss DG, Johnston TK. Procedural success and complications of large-scale screening colonoscopy. *Gastrointest Endosc.* 2002;55:307-314.
66. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps: the National Polyp Study Workgroup. *N Engl J Med.* 1993;328:901-906.
67. Zauber AG, Winawer SJ, Bond JH, et al. Can surveillance intervals be lengthened following colonoscopic polypectomy [abstract]. *Gastroenterology.* 1997;112:A50.
68. Rex DK, Cummings OW, Helper DJ, et al. 5-year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons [see comment]. *Gastroenterology.* 1996;111:1178-1181.
69. Avidan B, Sonnenberg A, Schnell TG, Leya J, Metz A, Sontag SJ. New occurrence and recurrence of neoplasms within 5 years of a screening colonoscopy. *Am J Gastroenterol.* 2002;97:1524-1529.
70. Hixson LJ, Fennerty MB, Sampliner RE, Garewal HS. Prospective blinded trial of the colonoscopic miss-rate of large colorectal polyps. *Gastrointest Endosc.* 1991;37:125-127.
71. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology.* 1997;112: 24-28.

72. Bensen S, Mott LA, Dain B, Rothstein R, Baron J. The colonoscopic miss rate and true one-year recurrence of colorectal neoplastic polyps: Polyp Prevention Study Group. *Am J Gastroenterol*. 1999;94:194-199.
73. Winawer SJ, Flehinger BJ, Schottenfeld D, Miller DG. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. *J Natl Cancer Inst*. 1993;85:1311-1318.
74. Berry DP, Clarke P, Hardcastle JD, Vellacott KD. Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening. *Br J Surg*. 1997;84:1274-1276.
75. Rasmussen M, Kronborg O, Fenger C, Jorgensen OD. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer: a randomized study. *Scand J Gastroenterol*. 1999;34:73-78.
76. Verne JE, Aubrey R, Love SB, Talbot IC, Northover JM. Population based randomized study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing. *BMJ*. 1998;317:182-185.
77. Levin TR, Allison JE, Sakoda L, et al. Adding new fecal occult blood tests to sigmoidoscopy: what is the added yield [abstract]. *Gastroenterology*. 2000;118:A441.
78. Kim LS, Koch J, Yee J, Halvorsen R, Cello JP, Rockey DC. Comparison of patients' experience during imaging tests of the colon. *Gastrointest Endosc*. 2001;54:67-74.
79. Kewenter J, Brevinge H. Endoscopic and surgical complications of work-up in screening for colorectal cancer. *Dis Colon Rectum*. 1996;39:676-680.
80. Blakeborough A, Sheridan MB, Chapman AH. Complications of barium enema examinations: a survey of UK Consultant Radiologists 1992 to 1994. *Clin Radiol*. 1997;52:142-148.
81. Johnson CD, Ilstrup DM, Fish NM, et al. Barium enema: detection of colonic lesions in a community population. *AJR Am J Roentgenol*. 1996;167:39-43.
82. Rex DK, Rahmani EY, Haseman JH, Lemmel GT, Kaster S, Buckley JS. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. *Gastroenterology*. 1997;112:17-23.
83. Law RL, Longstaff AJ, Slack N. A retrospective 5-year study on the accuracy of the barium enema examination performed by radiographers. *Clin Radiol*. 1999;54:80-83; discussion 83-84.
84. Strom E, Larsen JL. Colon cancer at barium enema examination and colonoscopy: a study from the county of Hordaland, Norway. *Radiology*. 1999;211:211-214.
85. Winawer SJ, Stewart ET, Zauber AG, et al. A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy: National Polyp Study Work Group. *N Engl J Med*. 2000;342:1766-1772.
86. Hara AK, Johnson CD, Reed JE, et al. Detection of colorectal polyps with CT colonography: initial assessment of sensitivity and specificity. *Radiology*. 1997;205:59-65.
87. Rex DK, Vining D, Kopecky KK. An initial experience with screening for colon polyps using spiral CT with and without CT colonography (virtual colonoscopy). *Gastrointest Endosc*. 1999;50:309-313.
88. Fenlon HM, Nunes DP, Schroy PC 3rd, Barish MA, Clarke PD, Ferrucci JT. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N Engl J Med*. 1999;341:1496-1503.
89. Fletcher JG, Johnson CD, Welch TJ, et al. Optimization of CT colonography technique: prospective trial in 180 patients. *Radiology*. 2000;216:704-711.
90. Hara AK, Johnson CD, Welch TJ, McCollough CH, Harmsen WS. CT colonography: single- versus multi-detector row imaging. *Radiology*. 2001;219:461-465.
91. Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology*. 2001;219:685-692.
92. Cotton PB, Durkalski VL, Palesch YY, et al. Comparison of virtual colonoscopy and colonoscopy in the detection of polyps/masses [abstract]. *Gastrointest Endosc*. 2002;55:A594.
93. Pescatore P, Glucker T, Delarive J, et al. Diagnostic accuracy and interobserver agreement of CT colonography (virtual colonoscopy). *Gut*. 2000;47:126-130.
94. Miao YM, Amin Z, Healy J, et al. A prospective single centre study comparing computed tomography pneumocolon against colonoscopy in the detection of colorectal neoplasms. *Gut*. 2000;47:832-837.
95. Spinzi G, Belloni G, Martegani A, Sangiovanni A, Del Favero C, Minoli G. Computed tomographic colonography and conventional colonoscopy for colon diseases: a prospective, blinded study. *Am J Gastroenterol*. 2001;96:394-400.
96. Zalis ME, Hahn PF. Digital subtraction bowel cleansing in CT colonography. *AJR Am J Roentgenol*. 2001;176:646-648.
97. Bond JH. Virtual colonoscopy—promising, but not ready for widespread use. *N Engl J Med*. 1999;341:1540-1542.
98. Akerkar GA, Yee J, Hung R, McQuaid K. Patient experience and preferences toward colon cancer screening: a comparison of virtual colonoscopy and conventional colonoscopy. *Gastrointest Endosc*. 2001;54:310-315.
99. Sonnenberg A, Delco F, Bauerfiend P. Is virtual colonoscopy a cost-effective option to screen for colorectal cancer? *Am J Gastroenterol*. 1999;94:2268-2274.
100. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759-767.
101. Sidransky D, Tokino T, Hamilton SR, et al. Identification of *ras* oncogene mutations in the stool of patients with curable colorectal tumors. *Science*. 1992;256:102-105.
102. Traverso G, Shuber A, Levin B, et al. Detection of APC mutations in fecal DNA from patients with colorectal tumors. *N Engl J Med*. 2002;346:311-320.
103. Ahlquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology*. 2000;119:1219-1227.
104. Dong SM, Traverso G, Johnson C, et al. Detecting colorectal cancer in stool with the use of multiple genetic targets. *J Natl Cancer Inst*. 2001;93:858-865.
105. Traverso G, Shuber A, Olsson L, et al. Detection of proximal colorectal cancers through analysis of faecal DNA. *Lancet*. 2002;359:403-404.

A teacher affects eternity; he can never tell where his influence stops.
—Henry Adams (1838-1918)