RELATIVE FREQUENCY OF UPPER GASTROINTESTINAL AND COLONIC LESIONS IN PATIENTS WITH POSITIVE FECAL OCCULT-BLOOD TESTS

DON C. ROCKEY, M.D., JOHANNES KOCH, M.D., JOHN P. CELLO, M.D., LINDA L. SANDERS, M.P.H., AND KENNETH MCQUAID, M.D.

ABSTRACT

Background Although bleeding lesions anywhere in the gastrointestinal tract can cause a positive reaction on guaiac-based fecal occult-blood tests, the relative frequency of upper gastrointestinal and colonic lesions is unknown.

Methods During a period of 30 months, we prospectively studied all patients with at least one stool specimen containing fecal occult blood who were referred for further evaluation. Fecal occult blood was detected by standard guaiac-based tests of stool specimens obtained as part of routine screening or of stool obtained by digital rectal examination. Patients with documented iron-deficiency anemia or active gastrointestinal bleeding were excluded from the study. All participants had a detailed history taken and underwent colonoscopy, followed by esophagogastroduodenoscopy.

Results Of the 409 patients with fecal occult blood who were referred, 310 were potentially eligible to participate, and 248 (mean age, 61 years; range, 40 to 89) were studied; 40 percent were women. We identified lesions consistent with occult bleeding in 119 patients (48 percent); in 71 bleeding lesions were found in the upper gastrointestinal tract, and in 54 they were identified in the colon. Six patients had abnormalities in both areas. The most common upper gastrointestinal lesions were esophagitis (23 patients), gastric ulcer (14), gastritis (12), and duodenal ulcer (10). Thirty patients with lesions in the upper gastrointestinal tract were long-term users of aspirin, ethanol, nonsteroidal antiinflammatory drugs, or a combination of these substances. The most common colonic lesions were adenomas more than 1.0 cm in diameter (29 patients), carcinoma (13), colitis (5), and vascular ectasia (5). Although the overall sensitivity of symptoms for the detection of gastrointestinal lesions was low, logistic-regression analysis demonstrated that the presence of symptoms in the upper gastrointestinal tract was associated with the detection of lesions in the upper gastrointestinal tract (odds ratio, 2.6; 95 percent confidence interval, 1.4 to 4.7). In both patients with symptoms and those without symptoms, the prevalence of lesions in the upper gastrointestinal tract was greater than or equal to that of colonic lesions.

Conclusions In a group of patients with positive fecal occult-blood tests who were referred for further evaluation, from which those with iron-deficiency anemia and active bleeding had been excluded, upper gastrointestinal lesions were identified more frequently than colonic lesions. (N Engl J Med 1998; 339:153-9.)

WHEN used to screen large populations, guaiac-based fecal occult-blood tests have been shown to prevent death from colorectal cancer.[1-3] Nonetheless, drawbacks associated with their use remain, including a high rate of false positive tests (i.e., a lack of specificity),[4-6] which can lead to further testing and expense.[5,7,8]

Bleeding lesions anywhere in the gastrointestinal tract may produce positive results on guaiac-based fecal occult-blood tests. Guaiac-based tests are thought to be unreliable for the detection of occult bleeding from the upper gastrointestinal tract because hemoglobin (or heme), which is the component in blood that causes a positive reaction, may undergo degradation. Although very small quantities of blood from the upper gastrointestinal tract (1 to 2 ml per day) do not cause tests to be positive,[9] slightly greater blood loss (5 to 10 ml per day), such as that associated with bleeding from many common gastrointestinal lesions, may yield positive results.[10-15] Therefore, we hypothesized that some proportion of positive guaiac-based fecal occult-blood tests could be the result of abnormalities in the upper gastrointestinal tract. We investigated the prevalence of lesions in the upper gastrointestinal tract among patients with positive guaiac-based fecal occult-blood tests and determined the correlates of positive endoscopic findings.

METHODS

We prospectively screened all patients who had at least one stool sample in which fecal occult blood was detected by a standard guaiac-based test (Hemoccult II or an equivalent test with non-rehydrated slides) from July 1, 1994, through December 31, 1996, and who were referred to the Gastroenterology Service at the San Francisco General Hospital or the San Francisco Veterans Affairs Medical Center. Fecal occult blood was detected in stool by one of two methods: by screening methods recommended by the manufacturer (with the customary restrictions on diet and medication) in three separate stool samples or by testing of a single stool sample obtained by a digital rectal examination as part of the physical examination or for screening purposes. Patients who had fecal occult blood detected by both methods were considered to have been identified by screening, which occurred first in all cases. Patients were excluded for the following reasons: active gastrointestinal hemorrhage, defined as hematemesis, melena, or two or more episodes

From the Division of Gastroenterology and the Department of Medicine, Duke University Medical Center, Durham, N.C. (D.C.R., L.L.S.); and the Division of Gastroenterology and the Department of Medicine, University of California, San Francisco (J.K., J.P.C., K.M.). Address reprint requests to Dr. Rockey at the Liver Research Laboratory, Duke University Medical Center, Sands Bldg., Rm. 334, Research Dr., Box 3083, Durham, NC 27710.

of hematochezia; iron-deficiency anemia documented by reduced hemoglobin and ferritin concentrations or by the absence of iron stores on examination of bone marrow; severe cardiopulmonary disease; or a decision by the patient not to participate in the study. This study was approved by the Committee on Human Research of the University of California, San Francisco, and met all guidelines for the ethical conduct of studies as delineated in the Declaration of Helsinki.[16] All subjects gave written informed consent.

A detailed history was obtained by interview and by means of a brief questionnaire focusing on gastrointestinal symptoms. Symptoms considered to be consistent with upper gastrointestinal disease included heartburn (more than one episode weekly); dysphagia; odynophagia; recurrent nausea, vomiting, or both; anorexia lasting more than one week; and dyspepsia (defined as upper abdominal pain or discomfort occurring more than once weekly). Symptoms considered to be consistent with lower gastrointestinal disease included hematochezia or blood coating the stool (no more than once within the previous month), a change in the caliber of the stool, diarrhea (more than three loose stools per day), constipation (beginning within the previous two months), and lower abdominal pain that was colicky or changed with the passage of stool. Weight loss and the use of aspirin, nonsteroidal antiinflammatory drugs, and ethanol were also quantified.

Colonoscopy was followed immediately by esophagogastroduodenoscopy. Before the study began, certain lesions were identified as consistent with a finding of occult blood in the stool.[10-15,17,18] In the colon, they were carcinoma, adenoma ≥1.0 cm in diameter (measured after removal and fixation), vascular ectasias ≥8 mm in diameter and five or more in number, active colitis, and one or more ulcers ≥1 cm in diameter. Diverticula and hemorrhoids were not considered to cause fecal occult blood; hemorrhoids were graded from 1+ (small) to 4+ (large and irreducible). In the upper gastrointestinal tract, the lesions selected were carcinoma, esophagitis with erosions or ulceration involving ≥10 percent of the distal 5 cm of the esophageal mucosal surface (grade 3 or 4 esophagitis),[19] erosive gastritis or duodenitis (defined as at least 50 erosions ≥1 mm in diameter with white bases encircled by erythema); a single duodenal or gastric ulcer ≥1 cm in diameter or two ulcers ≥0.5 cm in diameter (measured with expanded biopsy forceps), adenomas, and vascular ectasias (the last two as described above).

For patients in whom more than one lesion was identified, the most conspicuous lesion was classified as the lesion consistent with bleeding. Hiatal hernia and esophageal varices were not considered to be sources of blood loss. The following lesions were determined a priori to be inconsistent with bleeding and were labeled "minor" or "trivial": in the colon — adenomas less than 1.0 cm in diameter, vascular ectasias less than 8 mm in diameter and fewer than five in number, ulcers less than 1 cm in diameter (or multiple ulcers less than 0.5 cm in diameter); and in the upper gastrointestinal tract — grade 1 or 2 esophagitis,[19] mild or moderate gastritis or duodenitis (fewer than 50 erosions less than 1 mm in diameter), duodenal or gastric ulcers less than 1 cm in diameter (or multiple ulcers less than 0.5 cm in diameter), and adenoma or vascular ectasias (as described above).

Changes in management were considered to have occurred when, after esophagogastroduodenoscopy, a new medication was added, medications were discontinued, or a follow-up procedure that otherwise would not have been recommended was used.

Logistic regression was used to evaluate the effects of symptoms and selected covariates on the prevalence of lesions in the gastrointestinal tract.[20,21] It was also used in the assessment of interactions between symptoms and the method of detecting fecal occult blood.[20,21] Fisher's exact test was used to compare binomial proportions; all statistical calculations were two-tailed.

RESULTS

During the study period, 409 patients were referred for evaluation after fecal occult blood was detected. Ninety-nine were immediately excluded for the following reasons: documented iron-deficiency anemia, 76 patients; active bleeding, 14; severe cardiopulmonary disease, 8; and lack of documentation of fecal occult blood, 1. Of the 310 patients deemed eligible, 62 were excluded. Fifteen declined to participate, 3 had evidence of overt bleeding between enrollment and endoscopy, 8 had subsequent documentation of iron-deficiency anemia, 19 were lost to follow-up, and 14 did not undergo both colonoscopy and esophagogastroduodenoscopy. Two additional patients were excluded because the cecum was not visualized, and one because esophagogastroduodenoscopy could not be performed.

Seven of the 248 study patients (Table 1) were hospitalized during evaluation; the remainder were evaluated as outpatients. Fecal occult blood was detected by standard screening methods in 154 patients (14 of whom subsequently had occult blood detected by digital rectal examination). In the 94 patients in whom fecal occult blood was detected by digital rectal examination, 44 had blood detected as part of a physical examination, and in 50, digital rec-

TABLE 1. CHARACTERISTICS OF 248 PATIENTS WITH POSITIVE FECAL OCCULT-BLOOD TESTS.*

CHARACTERISTIC†	VALUE
Age — yr‡	61±10
Female sex — no. (%)	99 (39.9)
Underlying medical disease — no. (%)	92 (37.1)
Tobacco use — no. (%)	24 (9.7)
Use of nonsteroidal antiinflammatory drugs — no. (%)	34 (13.7)
Use of ethanol — no. (%)	26 (10.5)
Use of aspirin — no. (%)	56 (22.6)
Helicobacter pylori — no. (%)§	30 (12.1)
Hemoglobin — g/dl¶	14.6±2.3
Hematocrit — %	42.3±5.1
Mean corpuscular volume — fl	90±6.8
Platelets — $\times 10^{-3}$/mm^3	238±68

*Plus–minus values are means ±SD.

†Underlying medical diseases were atherosclerotic cardiovascular disease, excluding isolated hypertension (41 patients), carcinoma at a site other than the gastrointestinal tract, excluding basal-cell carcinoma (17), diabetes mellitus (12), hepatitis B, hepatitis C, or alcoholic liver disease, all without cirrhosis (11), history of peptic ulcer disease (9), chronic renal failure (5), cirrhosis (2), and miscellaneous medical problems (6). Eleven patients had more than one medical problem. Tobacco use was defined as smoking more than 10 cigarettes per day or more than 1 cigar per day, use of nonsteroidal antiinflammatory drugs as daily use, use of ethanol as consumption of more than 90 ml (3 oz) per day, and use of aspirin as use of 81 to 325 mg per day.

‡The age range was 40 to 89 years; eight patients were less than 45 years old.

§*H. pylori* was detected by histologic inspection of biopsy material or by serologic testing.

¶To convert the value for hemoglobin to millimoles per liter, multiply by 0.6206.

TABLE 2. ENDOSCOPIC LESIONS CONSISTENT WITH OCCULT BLOOD LOSS IN 248 PATIENTS.

TYPE OF LESION	PATIENTS WITH OCCULT BLOOD (N=248)	OCCULT BLOOD DETECTED BY SCREENING			OCCULT BLOOD DETECTED BY DIGITAL RECTAL EXAMINATION		
		ALL PATIENTS (N=154)	ASYMPTOMATIC PATIENTS (N=110)	SYMPTOMATIC PATIENTS (N=44)	ALL PATIENTS (N=94)	ASYMPTOMATIC PATIENTS (N=47)	SYMPTOMATIC PATIENTS (N=47)
		number (percent)					
Identified on esophagogastroduodenoscopy							
Esophagitis	23 (9.3)	13 (8.4)	5	8	10 (10.6)	3	7
Gastric ulcer	14 (5.6)	7 (4.5)	7	0	7 (7.5)	4	3
Gastritis	12 (4.8)	6 (3.9)	4	2	6 (6.4)	3	3
Duodenal ulcer	10 (4.0)	6 (3.9)	1	5	4 (4.2)	2	2
Carcinoma	4 (1.6)	0	0	0	4 (4.2)	1	3
Duodenitis	3 (1.2)	2 (1.3)	2	0	1 (1.1)	1	0
Vascular ectasia	3 (1.2)	1 (0.6)	1	0	2 (2.1)	0	2
Adenomatous polyp	2 (0.8)	1 (0.6)	1	0	1 (1.1)	0	1
Subtotal	71 (28.6)	36 (23.4)	21 (19.1)	15 (34.1)	35 (37.2)*	14 (29.8)	21 (44.7)
Identified on colonoscopy							
Adenoma ≥1.0 cm	29 (11.7)	17 (11.0)	13	4	12 (12.8)	7	5
Carcinoma	13 (5.2)	5 (3.2)	3	2	8 (8.5)	4	4
Colitis	5 (2.0)	3 (1.9)	1	2	2 (2.1)	1	1
Vascular ectasia	5 (2.0)	3 (1.9)	3	0	2 (2.1)	1	1
Ulceration	1 (0.4)	0	0	0	1 (1.1)	1	0
Trichuris trichiura	1 (0.4)	1 (0.6)	1	0	0 (0)	0	0
Subtotal	54 (21.8)	29 (18.8)	21 (19.1)	8 (18.2)	25 (26.6)	14 (29.8)	11 (23.4)
Total†	119 (48.0)	62 (40.3)	40 (36.4)	22 (50.0)	57 (60.6)‡	27 (57.4)	30 (63.8)

*P=0.02 for the comparison with the patients with occult blood detected by screening.

†Six patients (three identified by screening and three by digital rectal examination) had lesions identified during both colonoscopy and esophagogastroduodenoscopy.

‡P<0.001 for the comparison with the patients with occult blood detected by screening.

tal examinations were performed for screening purposes. The racial and ethnic makeup of the study population was as follows: 26 percent white, 25 percent black, 22 percent Asian, 20 percent Hispanic, and 7 percent other. The mean (±SD) time between the detection of fecal occult blood and the endoscopic procedures was 56±45 days for the patients identified through screening and 46±31 days for those referred after digital rectal examination.

Overall, 119 patients (48.0 percent) had lesions consistent with occult bleeding. Fifty-four patients (21.8 percent) had colonic lesions whose presence was consistent with blood loss, most of them of neoplastic origin (Table 2). Evidence of active bleeding was identified in 12 patients (3 with colitis, 1 with a large ulcerated adenoma, 7 with ulcerated carcinoma, and 1 with vascular ectasia). Fourteen adenomas were 1.0 to 1.4 cm in diameter, eight were 1.5 to 2.0 cm, and seven were more than 2.0 cm. Eleven patients had adenomas in the left colon, 2 in the transverse colon, and 4 in the right colon; 12 patients had multiple adenomas. Nine colon cancers were in the left colon, and four in the right colon. Six of the cancers were in Dukes' stage A, three in stage B, two in stage C, and two in stage D. Large external or internal hemorrhoids (or both) were detected in 20 patients.

Lesions consistent with blood loss were identified at the time of esophagogastroduodenoscopy in 71 patients (28.6 percent). Evidence of active bleeding was present in 12 patients with erosive esophagitis, 3 with gastritis, 2 with large gastric ulcerations, and 1 with Kaposi's sarcoma. Seven patients had multiple ulcers, and two had giant gastric ulcers (more than 2.0 cm in diameter). More than one lesion consistent with blood loss was identified in the upper gastrointestinal tract in nine patients. Six had lesions consistent with blood loss in both the colon and the upper gastrointestinal tract; all six had colonic adenomas, and in the upper gastrointestinal tract, two had esophagitis, two gastritis, one gastric ulcer, and one duodenal ulcer. Thirty patients with lesions in the upper gastrointestinal tract were long-term users of aspirin, ethanol, nonsteroidal antiinflammatory drugs, or a combination of these substances (16 in the group identified by screening and 14 in the group identified by digital rectal examination), although 12 of these patients had lesions, such as

esophagitis, that were unlikely to be associated with the use of these compounds.

We performed multivariable logistic-regression analysis to identify independent variables potentially associated with the presence of gastrointestinal lesions consistent with blood loss. Variables examined in the model included age, sex, the interval between the detection of fecal occult blood and the procedures, the method of fecal occult-blood detection (screening or digital rectal examination), the presence or absence of upper gastrointestinal symptoms, use or nonuse of aspirin and nonsteroidal antiinflammatory drugs, presence or absence of large hemorrhoids (4+), and use or nonuse of alcohol (more than 90 ml [3 oz] of ethanol per day). Of the variables examined, only the presence of upper gastrointestinal symptoms predicted that a site of blood loss would be identified in the upper gastrointestinal tract (odds ratio, 2.6; 95 percent confidence interval, 1.4 to 4.7; P=0.003). When lower gastrointestinal symptoms were used in the model in place of upper gastrointestinal symptoms, we found that the presence of lower gastrointestinal symptoms was predictive of a lesion in the lower gastrointestinal tract (odds ratio, 3.3; 95 percent confidence interval, 1.2 to 9.3; P=0.02). When we used any symptoms as the variable in the model, the presence of either upper or lower gastrointestinal symptoms predicted that a source of blood loss would be detected in the upper or lower gastrointestinal tract (odds ratio, 1.8; 95 percent confidence interval, 1.0 to 3.1; P=0.05).

Since symptoms were important predictors of gastrointestinal lesions in the logistic-regression model, we examined patients with symptoms and the likelihood of detecting gastrointestinal lesions in subgroups of patients. The sensitivity of the presence of upper or lower gastrointestinal symptoms in predicting a lesion in the corresponding portion of the gastrointestinal tract was low. Fourteen of 39 patients with upper gastrointestinal symptoms in the group identified by screening (35.9 percent) had a lesion, as compared with 19 of 39 (48.7 percent) in the group identified by digital rectal examination (P=0.36). The sensitivity of lower gastrointestinal symptoms in predicting lower gastrointestinal lesions and that of upper gastrointestinal symptoms in predicting lesions in the upper gastrointestinal tract were similar (data not shown).

There was a significant association between the method of detecting fecal occult blood (digital rectal examination or screening) and the identification of lesions in the gastrointestinal tract. After controlling for the presence of symptoms, we found that the odds of detecting a lesion in the screening group were one half of those in the digital-rectal-examination group (adjusted odds ratio, 0.5; 95 percent confidence interval, 0.3 to 0.8; P=0.01). We found no significant interaction between the presence of symptoms and the method of detecting occult blood. However, we considered the possibility that gastrointestinal symptoms led clinicians to perform digital rectal examinations, thereby increasing the likelihood of finding a lesion. Thus, we examined patients with and without symptoms separately for an association between the method of detection and the identification of gastrointestinal lesions. Among patients with symptoms, the rate of detection of a lesion was slightly lower in the group identified by screening, but the difference was not significant (22 of 44 patients in the screening group had lesions, as compared with 30 of 47 patients in the digital-rectal-examination group; odds ratio, 0.6; 95 percent confidence interval, 0.2 to 1.3; P=0.21). The likelihood of detecting a lesion was significantly lower among the asymptomatic patients who had fecal occult blood detected by screening (40 of 110) than among those identified by digital rectal examination (27 of 47) (odds ratio, 0.4; 95 percent confidence interval, 0.2 to 0.9; P=0.02).

The incidence of lesions that many clinicians consider minor or trivial was high (Table 3). Esophagogastroduodenoscopy led to a change in treatment for 59 percent (50 of 85) of patients in whom a trivial lesion was identified (Table 4). Since therapy was instituted in all patients in whom there was an upper gastrointestinal lesion defined as consistent with blood loss, a change in treatment occurred as a result of esophagogastroduodenoscopy in 49 percent of patients overall (121 of 248). In a logistic-regression model in which a change in treatment, such as discontinuation of nonsteroidal antiinflammatory drugs or use of a new medication, was designated the outcome variable, upper gastrointestinal symptoms were associated with such a change (odds ratio, 2.7; 95 percent confidence interval, 1.5 to 5.0; P<0.001), as was the use of nonsteroidal antiinflammatory drugs (odds ratio, 2.3; 95 percent confidence interval, 1.0 to 5.0; P=0.04).

DISCUSSION

Lesions in the gastrointestinal tract that were consistent with occult blood loss were present in 48 percent of the patients with positive fecal occult-blood tests (range in different subgroups, 36 to 64 percent). The prevalence of large colonic adenomas and carcinomas (in asymptomatic patients, 12.7 percent and 4.5 percent, respectively) was similar to that in other studies in which colonoscopy was performed in patients with evidence of fecal occult blood.[22-25] In addition, we found lesions that were consistent with occult gastrointestinal bleeding more frequently in the upper gastrointestinal tract than in the colon.

Although it is possible that the upper gastrointestinal abnormalities detected in our patients did not

TABLE 3. MINOR ENDOSCOPIC ABNORMALITIES IN 248 PATIENTS.*

TYPE OF LESION	PATIENTS WITH OCCULT BLOOD (N=248)	OCCULT BLOOD DETECTED BY SCREENING (N=154)	OCCULT BLOOD DETECTED BY DIGITAL RECTAL EXAMINATION (N=94)
		number (percent)	
Identified on esophagogastroduodenoscopy			
Gastritis	47 (19.0)	28	19
>1 lesion	11 (4.4)	10	1
Gastric or duodenal ulcer	10 (4.0)	9	1
Esophagitis	9 (3.6)	8	1
Duodenitis	6 (2.4)	5	1
Adenomatous polyp	2 (0.8)	1	1
Subtotal	85 (34.3)	61 (39.6)	24 (25.5)
Identified on colonoscopy			
Adenoma <5 mm	35 (14.1)	24	11
Adenoma 5–9 mm	29 (11.7)	19	10
Inflammation	2 (0.8)	1	1
Subtotal	66 (26.6)	44 (28.6)	22 (23.4)
Total†	122 (49.2)	84 (54.5)	38 (40.4)

*Endoscopic abnormalities defined as minor are described in the Methods section.

†In the screening group, 21 patients had minor lesions in both upper and lower gastrointestinal tracts; in the digital-rectal-examination group, 8 such patients were identified. Overall, 28 patients also had lesions consistent with occult bleeding (Table 2).

TABLE 4. CHANGES IN TREATMENT AFTER ESOPHAGOGASTRODUODENOSCOPY AMONG PATIENTS WITH MINOR ENDOSCOPIC LESIONS.

CHANGE	PATIENTS WITH LESIONS (N=85)	OCCULT BLOOD DETECTED BY SCREENING (N=61)	OCCULT BLOOD DETECTED BY DIGITAL RECTAL EXAMINATION (N=24)
		number (percent)	
Addition of histamine H_2-receptor antagonist	31 (36.5)	23	8
Addition of proton-pump inhibitor	12 (14.1)	6	6
Other*	4 (4.7)	4	0
Discontinuation of nonsteroidal antiinflammatory drug†	9 (10.6)	7	2
Eradication of *H. pylori*‡	14 (16.5)	9	5
Total§	50 (58.8)	36 (59.0)	14 (58.3)

*Other changes were the addition of measures against esophageal reflux (one patient) and follow-up endoscopy or further investigation (three patients).

†Four patients in the screening group and two in the digital-rectal-examination group also had pharmacologic therapy instituted.

‡All patients also had pharmacologic therapy instituted.

§Some patients had more than one change in treatment.

cause the positive fecal occult-blood tests, we believe this to be unlikely for several reasons. First, occult blood loss from the types of lesions we identified has been well established,[10-14,17] and such lesions have been shown to produce amounts of blood (5 to 20 ml per day) that are readily detectable by guaiac-based fecal occult-blood tests.[10-14,18,26,27] Second, previous endoscopic studies in asymptomatic patients revealed a much lower rate of abnormalities than we found in this study. Although caution must be exercised when previous studies are compared with ours, because of differences in the endoscopic assessment of lesions as well as differences in the populations studied, comparisons of specific lesions indicate that the frequency of substantial lesions in the upper gastrointestinal tract was much higher in our patients than in asymptomatic populations.[28,29] The combined prevalence of duodenal or gastric ulcer and erosive esophagitis was 3.7 to 6.5 percent in previous studies,[28,29] whereas their combined frequency was 14 percent (not including other important lesions) among the asymptomatic patients in our study.

As in clinical practice, we examined patients in whom fecal occult blood was detected by routine screening or digital rectal examination. Stool was obtained by digital rectal examination in some cases for purposes of screening (such patients were largely asymptomatic), whereas it was obtained in others as part of the physical examination, ostensibly for further evaluation of the gastrointestinal tract (mostly in patients with symptoms). This clinical scenario could in part explain the higher overall rate of detection of lesions in the gastrointestinal tract in the group in which stool was obtained by digital rectal examination (this is particularly true for upper gastrointestinal lesions in symptomatic patients [Table 2]) than in screened patients. Nonetheless, the high prevalence of gastrointestinal lesions in all subgroups implies that the finding of fecal occult blood identifies patients with an increased likelihood of having lesions in either the upper or the lower gastrointestinal tract.

Digital rectal examination may induce local trauma that leads to bleeding; alternatively, stool may contain nonhuman hemoglobin. Thus, many practitioners suggest that stool obtained during digital rectal examination should not be tested for occult blood. Furthermore, a preliminary study found that the positive predictive value (for a colonic lesion) of fecal occult-blood testing of stool obtained during a digital rectal examination was less than that of testing of stool collected by the patient for routine screening.[30] In contrast, we found that the rate of gastrointestinal lesions was slightly higher when stool was obtained by digital rectal examination, even in patients without symptoms. Other studies have demonstrated that patients with fecal occult blood detected by digital rectal examination have as many

colonic lesions as patients identified by routine screening.[31,32] Thus, the available data conflict, a fact that emphasizes the need for further investigation of the implications of positive fecal occult-blood tests after digital rectal examination.

We found that a substantial proportion of patients undergoing routine screening had gastrointestinal symptoms (most commonly dyspepsia or heartburn), perhaps because of the intensive nature of our system review. Moreover, although symptoms localized to either the upper or the lower gastrointestinal tract were associated with lesions in the corresponding portion of the gastrointestinal tract (irrespective of the method of detecting fecal occult blood), the sensitivity and specificity of symptoms for lesions in specific sites were low. The use of endoscopy in patients with evidence of fecal occult blood (upper endoscopy for patients with upper gastrointestinal symptoms or colonoscopy for patients with lower gastrointestinal symptoms) is controversial. Our data suggest that symptoms are important and that a careful history should be taken; however, it may still be necessary to evaluate areas of the gastrointestinal tract other than those suggested by the symptoms.

The value of esophagogastroduodenoscopy in asymptomatic patients with positive fecal occult-blood tests and no apparent source of colonic bleeding is also controversial. On the one hand, esophagogastroduodenoscopy is expensive and entails some risk. On the other hand, other studies have also found important lesions in the upper gastrointestinal tract in patients without symptoms.[33-36] Furthermore, minor lesions are common and lead to the institution of new therapy in many patients (Tables 3 and 4).

Our data have important implications for clinicians who use guaiac-based fecal occult-blood tests to screen patients for colorectal cancer. We examined several groups of patients with evidence of fecal occult blood who were typical of many seen in actual practice; even if one considers only patients without symptoms who were identified by routine screening, however, as many lesions were detected in the upper as in the lower gastrointestinal tract. Lesions in the upper gastrointestinal tract lead to positive test results that are assumed to be caused by lesions in the colon, and this then leads to potentially dangerous and expensive investigation (usually colonoscopy). Alternatives to the use of guaiac-based fecal occult-blood tests as a method of screening for colorectal cancer should be considered. For example, immunochemical tests for human hemoglobin, which detect primarily colonic bleeding,[22,27] could help focus the evaluation on the colon. Furthermore, a combination test[22,23] in which a guaiac-based test is followed by an immunochemical test, is attractive because it might differentiate bleeding in the upper gastrointestinal tract from that in the lower gastrointestinal tract.

We are indebted to the nurses, staff, residents, and fellows of the gastrointestinal units at San Francisco General Hospital and San Francisco Veterans Affairs Medical Center for their help; to Amy Auslander and Myron Scott for expert technical assistance; and to Paul Greenberg for helpful discussions.

REFERENCES

1. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993; 328:1365-71. [Erratum, N Engl J Med 1993;329:672.]
2. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467-71.
3. Hardcastle JD, Chamberlain JO, Robinson MHE, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-7.
4. Lance P. Fecal occult blood tests: what's new? Gastroenterology 1993; 104:1852-5.
5. Lieberman DA. Colon cancer screening: the dilemma of positive screening tests. Arch Intern Med 1990;150:740-4.
6. Ransohoff DF, Lang CA. Screening for colorectal cancer. N Engl J Med 1991;325:37-41.
7. Young GP, St John DJ. Screening for colorectal cancer: the accuracy of fecal occult blood. JAMA 1993;270:451-2.
8. Lieberman D, Sleisenger MH. Is it time to recommend screening for colorectal cancer? Lancet 1996;348:1463-4.
9. Greenberg PD, Cello JP, Rockey DC. Asymptomatic chronic gastrointestinal blood loss in patients taking aspirin or warfarin for cardiovascular disease. Am J Med 1996;100:598-604.
10. Ahlquist DA, McGill DB, Schwartz S, Taylor WF, Owen RA. Fecal blood levels in health and disease: a study using HemoQuant. N Engl J Med 1985;312:1422-8.
11. Morris DW, Hansell JR, Ostrow JD, Lee CS. Reliability of chemical tests for fecal occult blood in hospitalized patients. Am J Dig Dis 1976;21: 845-52.
12. Stroehlein JR, Fairbanks VF, McGill DB, Go VL. Hemoccult detection of fecal occult blood quantitated by radioassay. Am J Dig Dis 1976; 21:841-4.
13. Dybdahl JH. Occult faecal blood loss determined by a 51Cr method and chemical tests in patients referred for upper gastrointestinal endoscopy. Scand J Gastroenterol 1984;19:235-44.
14. Herzog P, Holtermuller KH, Preiss J, et al. Fecal blood loss in patients with colonic polyps: a comparison of measurements with 51chromium-labeled erythrocytes and with the Haemoccult test. Gastroenterology 1982;83:957-62.
15. Macrae FA, St John DJ. Relationship between patterns of bleeding and Hemoccult sensitivity in patients with colorectal cancers or adenomas. Gastroenterology 1982;82:891-8.
16. World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925-6.
17. Ferguson A, Brydon WG, Brian H, Williams A, Mackie MJ. Use of whole gut perfusion to investigate gastrointestinal blood loss in patients with iron deficiency anaemia. Gut 1996;38:120-4.
18. Dybdahl JH, Daae LN, Larsen S, Myren J. Occult faecal blood loss determined by a 51Cr method and chemical tests in patients referred for colonoscopy. Scand J Gastroenterol 1984;19:245-54.
19. Sontag SJ, Hirschowitz BI, Holt S, et al. Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the U.S. Multicenter Study. Gastroenterology 1992;102:109-18.
20. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. 2nd ed. Boston: PWS-Kent, 1988.
21. SAS/STAT user's guide. 4th ed. Vol. 2. Cary, N.C.: SAS Institute, 1990.
22. St John DJ, Young GP, Alexeyeff MA, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. Gastroenterology 1993; 104:1661-8.
23. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996; 334:155-9.
24. 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;112:328-33.
25. Lang CA, Ransohoff DF. Fecal occult blood screening for colorectal cancer: is mortality reduced by chance selection for screening colonoscopy? JAMA 1994;271:1011-3.
26. Ostrow JD, Mulvaney CA, Hansell JR, Rhodes RS. Sensitivity and re-

producibility of chemical tests for fecal occult blood with an emphasis on false-positive reactions. Am J Dig Dis 1973;18:930-40.
27. Rockey D, Auslander A, Greenberg P. Detection of occult upper gastrointestinal blood with fecal occult blood tests. Gastroenterology 1997; 112:Suppl:A40. abstract.
28. Akdamar K, Ertan A, Agrawal NM, McMahon FG, Ryan J. Upper gastrointestinal endoscopy in normal asymptomatic volunteers. Gastrointest Endosc 1986;32:78-80.
29. Johnsen R, Bernersen B, Straume B, Forde OH, Bostad L, Burhol PG. Prevalences of endoscopic and histological findings in subjects with and without dyspepsia. BMJ 1991;302:749-52.
30. Marks RD, Hall G, Veerapalli R, Singh S. Fecal occult blood testing: does the stool collection method affect outcomes? Gastroenterology 1997; 112:Suppl:A29. abstract.
31. Brint SL, DiPalma JA, Herrera JL. Is a Hemoccult-positive rectal examination clinically significant? South Med J 1993;86:601-3.
32. Eisner MS, Lewis JH. Diagnostic yield of a positive fecal occult blood test found on digital rectal examination: does the finger count? Arch Intern Med 1991;151:2180-4.
33. Geller AJ, Kolts BE, Achem SR, Wears R. The high frequency of upper gastrointestinal pathology in patients with fecal occult blood and colon polyps. Am J Gastroenterol 1993;88:1184-7.
34. Chen YK, Gladden DR, Kestenbaum DJ, Collen MJ. Is there a role for upper gastrointestinal endoscopy in the evaluation of patients with occult blood-positive stool and negative colonoscopy? Am J Gastroenterol 1993;88:2026-9.
35. Hsia PC, al-Kawas FH. Yield of upper endoscopy in the evaluation of asymptomatic patients with Hemoccult-positive stool after a negative colonoscopy. Am J Gastroenterol 1992;87:1571-4.
36. Zuckerman G, Benitez J. A prospective study of bidirectional endoscopy (colonoscopy and upper endoscopy) in the evaluation of patients with occult gastrointestinal bleeding. Am J Gastroenterol 1992;87:62-6.