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PROGRESS ARTICLE

Occult Blood Screening for Colorectal Carcinoma: A Critical Review

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The author reviews the literature on occult blood surveillance for colorectal carcinoma. The guaiac-based Hemoccult (SmithKline Diagnostics, Sunnyvale, Calif.) test is the most reliable and widely used. However, testing is complicated by several technical issues that can affect clinical results, and even successful screening programs will miss a high proportion of tumors. Public compliance is often poor, and a number of indirect and "hidden" costs make surveillance programs much more expensive than is usually claimed. Almost all published screening trials are uncontrolled. They generally detect about 3–20 colorectal malignancies for every 10,000 people enrolled, but only about 5%–10% of occult blood reactions are due to cancer. Though screen-detected tumors tend to be at a relatively early stage, this does not imply any benefit of surveillance because of lead time and length biases inherent in the screening process. Only controlled trials can answer the central question of whether screening decreases mortality from bowel cancer. Two such trials are underway, but mortality data are not yet available from either.

Colorectal cancer is both common and fatal. Indeed, in men it is exceeded only by cancer of the lung, and in women only by cancer of the breast, as a cause of tumor mortality in North America (1). Though many patients do survive this malignancy, the overall 5-yr survival rates are only 40%–45% (2,3). Moreover this figure has changed little for at least two decades (2). Thus earlier detection (4,5), rather than better treatment, probably offers the best hope for improving the outcome of this important disease.

During the past 15 yr interest has grown in the concept of screening apparently healthy populations for bowel cancer by means of fecal occult blood detection. A massive literature on this subject has accumulated, much of it confusing. The purpose of

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this review is to summarize and critically analyze the available information. Pertinent aspects of screening will first be noted, followed in turn by brief historical comments on occult blood detection; a review of available methods and of technical considerations; a discussion of clinical findings, including results of uncontrolled and controlled screening studies; and finally, a consideration of compliance and costs.

Screening for Bowel Cancer

Relevant Screening Concepts

The value of a screening test depends on its ability to separate those who have disease from those who do not. A sophisticated literature has evolved on the general principles of population screening, and several authors have commented on aspects relevant to bowel cancer (6–15). Criteria for a successful screening program have also been outlined (6,8,11). Only a few selected points are noted here, largely drawn from the excellent discussion by Cole and Morrison (8):

1. A test's sensitivity is defined by the proportion of diseased subjects who have a positive result (6,8). For colorectal screening, this requires comparison with "gold standard" colonoscopy on all subjects, which is obviously impossible. Alternatively, but much less accurately, all test-negative subjects can be closely followed to determine how many cancers soon turn up amongst them (8). Yet most authors make no organized attempt to detect subsequent cancer in their screen-negative subjects. Without this information, sensitivity claims are meaningless.
2. Specificity, the proportion of nondiseased subjects who have a negative test (6,8), is an equally important measure of screening validity. Even a test of 100% sensitivity will be of little clinical value if its specificity is low, because it will incorrectly single out too many healthy people. In general, sensitivity and specificity must be traded off against one another (8). For bowel cancer, this trade-off should preferably favor specificity, because the consequence of a positive test is an expensive, uncomfortable, and potentially harmful diagnostic work-up for colonic disease.
3. Predictive value, the proportion of positive tests actually due to the disease in question, is usually critically dependent on specificity—a minor increase in specificity often yields a dramatic improvement in predictive value (8). Predictive value provides a good overall reflection of a screening program's performance, and can be improved by screening higher prevalence (i.e., higher-risk) persons or by using a test with higher specificity, or both (8).
4. The terms "false-positive rate" and "false-negative rate" are ambiguous, inasmuch as clinicians and epidemiologists often view them differently. Moreover, as pointed out by Winawer et al. (16) and by Goulston (17), a falsely positive fecal occult blood test may mean that blood is present but is not due to cancer, that results are positive yet no blood is detectable by other techniques, that there are dietary or other interfering agents, etc. Thus investigators should specify their particular definition of a false-positive test; this in fact is rarely done.

Biases in Screening

There are important sources of bias or error in the interpretation of screening results, yet these are widely unappreciated.

Lead time bias (8,12–14). Screening programs for bowel cancer commonly report that detected tumors tend to be at an earlier Dukes' stage than usually discovered tumors (see below). Because the prognosis is better for early than for late disease (3,18), it seems self-evident that screening programs are beneficial; certainly most authors implicitly accept this.

Alas, this is fallacious reasoning, primarily because of bias due to lead time—the interval between detection by screening and the time when the disease would have been diagnosed without screening. Because of lead time, *tumors found by screening will have a longer observed course simply because of earlier discovery*, quite independently of whether any benefit results. As expressed by Eddy (9), screening may merely move forward the time of diagnosis without moving back the time of death. This point, though critical, does not destroy the justification for screening, but results must be interpreted with caution and efficacy requires proof of improved patient survival independent of lead time.

Length bias (8,12–14). When an asymptomatic population is screened at one point in time, malignancies with inherently slower growth will be disproportionately detected. The longer the preclinical duration of the disease, the stronger is this selection artifact, known as length bias. Because longer preclinical illness is equatable with a longer course, *individuals diagnosed by a screening program will always live longer on the average than the general diseased population*, even after adjusting for lead time. A related aspect of length bias is that tumors diagnosed by screening tend to be less aggressive and will therefore have a relatively favorable outcome. Clearly, therefore, an artifactually

apparent benefit of screening can result even if no true benefit exists (8,12–14).

Length bias is maximal when a population is initially screened; because most tumors are found at this initial testing, the bias diminishes during subsequent surveillance of the same population (8).

Patient selection bias (8,12,13). Screened populations may not accurately represent patients who develop a disease in general. For example, subjects in the Sloan–Kettering occult blood trial generally are middle class, highly motivated, and well educated (19). Perhaps the epidemiology and natural history of bowel cancer in such a group differs from that of a lower socioeconomic population which does not volunteer for screening. The impact of selection bias on screening programs is difficult to estimate, but any apparent benefit could at least partly be related to the type of patient selected.

The effectiveness of a colorectal screening program must ultimately rest on demonstration that screening reduces mortality from bowel cancer. This in turn requires statistically valid comparison with a comparable group of the population which is not screened. As touched upon by various authors (11,14), especially Prorok (15), randomized, controlled clinical trials are best able to minimize the biases discussed above. Various other quasi-experimental methods of evaluating screening programs have been attempted, but these are difficult to interpret (11). Unfortunately, among the vast literature on occult blood screening, only two ongoing studies are potentially able to determine the impact on mortality. These are detailed later.

Occult Blood Detection—History

The concept of occult blood detection is generally credited to Van Deen, who in 1864 used gum guaiac as an indicator reagent; his test was later modified by many others (discussed in References 20 and 21), and even today guaiac remains the most widely used indicator for occult bleeding. In the early 1900s Adler and Adler introduced benzidine as an alternative marker, and a host of technical variations followed (discussed in References 20–23). Over the years numerous other chemicals have been used to detect fecal blood, and new ones continue to be described to this day (20–29). Of all of these, only guaiac, benzidine, and orthotolidine have ever achieved any measure of acceptance. Moreover, since the late 1960s the latter two have fallen into disfavor—partly due to concern about their potential carcinogenicity (30–32), but mainly because they are too sensitive for clinical validity (see below).

Boas in 1901 apparently first emphasized the value of occult blood for the detection of bowel malignancy (20), but for two-thirds of a century little attention was given to the concept of screening apparently healthy populations. Credit for stimulating interest in this goes to Greegor, an Ohio internist. In the mid-1960s Greegor had guaiac-impregnated slides designed for his patients to use at home and mail to his office, and in 1967 he reported the detection of several asymptomatic tumors by this means (33). Subsequent studies confirmed the ability of this slide test, known as Hemoccult (Smith Kline Diagnostics, Sunnyvale, Calif.) to uncover subclinical bowel cancer. As a result, throughout the 1970s the literature on its use mushroomed and many screening studies were undertaken. Unfortunately these were too often ill designed and superficial, and only gradually has a more critical approach to screening developed. This process continues to evolve.

Chemical Tests

Nature of the Reaction (20,23)

Chemical tests for occult blood depend upon the oxidation of a phenolic compound to a quinone structure, which in turn changes color by an intermolecular reaction. Hydrogen peroxide facilitates the oxidation process, which is catalyzed by a number of naturally occurring peroxidases and catalases including hemoglobin. In the Hemoccult test, for example, gum guaiac is impregnated in a test paper and hydrogen peroxide is provided in a developer solution. The resultant phenolic oxidation of guaiac in the presence of blood yields a blue color (20,23). Guaiac is a heterogeneous natural product; details of the extraction and purification technique will therefore influence the amount of reagent in the test paper (34).

Chemical alteration of hemoglobin as it passes through the gastrointestinal (GI) tract can diminish its peroxidaselike activity and render stool tests negative (20,35,36). This is accelerated by pancreatic juice and trypsin (17,37). Individuals vary considerably in this regard (23), so no general rule can be applied to clinical settings. Because of this, however, occult upper GI bleeding is more likely to go undetected than equivalent oozing from the lower gut. In the context of screening for colorectal cancer, this is an advantage, as it decreases the number of positive results from other sources.

Commercial Tests

Over the decades literally scores of test variations have been described, but only a few commer-

cial preparations are currently in widespread clinical use. Of these, by far the most popular and the best studied is Hemoccult. This has been available for more than 15 yr; modifications around 1977 led to the currently distributed Hemoccult II slides (SmithKline Diagnostics, Sunnyvale, Calif.). Each slide contains two windows of guaiac-impregnated paper, on which the patient smears a small amount of stool with a supplied applicator. This is usually repeated with two subsequent bowel movements, then the three-slide package is returned to the laboratory. Even a single reaction among the six smears is termed a positive test on that patient, and further investigations are advised.

Numerous other commercial tests using guaiac have been marketed. These include Fecatest (Labsystem Oy, Helsinki, Finland), Quik-Cult (Laboratory Diagnostics, Morganville, N.J.), ColoScreen (Helena Laboratories, Beaumont, Tex.), FeCult (Gamma Diagnostica, Houston, Tex.), Colo-Rect (Roche Diagnostics, Nutley, N.J.), Haemoscreen (E. Merck Diagnostica, Darmstadt, Federal Republic of Germany), HemaChek (Miles Laboratories, Elkhardt, Ind.), Camco Pak (Cambridge Chemical Products, Fort Lauderdale, Fla.), and many others. Most are based on guaiac-impregnated paper, similar to Hemoccult, but few have been objectively compared with other techniques. None has achieved widespread popularity.

The only important commercial preparation based on orthotolidine is Hematest (Miles Larobatories, Elkhardt, Ind.). Marketed as a tablet with accompanying filter paper, it is still widely used by many physicians and hospitals.

Unlike all of the above, Hemo-Fec (Med-Kjemí A/S, Høn, Norway) uses a benzidine derivative, tetramethylbenzidine, as the indicator reagent. Marketed in the form of cardboard slides, it has undergone some comparative testing in Germany (38) but is not widely popular.

Other Tests

Among the numerous "new" methods for occult blood detection that continue to appear in the literature, two are worth noting because of their potential importance:

HemoQuant. This unique, quantitative assay was recently devised by Schwartz et al. (39a,b). Based on the conversion of heme to fluorescent porphyrins, it is exquisitely sensitive, gives virtually quantitative recovery of fecal hemoglobin over a wide range, and is unaffected by several factors (discussed below) that can influence Hemoccult, including stool hydration and storage, dietary peroxidases, iron, and ascorbic acid. Moreover, HemoQuant measures not only intact heme, but also hemoglobin already degraded during gut transit (the "intestinal converted fraction") (39a,b). Thus, unlike other assays, it should detect both upper and lower GI bleeding with equal sensitivity. Although this will probably prove a disadvantage for colorectal screening, comparison of the converted fraction with total fecal heme could potentially provide a clue to the approximate level of a bleeding source.

HemoQuant is relatively complex technically and has not yet been applied to clinical screening situations. However, its quantitative capacity and apparent accuracy render it an exciting development that may herald a new era in occult blood detection.

Immunochemical detection. Barrows and Songster and their coworkers have developed an immunochemical technique for occult blood that shows considerable promise (40–42). It is said to specifically detect human hemoglobin free of cross-reaction with various foodstuffs, animal heme, drugs, etc. (40), and the authors have adapted the technique to a relatively simple filter paper ("punch disc") suitable for clinical screening (41,42). A similar concept is also being developed by others (43,44).

Immunochemical methods require further validation and clinical testing, but are a major theoretical advance. Specificity of the procedure is much improved, and dietary and chemical restrictions for test subjects can be eliminated. An additional advantage is stability of the smear for up to 30 days (42). Disadvantages include a 24–48-h delay between receiving and interpreting the test (42), as well as greater technical complexity and cost compared with simpler tests. If proven clinically valid, immunochemical methods could eventually render current occult blood techniques obsolete.

"Normal" Gastrointestinal Blood Loss

Accuracy of chemical methods for the detection of fecal blood depends on comparison with a "gold standard." Since the late 1950s, quantitation of ^{51}Cr-labeled red blood cells has been generally accepted as the most accurate indicator of intestinal blood loss. Studies with this method have been remarkably consistent, demonstrating "normal" blood loss of about 0.5–2.0 ml daily (45–48). Hence there is general agreement that losses should not exceed 2 ml per day, though some accept 3 ml.

As an aside, some authors express fecal blood levels as milligrams of hemoglobin per gram of stool rather than milliliters of blood per day, because spot tests depend upon the concentration rather than the absolute amount of hemoglobin in the stool. The two are easily compared, inasmuch as 2 ml/day is deemed equatable with 2 mg of hemoglobin/g of stool; this equivalence, though crude, is based on 150 g of stool passed per day and a blood hemoglobin of 15 g/dl in the average person (49).

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Specific Test Sensitivities

"Sensitivity" in this context does not refer to the epidemiologic definition noted above, but rather to the capacity of a test to detect blood.

Ostrow and coworkers (50) were the first to compare the sensitivity of chemical tests directly with ^{51}Cr-labeling methodology; in 1973 they reported an unacceptably high frequency of false-positive reactions with Hematest. In contrast, Hemoccult was only about one-quarter as sensitive but had few false-positive reactions and was highly reproducible (96%) (50). Other authors of the modern era have also condemned Hematest as yielding both too many false-positive (49–52) and too many false-negative (50,53) results. The test is also poorly reproducible and there is remarkably high discordance in interobserver readings of the results (50). Hematest is therefore clearly unreliable and should be abandoned as a test for fecal occult blood.

Liquid quaiac or benzidine preparations give far too many false-positive results for valid clinical use (20,49–53). Hemoccult fares much better, primarily because of its lesser sensitivity; in objective comparisons with ^{51}Cr-labeled red blood cell losses, only ~7%–12% falsely positive results are generally recorded (49,54). This is at the price of missing pathologic amounts of blood, however. A number of studies have shown a high proportion of negative Hemoccult reactions when bleeding is in the 5–10 ml/day range (38,49,50,54–56), and losses >20 ml/day are necessary to achieve 80%–90% Hemoccult positivity (49,54,55). Indeed, Heinrich and Icagic (38) found that Hemoccult not uncommonly missed 40 ml/day, though this is contrary to all other studies.

In vitro studies indicate that Hemoccult sensitivity can be markedly influenced by seemingly minor technical factors such as the matrix in which hemoglobin is contained and whether the red cells are lysed or intact (57). Moreover, sensitivity of the commercial test has apparently changed over the years (58), and the currently marketed Hemoccult II seems more sensitive than some of the older preparations on which the above data are based (19,59). This has actually affected the rate of positivity and the predictive value of the test in clinical screening situations (16,19,60). Because formal studies directly comparing Hemoccult with Hemoccult II results have never been published, the sensitivity data derived on the 1970s cannot be assumed applicable today.

Only limited comparative information is available on other commercial tests. Both Fecatest and Colo-Rect appear to be more sensitive than Hemoccult (38,56), and Hemo-Fec less sensitive (38). However, some comparative results have been challenged on technical grounds, resulting in a lively debate in the literature (58,61). From a review of the evidence it is clear that sensitivity data must be determined independently for each commercial test. Results on one preparation cannot be extrapolated to another, even if based on the same reagent and appearing essentially similar.

Technical Factors Influencing the Reaction

The above discussion indicates that the seemingly "simple" occult blood reaction is actually highly complex. Other technical issues complicate the situation even further. A number of these have clinical implications, but unfortunately the literature is a morass of often conflicting information.

Dietary Peroxidases

The occult blood reaction is not specific for human hemoglobin but is affected by peroxidases and catalases in various foodstuffs including red and white meats, fish, fresh fruits, and uncooked vegetables (20,23,62). How important this is for clinical screening is debated. Greegor (63), the first physician to report the use of Hemoccult, noted that a meat-free diet cut down the number of positive reactions in his clinical practice. Ever since, his dietary advice has been followed by a number of authors, including the group at the Sloan–Kettering Institute who are leaders in the study of colorectal cancer (19). Many other authors, however, ignore diet in their screening programs (see Table 1). This makes comparison of clinical studies difficult.

A controlled trial on this point has never been carried out, and the available data differ (17,50,64,65). The most carefully designed dietary study was recently reported by Macrae and colleagues (66). Using Hemoccult II, they concluded that positive results on an unrestricted diet deserve investigation if the test slides are not hydrated, but that red meat in the diet is unacceptable if the slides are rehydrated (66). Rehydration of slides as a technical factor in test positivity is discussed further below.

Clinical trials are needed to establish whether a low-peroxidase diet is justified for screening programs; on present evidence this remains uncertain. It is worth stressing, however, that even a minor diet-related decrease in false-positive results may be clinically important. This is because a small increase in specificity can have a major impact on the predictive value of a positive test (8), thereby diminishing needless investigations on healthy people (see above).

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Dietary Residue

This is another dietary factor open to argument. Credit or blame again goes to Greegor (63), who arbitrarily put his patients on a high-residue (in addition to meat-free) diet. His rationale was "to guard against the unwitting use of a too bland diet" and to help ensure bleeding from any colorectal lesion present (63). Use of this dietary advice has been widely adopted, but as pointed out by Ostrow (67), has never been validated. Indeed high-roughage intake theoretically could have two unfavorable effects on occult blood screening: its high peroxidase content might increase the number of false-positive tests, and its high bulk might dilute any fecal hemoglobin to undetectable concentrations (67). These points have not been subjected to proper testing, though Hellerstein et al. (68) found that a high-fiber diet did not enhance bleeding from colonic polyps.

On available evidence, use of a high-residue diet for occult blood testing appears arbitrary and without scientific validation.

Slide Storage and Rehydration

In 1976 Morris et al. (49) noted that 14% of positive Hemoccult results on fresh stool became negative after the slides were left at room temperature for 2 days. Subsequent authors have confirmed this tendency (69,70). Though some of the data have been criticized (71), it appears that weakly positive Hemoccult reactions may yield negative or equivocal results after 2–4 days of storage, whereas a strong reaction will remain positive for at least 10 days (57). Reasons for this storage artifact are uncertain. The problem is not fading of the color reaction per se, but presumably dessication of stool on the slide over a period of time (71). Precisely how this alters the chemical reaction has not been ascertained. Tests that fade may mainly be falsely positive anyway (71), but this requires substantiation.

The clinical implications are obvious, inasmuch as it is common practice for the patient to collect three consecutive stools before returning the test slides to the physician, often by mail. Thus artifactually negative results due to storage might seriously impair the value of screening programs.

To help solve this problem, Wells and Pagano (72) suggested rehydration of Hemoccult slides with a drop of water before testing. This presumably assists dissolution of dessicated hemoglobin (57) and might also lyse red cells with release of free hemoglobin (73). Hydration clearly does enhance sensitivity of the Hemoccult test and restores positive reactions (57,72,73). The question, though, is whether it enhances sensitivity too much. A variety of interfering peroxidases are presumably also reactivated and can increase the number of false-positive results (57). In fact, rehydration increases sensitivity of all Hemoccult II slides, not just those stored for several days, and this does produce more false-positive readings (73).

This point can probably explain clinical results from the Sloan–Kettering screening program, in which hydration of Hemoccult II slides increased overall screening positivity from 3.7% to 5.4% (16). Unfortunately but not surprisingly, this was accompanied by a sharply decreased predictive value for neoplasia from 44% to only 19% (16). Thus the benefit of slide hydration is probably outweighed by an unacceptable decrease in test specificity. Macrae's dietary studies cited above (66) suggest that a strict meat-free diet may minimize the problem, but this remains to be tested in clinical trials.

It is apparent from these data that storage and hydration of Hemoccult slides can have an important impact on clinical screening programs, but the optimal clinical application of these variables is not yet clear.

Drugs

A number of drugs can influence the occult blood reaction. The clinical potential of this is self-evident.

Iron. Oral iron preparations have been blamed for producing falsely positive tests for over half a century, though a number of authors have disputed this (reviewed in References 20 and 74). Lifton and Kreiser (74) recently documented that ferrous sulfate and ferrous gluconate produce a high number of positive reactions in healthy subjects. Though these results could conceivably represent true positives due to GI mucosal irritation (75), ferrous salts in vitro also give positive Hemoccult reactions (74). In either case, it seems wise to avoid oral iron compounds before occult blood testing.

Aspirin. Aspirin is a well-known irritant to the GI tract and is commonly blamed for inducing GI hemorrhage (76). Studies with ^{51}Cr have documented that the drug increases fecal blood loss in healthy subjects, though usually by only a small amount (77,78). Because of this, it is commonly believed that acetylsalicylic acid can produce positive occult blood tests in the absence of GI pathology. Some new evidence, however, casts doubt on this (55,68,79), and the problem is probably not as important as feared. Nevertheless, it seems wise to interdict acetylsalicylic acid before occult blood testing if possible. Aspirin ingestors with positive results should probably be retested before colonic investigations are undertaken, because the likelihood of tumor is reportedly not increased unless tests remain positive after the drug is stopped (80).

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Ascorbic acid. This vitamin acts as an antioxidant and therefore interferes with the pseudoperoxidase reaction, yielding falsely negative results (81,82). This could be bothersome in view of the recent fad for high-dose ascorbic acid ingestion to ward off colds and other diseases.

Miscellaneous. Cimetidine may produce falsely positive Hemoccult reactions in gastric aspirates (83–85), but this does not appear to be the case in stool specimens (86,87); hence on current evidence this widely prescribed drug need not be feared in fecal occult blood studies. Povidone iodine, a surgical antiseptic, will produce positive reactions due to the strong oxidative properties of iodine (88,89). Barium sulfate in the stool after GI x-ray examinations does not influence the reaction (49), but laxatives may tend to diminish both false-positive and false-negative results (49). The possible influence of laxatives deserves further study. The long-standing belief that falsely positive guaiac tests can be produced by glyceryl guaiacolate (guaifenesin), a common cough medicine, has now been refuted (90,91). Finally, if stool specimens are preserved in formalin, a falsely positive benzidine reaction may result (92).

In summary, a number of technical factors can affect the clinical reliability of occult blood tests, yet considerable confusion still permeates the literature on many of these factors. Further clinical observations, especially well-designed controlled studies, may clarify some of the issues. However, greater hope probably lies in the evolution of better screening tests that are less subject to technical artifacts, for example, the immunochemical assays mentioned earlier (40–44).

Occult Bleeding in Known Colorectal Tumors

Reasons for Falsely Negative Tests

Earlier discussion emphasized falsely positive occult blood tests. Equally important is the problem of an unreactive test despite the presence of colonic neoplasm. This can occur for at least three reasons.

Test insensitivity. As noted above, fecal blood losses exceeding ~20 ml/day are needed for reliably positive Hemoccult reactions (38,49,54,55). Hence losses up to ten times "normal," and occasionally even more, can be missed. A rarer technical cause of false negativity is vitamin C ingestion (81,82), also noted above.

Non-bleeding of the tumor. Clinicians have long known that bowel cancers do not always bleed, yet surprisingly few quantitative data are available on this point. Doran and Hardcastle (55) recently documented large daily fluctuations from 0 to 75 ml/day in individual patients; values exceeded 10 ml in fewer than 25% of all daily collections. Macrae and St. John (73) also recorded highly variable losses, averaging only ~9 ml/day for right-sided lesions and <2 ml/day in left-sided carcinomas. Benign colonic polyps bleed even less (48,73). Recent colonoscopic correlations suggest further that only ulcerated tumors bleed (93,94). This is not surprising and is probably another reason for the absence of detectable blood with many neoplasms.

Chromium 51/chemical disparities. Occult blood is not uniformly distributed in feces, even if from an upper intestinal source (95); small stool samples can therefore test negative even though blood is readily demonstrable in other portions. By the same token, a single drop of blood from a low colorectal lesion will be detected by Hemoccult smear but not by abnormal ^{51}Cr-labeled red blood cell counts in the total stool (73). Radioassay might also detect labeled red cell debris not containing hemoglobin (34). Finally, hemoglobin degradation along the gut weakens pseudoperoxidase activity with resultant diminution of the chemical reaction (see above) but without loss of radioactivity. For these reasons comparison of chemical techniques with ^{51}Cr data is not always valid (34,73).

Clinical Findings

In view of the above points, it is not surprising that clinical studies have repeatedly documented a high proportion of negative tests in known bowel cancer. Indeed, modern figures show positive Hemoccult reactions in only ~50%–66% of patients with proven malignancy (41,55,73,94,96). Results are more likely to be negative in left-sided than in right-sided lesions (41,73,94), perhaps because of higher average blood losses from cancers in the cecum and ascending colon (73). Negative Hemoccult tests are even more common with benign colonic adenomas. Macrae and St. John (73) found that only polyps larger than 2 cm produced detectable bleeding, and several authors have reported negative Hemoccult reactions in >75% of patients with endoscopically proven adenomas (16,47,94,97).

Increasing the number of tests on each tumor patient will enhance the yield. Early on, Greegor (63) advised six Hemoccult smears on each subject, representing two separate portions of three consecutive bowel motions. This number has been widely adopted, even though arbitrarily determined. Several authors have documented that this does increase the yield over single testing (19,73,98), and the three-stool, six-smear Greegor program probably offers a reasonable compromise between undue inconvenience and undue false negativity. As discussed

later, however, whether this is optimal from a cost-benefit point of view is another question.

The yield can also be increased by rehydration of Hemoccult slides before addition of the test reagent (73). This decreases specificity (16,73), however, and on balance, slide hydration is probably not advisable (see above).

The above-noted results have major import for population screening programs. *The implication is that at least 33%, and perhaps 50%, of colorectal cancers in the screened population will be missed.* In fact, the figure may be even higher than this if subclinical cancers bleed less than the symptomatic growths from which the above data were derived. Thus the sensitivity (in the epidemiologic definition) of occult blood testing is actually quite low, probably only in the 50%–65% range. This important point is usually overlooked or minimized in discussions of screening results. If surveillance programs actually do miss ~50% of the potentially discoverable cancers, the overall value of the exercise may be considerably less than its proponents claim.

Uncontrolled Screening Studies

Reported screening studies fall into two groups, uncontrolled and controlled. Almost all are the former—in fact, all but two. They vary widely in size, recruitment methods, technical aspects, extent of investigation of test-positive individuals, etc. Most importantly, none compares outcome with that of a control group not subjected to screening.

Table 1 summarizes most of these studies (6,63,99–118). Selectively included are the important trials published in English; foreign-language papers and studies enrolling fewer than 2000 subjects are omitted, except for Greegor's original series (63). All listed studies used either Hemoccult or Hemoccult II, primarily the former. (*N.B.*: some of the data in Table 1 have been calculated from the authors' raw data).

Analysis reveals a number of important general points:

1. Published screening trials have varied enormously in scope, from a few hundred subjects (not

Table 1. Selected Uncontrolled Studies of Occult Blood Screening

Year, authors (reference)	No. enrolled	No. tested (%)[a]	Minimum age	Diet[b]	No. of tests	No. positive (%)[c]	No. of cancers/ polyps	Predictive value cancers/ polyps[d] (%/%)	% enrolled with cancer[e]
1969 Greegor (63)	—	278 (—)	"most" >40	Yes	6	24 (8.5)	2/3	8/14	0.72
1974 Hastings (99)	3,450	2,625 (76)	None	Yes	3	159 (6.1)	5/—	3/—	0.14
1977 Miller and Knight (100)	2,332	2,278 (98)	20	No	3	64 (2.7)	1/7	2/11	0.04
1977 Goodman (101)	2,500	1,749 (70)	35	Yes	3	9 (0.5)	0/—	0/—	0
1977 Helfrich et al. (102)	—	8,930 (—)	18	No	—	157 (1.8)	3/2	2/1	0.03
1978 Fruhmorgen and Demling (103)	6,007	5,016 (84)	40	Yes	3	136 (2.7)	13/83	10/61	0.22
1978 Heeb and Ahlvin (104)	5,740	3,956 (69)	—	Yes	3	79 (2.0)	5/5	6/6	0.09
1978 Elwood et al. (105)	11,115	1,690 (15)	55	Yes	3	58 (3.4)	2/—	3/—	0.02
1979 Bralow and Kopel (106)	3,798	3,008 (79)	40	Yes	—	329 (10.9)	7/11	2/3	0.18
1980 Winchester et al. (107)	54,101	14,074 (26)	-	Yes	6	617 (4.4)	30/40	5/7	0.06
1980 Kurnick et al. (108)	—	5,420 (—)	—	No	4	120 (2.2)	9/—	8/—	0.17
1980 Gnauck (6)	—	16,100 (—)	45	—	—	531 (3.3)	75/106	14/20	0.47
1980 Schwartz et al. (109)	—	3.48×10^6 (—)	30	—	—	38,030 (1.1)[f]			0.01
						4,262	332/—	8/—	
1980 Larkin (110)	5,840	5,565 (95)	—	Yes	3	780 (14.0)	4/6	1/1	0.07
1980 Chambers and Morgan (111)	2,500	1,160 (46)	40	No	3	68 (5.9)	3/10	4/15	0.16
1981 Stuart et al. (112)	6,574	4,498 (68)	None	—	1	234 (5.2)	13/31	6/13	0.20
1981 Farrands et al. (113)	8,925	2,439 (27)	40	No	3	124 (5.1)	4/8	3/6	0.04
1982 Million et al. (114)	5,812	1,646 (28)	40	No	6	37 (2.3)	2/5	5/16	0.03
1983 Sontag et al. (115)	13,522	2,964 (22)	40	Yes	6	135 (4.6)	14/44	10/33	0.10
1983 Hardcastle et al. (116)	9,807	3,613 (37)	45	Yes	3	77 (2.1)	12/27	16/35	0.12
1983 Siba (117)	—	3,791 (—)	45	No	6	97 (2.6)	6/18	6/19	0.16
1983 Habba and Doyle (118)	2,143	1,628 (76)	40	No	6	37 (2.3)	5/6	14/16	0.23

[a] Number and percentage of enrolled subjects who returned the test slides (compliance). [b] Low-peroxidase, high-residue diet advised before testing. [c] Number and percentage of tested subjects with at least one positive result. [d] Predictive value of a positive test for cancer and for benign polyps. [e] Percentage of enrolled subjects found to have bowel cancer through occult blood testing. In studies not giving number of enrolled subjects, percentage of tested subjects. [f] Larger number = overall positive tests. Smaller number = reported subgroup examined for cancer.

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included in the table) to a massive German project involving over 3 million people (109). Most studies enrolled 2000-5000 subjects, with only a handful exceeding 10,000.

2. Compliance also varied widely. In a number of trials only 15%–30% of enrolled subjects returned the slides, although most figures were in the 50%–70% range. Compliance is an important subject and is therefore discussed more fully below.
3. About half of the authors advised a meat-free, high-roughage diet before stool collections, whereas the other half imposed no dietary restrictions. Diet was not associated with any discernible trend in the yield of occult bleeding or in the predictive value of a positive test.
4. Most screening programs had an overall positivity rate of between 2% and 6% of tested individuals. Rates were only occasionally in the 10% range. Only in the study by Bralow and Kopel were the slides routinely rehydrated before testing; of interest, this trial yielded both an unusually high rate of positivity (10.9%) and an unusually poor predictive value for cancer (2%) (106).
5. In most studies the predictive value of a positive test for colorectal carcinoma was only in the 5% range, and in several trials cancer was uncovered in 2% or fewer of test-positive individuals. Only a handful of authors reported a predictive value as high as 10%. *Thus only a small minority of positive test results was due to cancer.*
6. Benign colonic polyps were detected in almost all studies, usually more frequently than cancer. Even so, the predictive value for polyps was usually <20%, although figures varied quite widely. The variation was undoubtedly due in part to the vigor with which patients were investigated, in particular whether colonoscopy was undertaken.
7. Most of the positive results, when stated by the authors, were associated with trivial pathology such as hemorrhoids, and colonic diverticula (data not shown in Table 1). A few cases of upper GI pathology were uncovered by some authors (data not shown). In some studies, positive results were not corroborated on retesting, with or without dietary restrictions. The remaining occult blood-positive subjects had no discernible GI lesions.
8. Overall, most screening programs uncovered colorectal cancer in ~0.03%–0.20% of all persons initially enrolled (last column in Table 1); i.e., 3–20 persons for every 10,000 entered. A few trials had even lower figures; a few had higher. This variation is explicable by differences in compliance, population selection, number of samples tested, aggressiveness with which positive results were pursued, etc. A potentially important factor, ignored by almost all authors, is storage artifact. Almost certainly several days passed in most studies before the Hemoccult slides were tested, which is known to weaken or negate some positive results (as is discussed above).
9. A number of authors reported that detected tumors tended to have an earlier Dukes' staging than might be expected from general experience (101,106,107,110,112,115,116,118). This point is repeatedly cited as evidence for the efficacy of screening in effecting a better prognosis (101,107,110,115,119). As stressed from earlier discussion, however, this is fallacious reasoning and no such conclusion can in fact be reached—lead time bias and length bias will automatically ensure an earlier average Dukes' stage for screen-detected cancers, quite independently of whether any prognostic advantage ensues (8,12–14).

Controlled Screening Studies

Despite the huge literature on occult blood screening, it is quite remarkable that only two controlled studies are available to assess its value. Both are ongoing projects, still underway.

University of Minnesota Program (60,98,120–123)

This is a 10-yr trial conducted by Gilbertsen and his associates at the University of Minnesota. It involves ~45,000 subjects aged 50 yr or more, randomized (60) into one control and two experimental groups. The latter are tested for occult bleeding every 1 or 2 yr, respectively; the Greegor regimen is used with a meat-free diet and six mail-in Hemoccult smears. Subjects having at least one positive test undergo sigmoidoscopy, colonoscopy with or without barium enema, and upper GI assessment in selected cases. The project involves 5 yr of testing plus an additional 5-yr follow-up period; the latter is still in progress. Gilbertsen et al. hope to demonstrate a significant reduction in mortality from colorectal cancer in the two screened groups compared with the control group.

Preliminary results have been published (60,98,120–123). These include:

1. Compliance with Hemoccult testing has been ~75% (60).
2. Overall Hemoccult positivity was initially 1.8% of the experimental subjects but jumped to 3.5% in mid-1977 when rehydration of the Hemoccult slides was introduced (60).
3. At latest report, more than 2000 test-positive people had been evaluated and over 100 cancers detected (including a few cases of gastric and pancreatic carcinoma) (120,123). The predictive

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value of a positive test was 8% for cancer and 29% for polyps overall, although values increased with patient age. Ongoing surveillance has yielded additional tumors, but with a lower predictive value than on initial screening (120).

4. Barium enema was inadequate for tumor detection, as it missed 33% of the cancers and 66% of the polyps found by colonoscopy (121).
5. Most of the detected cancers had favorable staging; in a 1980 report (121), 65% were Dukes' A and 13% Dukes' B, although updated 1982 figures were not quite so favorable (123). Whether this is translatable into a better long-term prognosis remains to be seen.

Comments. This is an important study. The parallel control group should eventually permit assessment of cancer outcome relatively free of lead time, length, and selection biases. There are sufficient entrants to permit statistically valid conclusions on mortality (60). A change to slide hydration in the middle of the protocol will probably affect ultimate results, but this is not a major problem. Another weakness is the use of mail-in slides with its attendant time delay before testing; undoubtedly fresh sampling would have detected more tumors. Additionally, other than general statements (98), no analysis of costs has been undertaken to date. This may eventually become a critical point, especially if screening is ultimately shown to benefit prognosis but only marginally.

Most importantly, until the follow-up period is complete around 1987, it is inappropriate to speculate whether the screened population will have a lower cancer mortality. Gilbertsen recognizes this central point and has frankly stated, "There is no proof of the merit of the Hemoccult examination in improving the prognosis for people with colorectal cancer" (98).

Sloan–Kettering Program (16,19,124–127)

This project is under the direction of Winawer and his colleagues at the Memorial Sloan–Kettering Cancer Center and its affiliated Strang Clinic in New York City. It involves ~22,000 subjects aged 40 yr or more, all of whom had sigmoidoscopy. The study group, comprising about 66% of the subjects, additionally underwent Hemoccult testing using the Greegor dietary regimen. Thus unlike the Minnesota study, this program compares a test group undergoing sigmoidoscopy plus occult blood screening with a control group having sigmoidoscopy alone.

In the midst of the study Hemoccult was replaced by Hemoccult II because of the manufacturer's substitution. Slide hydration was later introduced at one point but was soon abandoned because of lower specificity (16,19). Throughout, however, slides have been examined within 4 days of stool collection in order to minimize storage artifact. As in the Minnesota program, test-positive subjects undergo thorough colonic evaluation. Annual follow-up with repeat testing is urged but is not essential to the protocol.

Preliminary results have appeared in several publications (16,19,124–127). These include:

1. Compliance with Hemoccult testing has been ~75% overall, similar to the Minnesota experience. Initial cooperation was somewhat better than with repeat testing (19).
2. Overall positivity varied from ~1% with Hemoccult to 5.4% with hydrated Hemoccult II (16,19). Test positivity increased with patient age (19,127).
3. At latest report ~400 test-positive individuals had been investigated, with an overall predictive value of 12% and 36% for cancer and polyps, respectively (126). With the original Hemoccult, 50% of positive subjects had colorectal neoplasia (12% carcinomas and 38% adenomas) (16,19), but the predictive value fell to 44% with Hemoccult II and plummeted to only 19% when slide hydration was temporarily introduced (16,19). The authors did not state the relative proportions of cancer and of polyps in this 19%, but malignancy was probably found in only ~5% of subjects who gave positive tests with hydrated Hemoccult II. As with Gilbertsen's Minnesota experience, the predictive value of a positive test increased with patient age (126).
4. Detected cancers generally had favorable Dukes' staging (19,125), although the reported numbers are too low to make definite statements.
5. Some data comparing Hemoccult testing with sigmoidoscopy are available. Hemoccult missed ~25% of the cancers and no less than 75% of the benign polyps detected by sigmoidoscopy (16). These figures may not necessarily apply to lesions above the rectosigmoid area, but it is nevertheless clear that occult blood screening failed to detect a very substantial proportion of neoplasms.

Comments. The Sloan–Kettering program has already yielded a lot of valuable information. Overall results are similar to the Minnesota findings, which lends credence to both studies. Important additional information is also provided, for example, the data on false negativity of Hemoccult in rectosigmoid lesions. As with the Minnesota study, however, the data do not yet permit conclusions on whether occult blood screening improves survival. Several more years will likely be needed for this.

There are a number of weaknesses in this project, mostly minor. Fewer subjects are entered than in Minnesota, so more time will be needed for mortality results to achieve statistical validity. Enrollees all voluntarily sought health surveillance, and are primarily well-educated, middle class individuals (19); because of subject bias, results in this well-motivated group may not necessarily apply to the population at large. Test and control subjects were not statistically randomized, but were instead assigned by sequential calendar period (125); this was done carefully without patient or physician preselection (125), but patient allocation was nevertheless less ideal than the true randomization of Gilbertsen's design (60). A small proportion of test subjects already had colonic symptoms; this subgroup had a higher yield of lesions, thereby skewing results somewhat in favor of testing (125). Economic aspects of the program have not been reported, although Winawer et al. (125) apparently do plan to address this important issue. Finally, there is no control group of subjects who undergo neither occult blood testing nor sigmoidoscopy. Thus the Sloan–Kettering study can eventually provide conclusions on the incremental benefit of Hemoccult testing over sigmoidoscopic surveillance, but not on benefits compared with no screening at all.

Compliance

No cancer detection program will be successful unless the target population cooperates. This is a complex sociological issue believed to involve demographic factors (128–130) as well as individual beliefs and motivations (128). Nevertheless, a study of the Sloan–Kettering subjects revealed relatively few major differences between compliers and noncompliers (128). More research is obviously needed to clarify what inherent differences may exist between the two groups.

As shown in Table 1, individual compliance in reported occult blood trials has varied widely from a low of 15% to a high of 98%, with most figures in the 50%–70% range. Analysis reveals that authors reporting good compliance are usually dealing with a highly motivated or selected group of volunteers (or both), not typical of the general population (19,99,100,106,110,131). Probably more representative of general public attitudes are results from some of the disappointing screening trials (111,113,114,132,133). Moreover, the three most carefully documented studies of compliance with Hemoccult testing have all shown dismal results:

1. Elwood et al. (105) assessed five different methods of patient contact among some 11,000 subjects, ranging from impersonal mailings to individual home visits. Results showed an overall response of only 15%, and compliance was <30% even with the best method of contact. The same authors incidentally found that neither dietary restrictions nor postage for the Hemoccult slides was a significant factor (105).
2. Sontag et al. (115) also assessed the method of contact on compliance, in a Veterans Administration setting. Overall, a mere 22% of the distributed Hemoccult kits were returned, though figures varied widely with the type of approach. Among patients regularly attending the outpatient clinic and given a personal explanation by the nurse, compliance was still a disappointing 30% (115).
3. Winchester et al. (107) analyzed a Chicago study in which >50,000 Hemoccult kits were distributed to people requesting them from the American Cancer Society. This followed a large-scale publicity campaign involving television, radio, and newspaper promotion. Despite the fact that subjects had to request the slides, only 26% returned them. Interestingly, compliance was better when people were charged $2.00 for the kits than when the Hemoccult was distributed free of charge (107).

Despite these discouraging findings, community screening programs can occasionally be more successful, though these successes clearly come at the price of extensive groundwork preparation and aggressive public education programs (104,106,134).

Several authors have found that the elderly are less compliant with occult blood programs than middle-aged subjects (105,113,114,116,129,132). This is a major weakness of the whole screening concept, in that the risk of bowel cancer (135), the likelihood of a positive test (19,127), and the predictive value of a positive result (120,126) all progressively rise with age. Thus those individuals most likely to be helped by screening are paradoxically least likely to cooperate.

A separate but equally important issue is patient failure to undergo colonic investigations once occult blood is detected. Several authors have commented on this problem (99,107,136,137). For example, Hastings (99) found that only ~33% of occultly bleeding subjects were properly evaluated, and 33% of Sterchi's (136) patients were lost to follow-up despite "great effort and a significant amount of manpower." More than 33% of cases were also lost in the large Chicago study cited above, despite three written notices followed by three telephone calls to Hemoccult-positive people (107).

This problem is not due entirely to patient reluctance. Withers and Wienke (138) found that the majority of Hawaiian physicians who frequently used Hemoccult failed to arrange the appropriate investigations on test-positive patients, and Macrae

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et al. (139) recently reported similar misconceptions among Australian physicians: <60% would advise sigmoidoscopy for occultly bleeding patients, and only 33% would recommend colonoscopy. Thus physician ignorance is clearly a factor in the noninvestigation of Hemoccult-positive patients, and strategies to improve cooperation with public screening programs should be directed at physicians as well as the laity.

From these various studies, *it is apparent that poor compliance is an important stumbling block to the adoption of occult blood screening programs for the general public.* A high level of community awareness and education can enhance cooperation among both the public and physicians, but this requires extensive resources, manpower, and time to achieve.

Costs

Questions of cost may be distasteful to scientists but are critical to society. Yet this vitally important issue has received remarkably little attention in the massive literature on occult blood testing. Occasional authors have made superficial comments on the immediate costs of their screening programs (106,118,140), but most do not even mention the subject. Only a few have devoted deeper thought to this issue, most notably Eddy (141,142) and Neuhauser and Lewicki (143,144). Admitting the complexity of the situation and conceding that there is no "correct" answer, Eddy has pointed out a number of cost-relevant factors in bowel cancer surveillance such as choice of tests, age limits for screening, and frequency of surveillance. Decisions on these issues can have a profound impact on cost effectiveness (141). Eddy also puts matters into perspective by pointing out that even effective cancer detection programs would have only a minor impact on average life span, and that resources are often much more economically spent on primary rather than secondary prevention—e.g., convincing the public to stop smoking instead of screening for lung cancer (141).

On the face of it, occult blood screening seems cheap. A kit of three Hemoccult slides costs little and is usually given to patients either free of charge or for a nominal fee. But *the bulk of the costs lies in the investigation of false-positive results.* Data from most screening programs show that ~2%–6% of screened subjects are Hemoccult positive, but only ~5–10% of these have cancer (see earlier discussion). Thus ~2%–5% of all screened subjects will needlessly undergo sigmoidoscopy, air-contrast barium enema, or colonoscopy, or all of these. These are expensive tests.

Even with these considerations, the few authors who do comment on their screening costs claim that occult blood surveillance is inexpensive. Bralow and Kopel (106), for example, estimated an expense of <$2500 for each cancer found, excluding physicians' fees, and Norfleet and Roberts (140) claimed that the investigation of 14 Hemoccult-positive patients totalled <$4000. Such estimates are remarkably naive. None of the authors has even mentioned, let alone analyzed, the combination of direct, indirect, and "hidden" costs, which should be considered.

Direct Costs

These include the Hemoccult kits, which are cheap; fees for sigmoidoscopy, air-contrast barium enema, or colonoscopy (or all of these) for ~2%–5% of all screened subjects, which is not cheap; and physicians' fees. The latter will often involve not only the patient's own doctor, but also a gastroenterologist or surgeon for consultation and colonoscopy on test-positive subjects; none of the literature mentions this.

Indirect Costs

These include expenses of establishing and running the program such as resource personnel, secretaries, postage, and cost of nurses' or receptionists' time for contacting patients and pursuing noncompliant subjects. From reading between the lines of many reports, it is clear that these expenses are often considerable. Additional indirect costs arise from public education programs—such as media charges and publicity. These expenses can be high. For example, in Bralow and Kopel's project a massive community education effort was expended including the importing of nationally prominent scientists, promotion via television, radio, newspapers, and posters, and establishment of county-wide distribution centers. These expenses were all conveniently ignored in the cost calculations (106).

"Hidden" Costs

Occult blood programs have a number of important additional "costs" which are not readily apparent.

1. Patient time and inconvenience. About 2%–5% of all screenees will needlessly waste many hours visiting doctors and undergoing uncomfortable and traumatic investigations. Time lost from work, transportation expenses, etc. are hidden costs of considerable magnitude. *It must also be remembered that 10–20 asymptomatic people will undergo these procedures for every one in*

whom bowel cancer is detected (based on a predictive value of 5%–10%; see above).
2. The physical hazard of unnecessary colonic investigations. Sigmoidoscopy, barium enema, and colonoscopy are not only expensive, uncomfortable, and often painful—they also carry a small but finite hazard.
3. Emotional agony. Fear of malignancy, stress from undergoing complex tests, etc. are an important "cost" for test-positive subjects, which are not always appreciated.
4. A false sense of security can be engendered in screen-negative subjects, who may then fail to seek medical attention if bowel symptoms do develop. This is probably a real but minor problem.
5. Finally, a critically important cost is the waste of precious medical resources for the evaluation of false-positive results. Physician and clinic time, radiologic and endoscopic facilities, etc. are needlessly occupied. This is not mentioned in papers on the subject but is important. Thus, if nationwide programs of occult blood detection were instituted in the United States and Canada for all citizens over 40, each year literally hundreds of thousands or even millions of people would require colonic investigations, the large majority of whom would have no significant bowel pathology. This would impose a major logistic and economic burden on the health care system and would seriously detract from the more fruitful use of medical resources.

All these costs must be weighed against the savings that would accrue from success of the screening program. Thus early surgical intervention as a result of screening might decrease expenses from advanced malignancy, increase productive life span, minimize grief and suffering, etc. Attempts have been made to estimate such savings (142,145,146), but these are crude and subject to major error. Complex computer models of cost-affecting factors have been designed (142,147), and opaque mathematical papers have even been written on the subject (148). Whether this approach will prove helpful remains to be seen. Currently, however, estimates on both sides of the equation are so prone to error that a reasonably accurate estimate of costs versus savings seems an almost impossible goal. Furthermore, even if better estimates were available, they would not solve the central philosophical issue of how much improved health is "worth"; this is a question of personal and political values, not scientific fact.

Arguments about the polyp–cancer sequence (149–151) are also relevant to cost considerations. Benign polyps are detected more frequently than cancer in most screening studies, certainly when colonoscopy is included in the evaluation (see above). Moreover, most authors remove polyps discovered at colonoscopy; this adds substantially to the costs (and risks) of the patient's evaluation. If one accepts the polyp–cancer sequence (149,150), then removal of benign adenomas discovered through occult blood detection can be viewed as true prevention of cancer. On the other hand, polyps are common in the general population (152) and only a very small fraction are invasively malignant (150,153). Whether one can justify the massive effort and costs involved in removing benign lesions from a large number of asymptomatic people is therefore a complex issue. The question cannot be debated here, but its resolution will bear on the cost effectiveness of occult blood screening.

Cost-benefit aspects of Hemoccult programs are also influenced by the number of tests done on each individual. The six-smear regimen devised arbitrarily by Greegor (63) is widely used, and it is certainly true that increasing the number of tests will enhance the yield of tumors (19,73,98). However, there is little scientific evidence to determine just where the line should be drawn. In an important but controversial paper, Neuhauser and Lewicki (143) attempted to analyze the marginal costs of each additional Hemoccult test. Using Greegor's original data, they concluded that the sixth test actually costs millions of dollars for every additional cancer detected (143)! Neuhauser subsequently commented further on his original calculations (144). Though Neuhauser and Lewicki's study (143) involved a number of undoubtedly fallacious assumptions, their basic thesis seems valid—i.e., that a seemingly cheap test can actually become very costly in relation to the number of cases detected. It is certainly possible that the marginal cost of each additional test beyond, say, two or three, may quickly become prohibitive. Objective data are needed to clarify this point.

Finally, but not least, *cost considerations are meaningless unless the screening procedure is of proven benefit.* As discussed earlier, any putative mortality benefit from occult blood screening is as yet unproven, and the jury will remain out until results from the Minnesota and Sloan–Kettering trials become available. For this reason alone, a serious argument can be advanced that any money spent on additional uncontrolled occult blood testing is unjustified.

Conclusions

Occult blood surveillance for colorectal cancer is an important concept with several arguments in its favor. These include the high prevalence of the

tumor, longer patient survival with earlier disease stage, and the potential to abort cancer by detection of premalignant polyps. Moreover, occult blood testing appears simple, safe, and cheap, and clinical experience has amply proven that it can in fact uncover asymptomatic bowel cancer. To many, these points make the value of occult blood surveillance self-evident.

Potent counterarguments exist, however, some of which are not widely appreciated. Due to lead time and length biases, earlier disease detection is not equatable with improved survival. The occult blood reaction is actually far from "simple," and is beset with technical issues that influence clinical results. Sensitivity and specificity are both relatively low; as a result, many tumors are overlooked and too many healthy people are needlessly put through colonic investigations. Public compliance is often poor, and a number of indirect and "hidden" costs make surveillance programs much more expensive than is superficially apparent. Most importantly, controlled data are not yet available to answer the central question of whether screening decreases mortality from colorectal cancer.

At the moment, therefore, occult blood surveillance remains an appealing but unproven concept. On balance, it may be prudent to hold further screening programs in abeyance until mortality results from the Minnesota and Sloan–Kettering controlled trials become available. Further uncontrolled studies are unlikely to provide much useful information, as those already reported have generally yielded similar results and have pretty much milked the subject dry.

Some of the problems with occult blood screening may be minimized by the further evolution of immunochemical tests specific for human hemoglobin. This would diminish false-positive reactions, the dominant factor now limiting cost effectiveness of Hemoccult screening. Immunochemical specificity may be sufficiently important to swing the pendulum in favor of surveillance programs eventually, but further studies are needed to assess the method's clinical validity.

In 1978 the National Institutes of Health held a "Consensus Conference" devoted to screening and early detection of colorectal cancer. Though many conflicting opinions remained unresolved, the gathered experts agreed on a summary statement (154). The following quote is taken from that summary:

> There are insufficient data to indicate that screening for colorectal cancer by stool occult blood testing reduces mortality from the disease in screened populations participating in clinical trials. More time is needed for the ongoing clinical trials to collect enough additional data for assessment of survival benefit, risk possibilities, and economic feasibility. Although it is recognized that decisions must sometimes be based on incomplete evidence, caution is advised in the development of recommendations about mass screening programs for colorectal cancer at this time. This caution is based on the absence of a clear demonstration of (a) improved survival rates in screened individuals with colon cancer or (b) a net margin of benefit to health in comparison with the costs and risks entailed in the further study of all positive occult blood reactions by barium enema and/or endoscopy (154).

This overall conclusion seems as appropriate today as when it was written 7 yr ago.

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