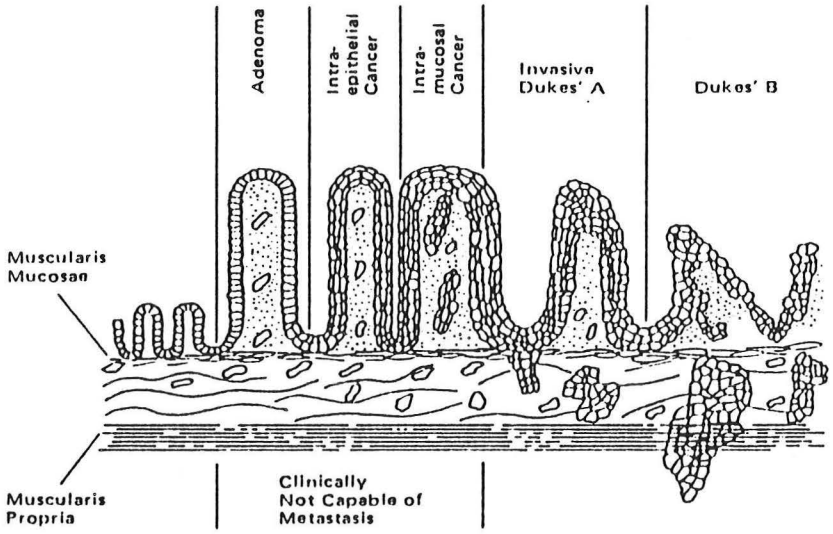
SCREENING FOR COLORECTAL CARCINOMA



Schematic diagram of the continuum of colorectal neoplasia. [1]

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INTRODUCTION

Cancer of the colon and rectum is now the second leading cause of cancer deaths in men and the third leading cause of cancer deaths in women. Estimates by the American Cancer Society for 1988 included 147,000 new cases with 61,500 projected deaths. Unfortunately, age-adjusted death rates for this disease have remained relatively stable for the past 30 years. Roughly 6% of our population will develop colorectal carcinoma over the course of their lifetime, and 6 million Americans currently alive will ultimately die because of this (2).

What can be done to reduce the morbidity and mortality of this disease? Approximately 60% of patients currently present with advanced colorectal carcinoma (Dukes' B_2 - D) (3). Treatment of the latter has traditionally been a frustrating exercise in futility with an overall 5 year survival of 25% (4). As reviewed by Dr. Graham Smith in a recent Grand Rounds, new data from large well -designed clinical trials demonstrate a small but reproducible benefit to post - surgical adjuvant chemotherapy for Dukes' B_2 and C colon cancer (4). It is unlikely, however, that this will translate into dramatically improved survival for most patients.

A decrease in the incidence of colorectal cancer through primary prevention would require the identification of specific genetic, biologic, or environmental factors that are etiologic, and altering their effects on carcinogenesis (5). Although epidemiologic data exist to support the role of high intake of dietary fat and reduced intake of fiber and calcium in the pathogenesis of this disease, it would take decades to measure the benefit of any dietary changes that Americans, as a group, are not particularly willing to embrace (6).

Similarly, despite recent advances in our understanding of the somatic genetic alterations in sporadic colorectal carcinoma and germ cell alterations in familial

polyposis syndromes that underlie the progression from benign polyp to true cancer, practical applications with regard to disease prevention are remote (4).

Secondary prevention - a reduction in the consequences of a disease through early detection and treatment - would seem the most sensible approach, given the high survival reported for patients with localized, surgically resectable disease (Dukes' A-B_1; 80-65%) (7). As noted by Bresalier and Kim, however, "the implicit but unproven assumption is that early detection improves prognosis" (5). This morning I would like to review the various approaches that are currently recommended to screen for colorectal cancer and the evidence for and against these modalities in specific risk groups and the population as a whole.

THE ADENOMA - CARCINOMA SEQUENCE

It is likely that early detection of colorectal carcinoma is an inferior method compared to that in which treatment is applied to the benign premalignant lesion, the adenomatous polyp (8). For this reason, it is appropriate to review what is currently known about the adenoma - carcinoma sequence.

Colonic polyps may be divided into 2 major groups - neoplastic which include the adenomas and carcinomas, and non - neoplastic. The latter includes mucosal polyps, hyperplastic polyps, juvenile polyps, and inflammatory polyps, all of which seem to lack neoplastic potential (9). It is now generally accepted that most colorectal carcinomas arise from previously benign adenomatous polyps. Although the adenoma - carcinoma sequence has not been proven directly, there is much data in the literature to support this concept:

1) There are anecdotal reports of patients refusing polypectomy of adenomatous polyps (biopsied and found to be histologically benign) that subsequently were replaced by in situ cancer (11, 12).

2) Clinical studies have reported a reduced incidence of rectal cancer in populations followed by rigid sigmoidoscopy and polypectomy (13).

3) There is a good epidemiologic correlation between the prevalence of adenomas and carcinomas within a population; multiple adenomas are associated with a higher incidence of cancer in given indindividuals (14). As for prevalence as a function of age, adenomas initially occur between 40 and 45 years of age and then increase steadily with each decade, while the occurrence of colorectal cancer is delayed by 5-10 years and then follows the same proportional increase (11, 12).

4) A synchronous adenoma can be found in 1/3 of colons containing 1 cancer, and in 2/3 of colons containing 2 or more synchronous cancers (15,16).

5) Invasive cancer is frequently contiguous with adenomatous tissue (11, 12).

6) Well - described patterns of cellular dysplasia (11,12,16) and chromosomal aberration are described in adenomas of increasing size (17).

7) Adenomas of familial polyposis, a recognized premalignant state, are similar to adenomas in the general population (11, 12).

Knowledge of the prevalence, growth rates, and transformation of adenomatous polyps is obviously crucial to the design of a cancer screening program (9). I will therefore summarize the literature that presently exists on these subjects.

Adenomatous polyps occur at approximately one-tenth of the frequency of hyperplastic polyps. They demonstrate all sizes and shapes, and they grossly are pedunculated, sessile, or semi- sessile. Irrespective of gross appearance, they have all the cytologic characteristics of neoplasia. Cell division (restricted to the lowest one-third of the crypts of Lieberkühn in normal tissue) is unrestricted and is observed at all levels of the adenomatous crypt (18). In Muto's pathologic review of 2506 adenomatous polyps 70% demonstrated mild dysplasia, 20% moderate

dysplasia, and 10% severe dysplasia. One-third of the latter also demonstrated foci of invasive carcinoma. This is similar to proportions noted by other authors (16).

Adenomas may also be classified into three histologic types: adenomatous polyp (tubular adenoma), villous adenoma, and an intermediate type (tubulo - villous adenoma). The adenomatous polyp demonstrates branching tubules embedded in lamina propria. These polyps are most frequently pedunculated but may be sessile and occasionally quite large. The typical villous adenoma consists of pointed or blunt finger - like processes of lamina propria covered by epithelium which frequently reaches down to the muscularis mucosae. These are more frequently sessile than pedunculated and can cover a large surface area. The tubulo - villous adenoma demonstrates a mixed or intermediate picture (16). In Muto's series, 75% of the polyps were tubular, 15% intermediate, and only 10% villous (16).

Three factors have been determined from large pathologic reviews to correlate with increasing malignant potential. These include size, histologic type, and degree of dysplasia (9,16). The following tables (1-3) (16) summarize this data:

Adenomatous Polyps and Villous Adenomas:
Size and Percent of Carcinoma

Size of tumor	Total number	Number with malignancy	Percent
Under 1 cm	1479	19	1.3
1-2 cm	580	55	9.5
Over 2 cm	430	198	46.0

Adenomatous Polyps and Villous Adenomas:
Relationship of Histological Type to Percent of Carcinoma

Histological type	Total number	Number with malignancy	Percent
Tubular adenoma	1880	90	4.8
Intermediate type	383	86	22.5
Villous adenoma	243	99	40.7

Adenomatous Polyps and Villous Adenomas:
Grade of Atypia and Percent of Carcinoma

Grade of atypia	Total number	Number with malignancy	Percent
Mild	1734	99	5.7
Moderate	549	99	18.0
Severe	223	77	34.5

The relative importance of these different factors is difficult to assess. Table 4 summarizes the effect of their interactions.

Table 4

	PERCENT WITH CARCINOMA		
	Size		
Histological type	Under 1cm	1-2cm	Over 2cm
Tubular	1.0%	10.2%	34.7%
Intermedidte	3.9%	7.4%	45.8%
Villous	9.5%	10.3%	52.9%
Grade of Atypia			
Mild	0.3%	3.0%	42.3%
Moderate	2.0%	14.4%	50.0%
Severe	27.0%	21.1%	48.0%

(Adapted from references 9 and 16)

What then is the probability of a given adenomatous polyp becoming a cancer? Moore and La Mont estimate the risk to be approximately 1 in 100, others higher (6,8).

What is the prevalence of adenomatous polyps in the general population? The only available data to answer this question come from autopsy series in various parts of the world and endoscopic examinations in asymptomatic people. The former series indicate that adenomas can be found in 12% of low risk populations and up to 40% of high risk populations, with the U.S. falling in the middle of this spectrum (9). Since age is the single most important predictor of adenoma prevalence, this could translate into a 50-60% occurence in older Americans (19). Flexible sigmoidoscopy has demonstrated adenomatous polyps in 8-12% of asymptomatic Americans over 40 (10,19A), 100cm colonoscopic examination 17% (19B).

What is known about the transformation interval from adenomatous polyp to malignancy? Information pertaining to this question traditionally comes from two sources - autopsy series comparing the average age of patients with adenomas of various stages and invasive cancer,and studies in patients where polypectomy or surgery was deferred and patients were followed by sequential endoscopic or radiographic examinations. In the following table data from Kozura et al (20) suggests that it takes on the average 11.5 years to go from minimal dysplasia to invasive cancer.

TABLE *Average Ages of Patients with Polyps and Invasive Cancer*

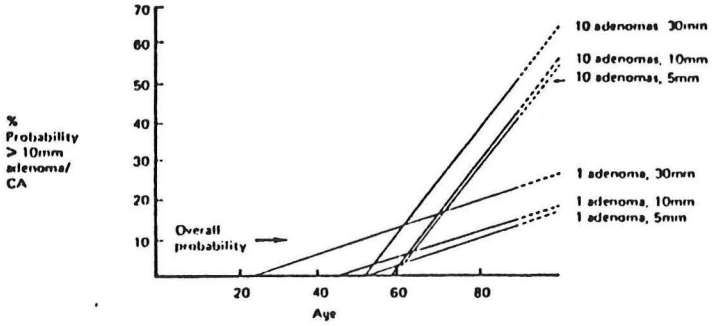
	Number of Patients			Average Age Patients (Years)	Age Difference from Patients Whose Cancers Were Found at Autopsy (Years)
	Male	Female	Total		
Grade 0	13	3	16	43.6 ± 15.5	15.1
I	36	10	46	40.7 ± 14.1	18.0
II	63	18	81	45.6 ± 13.7	13.1
III	55	20	75	47.3 ± 14.9	11.4
IV	45	21	66	50.4 ± 14.6	8.3
V	28	19	47	55.1 ± 15.4	3.6
Invasive cancer in surgical specimen	147	114	261	55.6 ± 14.7	3.1
Invasive cancer found at autopsy	1,857	1,321	3,178	58.7 ± 15.2	

Tada et al estimated volumetric doubling times from sequential double contrast barium enema exams in 11 patients with benign adenomas. It is important to note that 5 of these did not grow at all during the follow-up period which ranged from 420-816 days. However, calculations based on the remainder would suggest that even adenomas that grow do so very slowly (21).

Most recently, preliminary data from the National Polyp Study which will be discussed further later in this Grand Rounds indicates that it takes an average of 10 years for a neoplastic polyp to form from normal appearing colonic mucosa and degenerate into an invasive cancer (22).

What is the risk of synchronous or metachronous adenomas and cancers in patients with 1 or more adenomatous polyps? A patient with one known neoplastic polyp in the colon or rectum has a 30-50% chance of having at least one other synchronous adenoma elsewhere (23,24). The risk of subsequent neoplasm is 20-40% (24,25) and as the following figure shows increases progressively with age and number and size of adenomas at initial polypectomy.

Figure 1 (25)



Relationship between the combination of age, number of adenomas, and largest size of adenoma at initial polypectomy and the probability of finding a larger adenoma or carcinoma at follow-up.

ISSUES IN SCREENING

In 1979 the Canadian Task Force issued a report stating that there was fair justification for including yearly fecal occult blood testing in the periodic health examination of people over 45 years of age (26). In 1989, they re-reviewed the literature and concluded that there was "insufficient evidence to recommend the inclusion of screening for colorectal cancer by means of fecal occult blood testing or sigmoidoscopy in the periodic health examination of people over 40 years who have no risk factors for colorectal cancer." The evidence was "equally insufficient, however, to warrant stopping this practice where it already exists" (27).

This reversal of opinion brings to light many of the controversial issues involved in designing screening programs to detect cancer, and how these issues impact on our evaluation of the suitability and efficacy of currently available screening methods. Criteria for a successful screening program have been outlined by several authors (28-30) and include the following:

1) the disease must have an asymptomatic period during which cases detected by screening can be expected to have an improved prognosis as compared to cases detected after symptoms occur

2) the disease must have serious consequences for the population

3) available screening techniques must be sensitive enough to make detection likely

4) screening techniques must be specific enough to make follow-up to differentiate between false positives and true negatives worth the expense and risk

5) the incidence of the disease must be high enough to justify the cost of screening.

Agreement exists that colorectal cancer satisfies the first 2 criteria; evidence concerning the latter 3 is conflicting (5). In a critical review of occult blood screening, Simon (31) noted that many studies report sensitivity figures derived from patients with proven, clinically apparent bowel cancers. This procedure is flawed in that when the test is then used in a population of asymptomatic persons, the sensitivity is likely to be much lower than the estimate based on persons with manifest disease. In the case of the fecal occult blood test one way to determine true sensitivity would be to colonoscope all (+) and (-) cases however this is obviously impossible. Alternatively, all test negative subjects can be followed to determine how many cancers eventually turn up among them - this requires a lengthy careful follow-up and is frequently not pursued.

Specificity refers to the proportion of non-diseased subjects in whom a test is appropriately negative. In the screening of asymptomatic persons this is as important as sensitivity, because false positive tests expose normal individuals to further evaluation that can be expensive and risky (32). To put this in perspective, the specificity currently quoted for Hemoccult is 97-98%. While this seems high - a false (+) rate of only 2-3% in the screened population - many feel it is not high enough (31). A (+) result necessitates a minimum evaluation with sigmoidoscopy and air contrast barium enema, and preferably colonoscopy. If all persons over the age of 50 followed the American Cancer Society guidelines and received annual Hemoccult testing, the evaluation of patients with falsely (+) tests alone would cost a minimum of $670 million dollars in the 1st year and could easily be twice that much (33). As noted by Cole and Morrison, a very "small" change in specificity can exert a major impact on the clinical value of screening programs (32). For example, an increase in specificity of the fecal occult blood test from 98-99% would halve the number of false-positive reactions and halve the cost noted above (31).

There are also important sources of bias or error in the interpretation of screening results, yet these are frequently ignored (31-37). Lead time refers to the interval between the 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" (31). To prove efficacy of a test then there must be improved patient survival independent of lead time.

Length bias refers to the fact that when an asymptomatic population is screened at one point in time, cancers with inherently slower growth rates will be disproportionately detected. Length bias has received less attention than lead time bias because length bias is difficult to measure and has not been estimated for any screening programs. The longer the presymptomatic phase of the disease, the more important this will be. Because a longer presymptomatic phase is equatable with a longer course, the mean survival for individuals diagnosed by a screening program will always be longer than that for the general diseased population, even after adjusting for lead time (31). The effect of length bias is maximal when a population is initially screened. However, if repetitive screening is done at short intervals, the survival experience of cases detected at subsequent examination should be nearly free of length bias (32).

Finally, one of the most important biases that enter into a screening study, particularly those involving volunteers, is the selection of the screened group. It is more likely that well motivated, health conscious individuals will participate in a screening program, and it is possible that this type of individual will have a better prognosis than those who are not volunteers. Similarly, compliance results from volunteer studies are unlikely to be valid for the general population (32).

Thus, as Simon has noted (31), ultimately the efficacy of a colorectal screening program must be judged from studies that demonstrate a reduction in mortality from screening when compared with a comparable group of non-screened subjects. Randomized clinical trials such as the Health Insurance Plan trial of breast cancer screening (38) in the early 1960's minimize the biases previously discussed and provide a sound basis for prediction of the suitability of the screening test for various program settings (31,32).

SCREENING TECHNIQUES

HISTORY OF THE FECAL OCCULT BLOOD TEST (FOBT)

Testing stools for the presence of occult blood as an early indicator of gastrointestinal malignancy is not a new concept. This is generally credited to Van Deen, who in 1864 used gum guiac as an indicator reagent (31). Others would subsequently introduce benzidine and orthotolidine as alternative markers with numerous variations suggested (31). Originally, patients were requested to bring in one or more stool samples to the office for testing with one of these reagents. There was no quality control of the stability of the reagents used, and no dietary restrictions were employed (3). Benzidine and orthotolidine subsequently fell into disfavor because of the high percentage of false positives, although despite this Hematest (orthotolidine) is still widely used by many physicians and hospitals (31).

Credit for the concept of screening asymptomatic populations for gastrointestinal malignancy belongs to Greegor, an Ohio internist who reintroduced the guiac test for occult blood in the stool in the late 1960's (39). He requested patients to smear two samples of stool per day for 3 days onto slides impregnated with guiac, and subsequently reported detecting subclinical bowel cancer in this manner (39). Later studies confirmed his results with this slide test, known as Hemoccult, and within a few years a voluminous literature developed on this subject with numerous authors reporting results of screening large populations for colorectal cancer (31). In 1975 and 1977 respectively, Frame and Carlson (28) and Breslow and Somers (40) recommended testing the stool for occult blood every two years in all persons ages 40 to 50 and yearly thereafter. In 1979 the Canadian Task Force recommended testing the stool for occult blood in all persons over the age of 45 at intervals no more frequently than yearly (26). Finally, in 1980 the American Cancer Society recommended testing the stool for occult blood yearly in all persons over the age of 50 (3).

FECAL OCCULT BLOOD TESTING

Technical Aspects

The principle of the guiac test is based on the pseudo-peroxidase activity exhibited by hemoglobin. Filter paper, impregnated with guiac undergoes phenolic oxidation in the presence of hemoglobin in the stool, and hydrogen peroxide in the test reagent. A positive test result is defined as a blue color diffusing into a 0.5cm

margin around the stool specimen within one minute after application of the developer (59). Guiac is a naturally occurring heterogeneous compound and the concentration and degree of heterogeneity of the guiac vary with extraction procedures and purification techniques which may affect the amount of guiac impregnated on the paper (75).

The peroxidase - like activity of hemoglobin may be significantly diminished as it passes through the gastrointestinal tract and thus render occult blood tests negative. In regard to screening for colorectal cancer, this is a plus as it decreases the number of false positives from other sources (31). Hemoccult II is the best studied of the commercial guiac tests currently in use and each slide consists of two windows of guiac impregnated paper, on which the patient applies a thin smear of stool (from 2 separate parts of the stool). This is repeated with 2 subsequent stools and then returned for processing. A single reaction of 6 is termed a positive test (3).

Dietary Factors

The occult blood reaction is not specific for human hemoglobin but is affected by foods such as fresh fruit and uncooked vegetables or by nonhuman hemoglobin present in raw red meat. Greegor reported that a meat-free diet cut down on the frequency of positive reactions (39). He also felt that increasing dietary fiber would stimulate neoplastic bleeding. Macrae (76) found that .4% of slides were positive in healthy young subjects when consuming diets containing rare red meat and foods particularly high in peroxidase as long as the slides were not rehydrated. Rehydration increased this to 17%. The latter figure could be reduced to 1.5%, even with rehydration, if red meat was excluded. If patients followed a strict low peroxidase diet in addition, this further decreased to 0.6%. Norfleet (77) reported the effect of a red meat-free, high-fiber diet versus a control diet in patients tested for occult blood prior to undergoing colonoscopy for suspected polyps. He found no difference between groups in the sensitivity and specificity of the test for detection of cancer or polyps using non-hydrated slides. Simon (31) concluded that analysis of several uncontrolled trials (which varied in number and type of

dietary restriction), demonstrated no trends to substantiate the claims that dietary recommendations made a difference. This is an important issue since dietary restriction may decrease compliance with the test itself. Nonetheless, since even a minor diet-related decrease in false-positive results could have major consequences on the number of patients undergoing needless examinations (31) it is probably wise to follow the guidelines outlined in Table 6.

Slide Storage and Rehydration

Stool specimens cannot be stored indefinitely without hemoglobin losing its pseudo-peroxidase activity. Morris et al (78) reported that 14% of initially positive results became negative when slides were left at room temperature for 48 hours. Ahlguist et al (79) demonstrated a 30% decline in positive results after 4 days at room temperature which was somewhat improved by storage at 4 C.

Rehydration with a drop of water on the slide was originally suggested to minimize the false negatives from storage since rehydration enhances the pseudo-peroxidase activity of hemoglobin and increases test sensitivity dramatically (3). Despite this both of the controlled American trials have now concluded that the reduction in test specificity is too great to allow rehydration and have eliminated it from their protocols.It is therefore currently recommended that slides be processed as soon as possible, preferably within 4 days of collection.

Drugs

Iron compounds have been shown to increase false positive FOBT results (3). Aspirin is often blamed for positive test results, although several studies sugest that this is of little clinical significance (3). Some recommend the test be repeated off aspirin in the face of a positive result (31) others proceed directly to a work-up. High doses of vitamin C can produce false-negative results by interfering with the peroxidase reaction (3).

Sensitivity and Specificity

As previously noted, truly useful estimates for these can only be determined from evaluation of asymptomatic patient populations when compared with control groups followed over a long period of time. Nonetheless, a variety of studies have attempted to determine Hemoccult's ability to detect varying quantities of blood in different settings.

Quantitation of 51 Cr-labeled red blood cells has generally been accepted as the "gold standard" indicator of intestinal blood loss (31). Studies have demonstrated that the overwhelming majority of normal individuals lose less than 2 ml of blood (2 gm Hb/g of stool) per day. Macrae et al (80) looked at Hemoccult sensitivity in patients with known colorectal cancers or adenomas and reported 11% positive results when the Hb concentration was less than 2 mg/g of stool, 40% between 2-6mg/g and 63% when between 6-10 mg/g. Mean blood loss and Hemoccult positivity were significantly related to the site of the cancers (right colon greater than transverse and descending colon) but were unrelated to Dukes' staging. Day by day fluctuation of bleeding in individual patients with cancer, however, was related to Dukes' staging. Overall the Hemoccult II false-negative rate for cancer with 3-day testing was 31%, and for adenomas, under 2 cm, 85%. Ahlguist reported that 66% of patients with known colorectal cancer had negative Hemoccults during a 2 week stool collection.

Herzog (81) found that FOBTS were positive in 86% of patients with known polyps in the descending colon and rectosigmoid as long as bleeding exceeded 2 ml/day, whereas specimens were positive in only 26% of patients with polyps in the decending and transverse colon despite an equivalent blood loss. Thus the overall sensitivity for picking up adenomatous polyps in patients with known lesions was only 17% in the ascending and transverse colon compared with 54% in the descending colon and rectosigmoid. With regard to cancers the situation is reversed. Although for a given quantity of blood cancers of the right colon give a lesser percentage of positive results than cancers of the left colon, (probably due to greater degradation of peroxidases from a longer intestinal transit time), cancers

of the right colon bleed more than those of the left colon, and therefore more frequently give a Hemoccult positive result.

The best data on epidemiologic sensitivity and specificity for adenomas and carcinomas comes from the prospective study by Allison et al (59) to be discussed shortly.

Compliance

Compliance results from the uncontrolled and controlled trials will be discussed in these sections. Specific information regarding factors relevant to compliance can be derived from other sources. Several authors have found compliance to be highest when the Hemoccult test was offered to patients during a routine consultation at the office (82). Literature on the effect of educational material or symptom questionnaires distributed at the time of or preceding testing is conflicting (83-84). Several controlled trials have used reminder notices in patients not completing the test and one study found that the reminder post-card was the single most effective intervention, increasing compliance by 25% despite a very low cost (85). I could find no studies to determine if dietary restriction, etc. influenced compliance in any significant way.

Table 6 (30)

	RECOMMENDED METHODOLOGY FOR FECAL OCCULT BLOOD TESTING
Dietary Restrictions (2 days before and during testing)	Meat Free or Rare-Red Meat Free (Chicken and Fish allowed) High Fiber Low Peroxidase (Avoid Turnips, Horseradish, Broccoli, Melons, Cauliflower)
Medication Restrictions (1 week prior to and during testing)	Avoid Vitamn C (in excess of 250mg per day) Avoid Aspirin and other NSAIDs Avoid Iron Supplements
Condition Restrictions	Known GI Bleeding Menstruation Inflammatory Bowel Disease Familial Polyposis Syndromes
Number of Smears	Six
Type of Slides	Only Hemoccult II recommended
Rehydration	Not at present
Storage Interval	4 day maximum
Quality Control	Window or Lab Assay

I would now like to review the literature that exists from uncontrolled and controlled trials concerning the use of Hemoccult as a screening tool.

UNCONTROLLED TRIALS

Table 7 summarizes the main uncontrolled trials published after 1980. They vary widely in terms of number of patients enrolled, recruitment techniques and evaluation of positive results (31). Analysis of these studies reveals the following information (8,31,40-57):

1) Acceptance of the test varies widely (22-91%) with a mean of 46%.

2) Roughly one half of the investigators recommended a low peroxidase, high-fiber diet before and during testing, whereas the others refrained from dietary restrictions. As noted by Simon, "diet was not associated with any discernible trend in the yield of occult bleeding or in the predictive value of a positive test" (31).

3) The percentage of positives varied between 1.3% and 5.2% with a high number of results between 2% and 4%. Positive predictive values ranged from 3% to 16% for cancer and 6% to 35% for polyps.

4) Overall, most screening programs uncovered colorectal cancer in .09% of all persons enrolled (9 persons for every 10,000 enrolled) and adenomatous polyps in .19% (19 persons for every 10,000 enrolled).

(Table 7)

SELECTED UNCONTROLLED TRIALS WITH HEMOCCULT SINCE 1981

Year	Author(reference)	No. Enrolled	No. Tested	Min. Age	Diet	No. of Tests	Test Positive (%)	Predictive Value Cancers/ Polyps (%/%)
1981	Stuart (49)	6,574	4,498	none	-	1	5.2	6/13
1981	Farrands(50)	8,925	2,439	40	No	3	5.1	3/6
1982	Million(51)	5,812	1,646	40	No	6	2.3	5/16
1983	Sontag(43)	13,522	2,964	40	Yes	6	4.6	10/33
1983	Hardcastle(52)	9,807	3,613	45	Yes	3	2.1	16/35
1983	Siba(53)	-	3,791	45	No	6	2.6	6/19
1983	Habba(54)	2,143	1,628	40	No	6	2.3	14/16
1983	Winchester(55)	-	45,658	-	-	-	1.3	4/10
1983	Hoffman(56)	-	3,778	-	-	-	4.0	8/15
1985	Dubois(57)	-	12,902	-	-	-	2.6	4/25
1985	Allison(58)	14,041	10,255	45	Yes	3	2.8	10/15
1986	Cummings(42)	58,934	11,497	-	Yes	3	2.3	9/17
1987	Johnson(47)	62,030	29,786	-	Yes	3	1.5	10/29
1988	Chang(45)	41,519	18,198	-	Yes	3	3	6/16
1988	Miller(46)	72,000	23,000	-	Yes	3	6	6/15
1989	Khubchandani(48)	49,353	23,674	-	Yes	3	3.6	6/17
1989	McGarrity(44)	57,000	29,619	-	Yes	3	3.9	8/22

Adapted from Simon (31) and Bader (8)

5) Several authors noted that the cancers uncovered by this strategy were far more often at the Dukes' A and B stages than when the diagnosis is made because of symptoms. Examples include: Sontag et al (43) - 6 in situ or Dukes' A and 4 Dukes' B of 14 cancers (71%); Miller et al (46) -77% Dukes' A and B; Cummings et al (42) - 71% Dukes' A and B. This compares with 42% localized lesions (Dukes' A and B) when patients present symptomatically in the general population (3).

Criticisms of these trials primarily center around the absence of a control group such that selection bias, lead time bias, and length bias could account for these seemingly promising results. Similarly, virtually none of these studies has dealt with the issue of cost in any realistic way (31).

Before moving to the controlled clinical trials that are currently in progress, I would like to briefly review one additional recently published study. Allison et al (59) prospectively analyzed the sensitivity, specificity and predictive value for Hemoccult II in 15,188 patients ages 45 and older who had FOB testing during multi-phasic health evaluations from 1979-1980 at Kaiser Permanente. All patients with one or more positive slides were evaluated with colonoscopy, barium enema, or both and information from patients with negative test results who were subsequently diagnosed with cancer or polyps over a 4 year period was obtained from the local tumor registry and Kaiser Permanente pathology files. It was assumed that all colorectal neoplasms found within 2 years of a positive Hemoccult test were the probable cause of the positive test, and further that if a colorectal neoplasm was present at the time of a negative test result it would manifest itself within 4 years at subsequent screenings or by symptoms.

The authors report a 50% sensitivity for Hemoccult II for colorectal cancer diagnosed within 1 year of testing, 43% within 2 years, and 25% within 4 years. For polyps, sensitivity was 36% at 1 year, 28% at 2 years, and 17% at 4 years. Specificity was 99%. The predictive value of a positive test for colorectal cancer was 8% at 1 year, 10% at 2 years, and 11% at 4 years. For both adenomas and carcinomas the predictive value was 26% at 1 year, 29% at 2 years, and 34% at 4 years and was found to steadily increase with age.

This study is important because it is the only completed trial that has provided sufficient patient follow-up to generate reasonable sensitivity data in an asymptomatic population. Furthermore, the results as reported suggest that the sensitivity of the FOBT is considerably less than that determined from studies in patients with known malignancy (positive results in about two-thirds of patients with cancer (3)), a finding that is not surprising and awaits confirmation by other investigators.

CONTROLLED CLINICAL TRIALS

Five controlled studies evaluating the use of Hemoccult II screening in the population are currently in progress. It is hoped that one or more of these studies will provide definitive information regarding the value of screening for colorectal cancer with the FOBT in the general population (60).

A) University of Minnesota Colon Cancer Control Study (60-65)

This study was begun in 1975 and enrollment completed by 1977. Gilbertson and his colleagues recruited a total of 46,622 volunteer subjects who were then stratified by age, sex and geographical region

and randomized into one of three groups. Group I was screened annually with Hemoccult II for 5 years, Group II biannually for 5 years, and Group III was a control group. Hardcastle (60) notes that 30% of the subjects enrolled in this trial were volunteers recruited from the American Cancer Society Cancer Protection Study.

Participants in all 3 groups received a mail questionnaire annually to ascertain the occurrence of colorectal cancer and polyps among the control group as well as in FOBT (-) participants (interval cases) or those diagnosed in members of the screened groups who were unwilling or unable to submit the slides. To date only 0.7% of the participants have withdrawn from the study and refuse to respond to the annual solicitation. Originally, Hemoccult slides (which were mailed in) were processed without rehydration but during the study hydration was introduced to increase the sensitivity of the test. Colonoscopy was the primary modality used to evaluate positive test results. Preliminary results are as follows.

Compliance with Hemoccult testing has been about 75%. 205 cancers were detected in screenees and 183 were the result of a diagnostic evaluation within 12 months following a positive test. The remaining 22 were diagnosed within the 12 months following a negative test (interval cases). From these data overall sensitivity of the test was calculated to be 89.3% with a specificity of 92.7%. Of the 7230 participants with a positive Hemoccult test, 2.5% were diagnosed with colorectal cancer. The remaining 7047 were classified as false positives for cancer. Of the first 75 cancers diagnosed in screenees, over three-fourths were Dukes' A and B lesions. Rehydration resulted in an increase in positivity from 2.4% to 9.8% but a decrease in specificity (97.7% to 90.4%) and positive predictive value for cancer (5.6% to 2.2%).

Data on the control subjects is not yet available and according to Hardcastle (60) because of an inability to demonstrate the anticipated reduction in mortality during the designated follow-up period, (5 years of follow-up following 5 years of screening) it has been decided to reinstitute screening without rehydration of slides. The conclusion of the study is now projected for 1995. Criticisms (60) of this trial include:

1) the volunteer status of the participants which could lessen the impact of FOB testing in screenees (controls may also be receiving FOBTs outside the study)

2) a radical change in test procedure while the study was ongoing

3) a possible reduction in efficacy of the FOBT because slides were mailed in and significant delay prior to testing may have resulted.

B) Memorial Sloan-Kettering Cancer Center and the Preventive Medicine Institute Strang Clinic of New York

This trial (60,66-67) enrolled 21,756 subjects between 1975 and 1979. Predominantly (90%) asymptomatic men and women age 40 and over were entered into the study and allocated by calendar periods into either a control or screened group. The subjects were then sub-categorized into those who had been to the Strang Clinic at least once before (Annual Group) and those who had come to the clinic for the first time (Initial Group). All patients enrolled had a comprehensive medical examination and blood tests as well as medical questionnaire and rigid sigmoidoscopy. The study group received annual FOBTs, prepared while they were on a meat-free, high-bulk diet during the 4 days prior

to their examination. This was originally done with Hemoccult but subsequently Hemoccult II slides were used.

Initial results from the trial, which is still ongoing, reveal that participation in the Hemoccult test, particularly in the Initial Group declined substantially after the 1st year (80% - 20%), despite an intensive follow-up. The percentage of positive results varied from 1% without rehydration using Hemoccult to 5.4% with rehydration using Hemoccult II (overall 3.7% using Hemoccult II).

For the 400 persons found to be test positive at last report, the overall predictive value of Hemoccult II was 12% for cancers and 36% for polyps. In the initial screen, 65% of prevalent cases in the study group were In Situ, Dukes' A or B. According to Hardcastle, the preliminary analysis of mortality has shown a difference of borderline significance between the Initial and Control groups but no difference between the Annual group and Controls (60). Criticisms of this study include the heterogeneity and non-randomization of the Annual and Initial Groups and their controls, the volunteer status of all involved, no comparison with an absence of screening, and inclusion in the trial of rigid proctoscopy - an outdated technique (60). Further data is anticipated to be forthcoming over the next several years.

3) Goteborg, Sweden

Kewenter et al (60,68) designed a trial beginning in 1982 randomly dividing all inhabitants of Goteborg, Sweden between 60 and 64 years of age (27,000) into a test and control group. The 13,759 subjects in the test groups were invited by letter to perform Hemoccult II tests over 3 days on a low peroxidase diet, return tests by mail, and to repeat testing in 16-22 months. 66% completed the test at 1st screening, and 58% at the 2nd screen. In the first screening the study group was divided into

2 subgroups in which the FOBTs were rehydrated or not rehydrated before development. All tests were rehydrated at the 2nd screening. All test positive subjects were examined by flexible sigmoidoscopy and double-contrast barium enema.

Preliminary results include a 1.9% and 5.8% positive slide rate in the non-hydrated and rehydrated subgroups, respectively. 35 colorectal cancers were picked up at screening and an additional 26 subjects (non-responders and interval (+) cases) were also found to have cancer. This compared with 20 cancers in the control group. The distribution of cancers according to Dukes' classification is found in the following table:

Distribution of Carcinomas According to the Dukes Classification

	Diagnosed with Hemoccult II*		Screening group		Control group	
Dukes	No.	Percent	No.	Percent	No.	Percent
A	12	34	13	21	3	15
B	8	23	15	25	5	25
C	11	32	22	36	7	35
D	4	11	11	18	5	25
Total	35	100	61	100	20	100

* Diagnosed with Hemoccult II are those cases (35/61) in the screening group that were found with the aid of the Hemoccult II test.

In this study there was no significant difference in the Dukes' classification between the diagnosed carcinomas in the test and control groups. Colorectal adenomas were diagnosed in 162 subjects in the test group and 24 subjects in the control group ($p < .01$). 104 and 11, respectively, of these adenomas were > 1cm in diameter ($p < .01$). No data are yet available on mortality and the study has been increased to twice as many subjects for statistical purposes. Criticisms of this study

(60) include the fact that slides were mailed in causing a possible delay in processing (although Kewenter has noted that 96% were tested within 6 days) and the use of rehydration which has been demonstrated to result in a marked decrease in specificity from other trials. Nonetheless, this trial should give us important information on the effects of a screening program in the general population, although one with a higher incidence of colorectal carcinoma.

4) Funen, Denmark.

Kronberg et al (60,69-71) initiated a trial in 1985 randomizing 30,970 persons to screening with Hemoccult II and 30,968 to a control group, in a population of 140,000 between ages 45 and 74, all inhabitants of Funen, Denmark. Persons with known colorectal cancer, adenoma and distant spread from all types of cancer were excluded. Positive test results were evaluated by colonscopy.

Compliance with the initial test was 67% but 93% for those who were reinvited 2 years later. Slides were mailed in and 95% were tested within 5 days. Positive FOBTs were found in 215 (1%) and 159 (.8%) during the 2 screenings, respectively. A total colonoscopy was performed in 187 and 144, and cancer detected in 37 (17%) and 13 (8%) with adenomas in 86 (40%) and 76 (47%), respectively. Interval cancers had developed in 40 subjects (.2%) at the end of the 2nd screening, and 39 non-responders (.18%) had developed cancer. Cancer was diagnosed in 115 controls (.37%) and an adenoma in 100 (.32%) during the same period.

Interval cancers presented as rectal cancers more frequently than those detected by screening, suggesting that screening with Hemoccult II was less effective in the rectum.

The estimated death rate from colorectal cancer was 1.2 per 1000 persons in the screening group and 1.6 per 1000 persons among controls ($p=0.16$) although the follow-up interval is still short. The authors note that the very small numbers of cancers detected in individuals below age 55 suggests that screening may have a poor cost benefit ratio in this age group.

The study was designed to detect a possible reduction in mortality from colorectal cancer of 25% within 5 years after three screenings with intervals of 2 years. The last screening was just completed and the study is now in the follow-up phase. Overall, this is a very well-designed trial although some (60) question whether the sample size is indeed large enough to demonstrate significant differences in mortality.

5) Nottingham, England

In 1989, Hardcastle et al (72-74) published the preliminary results of the largest randomized trial to date, which is taking place in Nottingham, England. 107,349 subjects without symptoms of colorectal disease were identified from general practitioner records and randomly allocated to test and control groups (mailed requests and mailed slide returns). Test group subjects are offered screening every 2 years; both groups will be followed for a minimum of 7 years. The study design allows for detection of a 23% or greater reduction in mortality at an 80% confidence level after this time. The initial Hemoccult II tests were carried out <u>without</u> dietary restrictions and completed slides tested <u>without</u> rehydration. Test (+) subjects were asked to repeat the test over a 6 day period while on a low peroxidase, meat-free diet. Only subjects (+) on the 2nd test were further evaluated (most patients received colonoscopy). Subjects with a negative test after dietary restriction were asked to repeat the test again with dietary restrictions

after 3 months. If positive they were evaluated further, if negative they were returned to the general screening group.

Compliance with the initial test was 53%. Further investigation of the 618 (2.3%) with positive tests demonstrated 63 cancers (52% Stage A) ($p<.001$) and 367 adenomas. The stage of cancers in the test and control groups is found in the following table:

STAGE OF CANCERS IN TEST AND CONTROL GROUPS

Stage	No (%) in test group					No (%) in control group
	Screen-detected		Interval	Non-responder	Total	
	Initial	Rescreen				
A	33 (52)	7 (54)	6 (12)	10 (12)	56 (31)	13 (11)
B	16 (25)	4 (31)	4 (18)	30 (36)	54 (30)	40 (32)
C	12 (19)	1 (8)	6 (27)	16 (19)	35 (19)	40 (32)
D	2 (3)	1 (8)	6 (27)	25 (30)	34 (19)	26 (21)
Not staged	..	..	..	2	2	4
Total	63	13	22	83	181	123

The investigators also note a predilection for Hemoccult to detect left-sided tumors versus right-sided or rectal tumors.

This study has been criticized for the lack of dietary restriction in initial screenees and the requirement for a 2nd positive test to initiate work-up since this is likely to produce a significant number of false negatives. Similarly, there is a significant reduction of patients "offered" subsequent screening tests at 2 year intervals and the reasons for this are unclear. Nonetheless, this study should provide valuable information about the effectiveness of such a screening program in the general population.

To conclude, while 5 prospective, randomized, controlled trials are underway (2 with over 10 years of follow-up data) none has yet demonstrated a reduction in mortality from screening with the FOBT. While these studies have demonstrated reasonable compliance (53% to 75%) and a significantly higher percentage of localized cancers in screened patients versus controls, it is fallacious to equate earlier staging with a better average prognosis because of lead time bias and

length bias. Hopefully, specific results with regard to mortality will be available within 5 years.

EVALUATION OF A POSITIVE HEMOCCULT TEST

It is important to remember that a single Hemoccult positive slide is sufficient to qualify a patient for further evaluation if this is to be used as a screening tool. Likewise, all trials specify that a "weakly" positive test is considered positive. Given the nature of the Hemoccult reaction, its variable sensitivity to identical quantities of blood, and the intermittent nature of neoplastic bleeding, it is not surprising that diagnostic yield correlates poorly with the number of positive slides or the strength of the reaction (3).

Considerable debate has centered on the appropriate evaluation of a positive FOBT. First I'd like to address the question of whether both the upper and lower GI tract should be examined. As mentioned previously, chemical alteration of hemoglobin as it passes through the GI tract diminishes its peroxidase-like activity frequently rendering stools negative even in the face of a known upper GI lesion (31).

Stroehlein (86) noted that in a European series only 2 of 26 patients subsequently found to have esophageal cancer had occult blood in 1 or more of 6 specimens (87). Similarly, in a study of over 1000 asymptomatic patients with a positive FOBT, only 8% were found to have upper GI pathology (88). In the Minnesota trial, Stroehlein notes that most positive FOBTs in patients with upper GI bleeding were found secondary to prior surgery for peptic ulcer disease (86). Thus, evaluation of the upper GI tract is no longer recommended in the asymptomatic patient with a positive FOBT but should be considered if the patient has other signs or symptoms (86).

How then should we examine the lower GI tract? Critics of the literature argue that in the absence of good data gastroenterologists favor colonoscopy and inappropriately use it as the "gold standard" while radiologists report superior results with the double-contrast barium enema (DCBE). I would like to briefly summarize some of the literature bearing this topic but excluding the question of cost which will be discussed shortly.

The standard single-column barium enema has been demonstrated to be a low resolution, relatively insensitive method for the detection of potentially curable colorectal polyps and cancers (22). Gilbertson et al reported that single-column barium enemas failed to detect 19 of 45 Dukes A and B carcinomas in the University of Minnesota's occult blood screening program (89). De Roos et al prospectively compared single-contrast and double contrast colon examination in 425 consecutive patients for the detection of polyps and stricturing carcinomas. Each patient was examined with both single-contrast and double-contrast barium enemas during the same session. In patients with carcinoma, there was no significant difference between the two modalities but double-contrast was far superior to single-contrast for detection of colorectal polyps (90). Thus double-contrast barium enema is currently considered the radiologic procedure of choice for detection of colorectal neoplasia.

More controversial, however, is the role of the double-contrast barium enema with or without flexible sigmoidoscopy versus initial colonoscopy. Several studies have compared double-contrast barium enema alone versus colonoscopy. In most, colonoscopy has been about 12% more accurate (both from a false negative and false positive standpoint) (91). Hogan et al prospectively performed blinded colonoscopies in 50 individuals referred for polyps found on DCBE. Radiologic and

endoscopic examiners had comparable expertise and an identical colon cleansing prep was used for all studies. The endoscopist declared his findings to a referee during "staged -withdrawals" from the colon and conflicts were then resolved by reinspection. Results are shown in the following table (92):

	POLYPOID LESION			COMPARISON: Dx Accuracy			
				COLONOSCOPY		X-RAY	
SIZE	NO.	ADENOMA	CA	ERROR	%CORRECT	ERROR	%CORRECT
<0.5cm	57	1	-	5	91%	19	67%
.5-.9cm	31	20	-	3	90%	15	52%
>1.0cm	38	31	7	1	97%	7	82%
TOTAL/AV	126	52	7	9	94%	41	67%

A similar careful study was done at St. Marks' Hospital in London where 500 patients with a history of prior polypectomy were followed by rigid sigmoidoscopy, flexible sigmoidoscopy, colonoscopy and DCBE each visit. Patients having polyps greater than 7mm in diameter were recalled for subsequent endoscopic polypectomy after the barium enema. Where a discrepancy occurred between the findings of either technique, the patient was re-endoscoped, and an additional barium enema performed. They found the sensitivity of the colonoscopy to be 92% for detection of adenomas over 7mm in diameter versus 71% for double-contrast barium enema. Retrospectively 10/17 missed lesions could be seen on these films although these had been performed and then reviewed by a specialist radiologist at the time of the study. Figure 2 demonstrates the sites of these missed lesions (93):

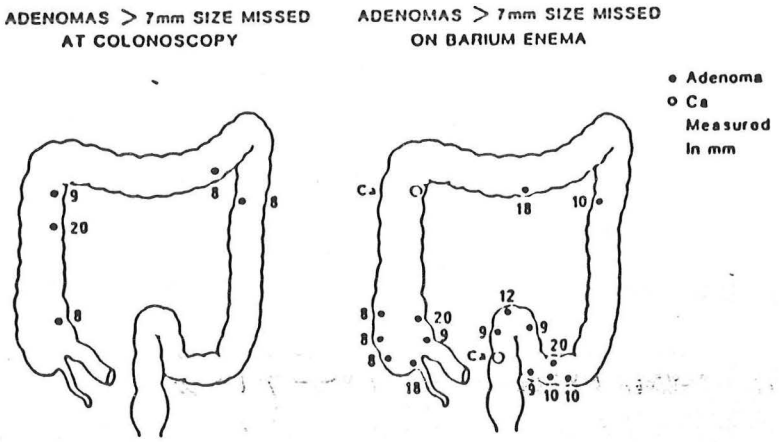


Fig. 2. Sites and sizes of adenomas and carcinomas missed on colonoscopy or double contrast barium enema.

Stroehlein (86) and Bond (22) note the particular difficulty of adequate examination of the left colon by barium enema, especially in the face of concurrent diverticulosis. Stroehlein reports for example, that in one large series, 77% of 39 polyps missed by DCBE were distant to the splenic flexure and 69% were in the rectosigmoid (86). These findings have led to the recommendation that flexible sigmoidoscopy be combined with DCBE if the former is used as the primary diagnostic modality.

Data from St. Mark's (93) (not reported) led the investigators there to conclude that combining flexible sigmoidoscopy and DCBE at a single outpatient visit with the same bowel preparation gave "acceptable" accuracy and was the procedure of choice for subsequent follow-up checks in those 30% of patients who were technically difficult to endoscope.

While colonoscopy also has its limitations (areas proximal to flexures and the ileo-cecal valve can be difficult to visualize; the endoscopist will not reach the cecum in 5-10% of patients (22)), most investigators (3,8,22,25,) recommend it as the initial diagnostic procedure as opposed to the combination of flexible sigmoidoscopy and DCBE because it allows simultaneous biopsy of suspicious lesions and resection of polyps. I was only able to find one prospective study reporting data on the diagnostic accuracy per se of coloscopy versus DCBE and flexible sigmoid exam. This was carefully done with methodology similar to that previously used by Hogan and the group at St. Mark's. Irvine et al (94) found a sensitivity of 82% for colonoscopy versus 73% for flexible sigmoidoscopy plus DCBE in the detection of all colorectal neoplasia and the discrepancy was much larger if only polyps greater than 5 mm were included. Likewise, the positive predictive value for colonoscopy was higher. To conclude then, colonoscopy is the generally preferred method to evaluate a positive FOBT, however the combination of flexible

sigmoid exam and DCBE provides a good alternative if colonsocopy cannot be performed. Only limited data exist to demonstrate that the latter is less accurate diagnostically.

COST OF SCREENING FOR OCCULT BLOOD IN THE STOOL

It is hoped that the five randomized, controlled trials worldwide will provide some concrete information regarding the true costs involved in fecal occult blood screening programs. Until then we can only estimate cost and a number of studies have tried to do this. Simon (31) has outlined the various issues to be considered in cost analysis and I will briefly review these first. While the cost of the Hemoccult test itself is nominal (less than $5.00) the bulk of the cost lies in the investigation of false positive results. As mentioned previously, a low estimate for false positive rate of 2% translates into a minimum national cost of $670 million dollars to evaluate positive FOBTs with colonoscopy (assuming cost of colonoscopy is $500, no biopsies necessary and a perforation rate of only 1/1000 procedures) (see page 11). Indirect costs, which are frequently ignored, include the cost of prior information campaigns, postal and secretarial costs, the cost of nurses' or receptionists' time for contacting patients and pursuing noncomplaint subjects, etc. "Hidden" costs (31) include time lost from work, transportation expenses and the like. This also includes the "waste" of limited medical resources for the evaluation of false-positive results.

The sum of these costs must be balanced against the savings from a successful screening program which might decrease expenses from advanced malignancy, increase productive life span, etc. Simon also notes that arguments about the polyp-cancer sequence are relevant to cost considerations. While polypectomy and subsequent surveillance measures add significantly to the cost of colonoscopic evaluation of the

hemeccult positive stool, they may be even more important in the ultimate prevention of colon cancer and thus afford significant savings.

It would seem difficult to evaluate the cost-effectiveness of a screening program when it is not yet clear how many cancers are avoided or cured by screening, and what the relative costs are for treatment of a cancer at Dukes' Stage A versus C or D (8). Nonetheless several studies have tried (95-98).

England et al (95) evaluated the cost of several different screening strategies for colorectal cancer. They concluded that screening with the FOBT followed by DCBE with colonoscopy if necessary to evaluate positive results was the most cost-effective strategy. They estimated that the cost per subject screened was $17 with 65% of cancers being detected and a marginal cost per year of life gained of $3400. This cost was only slightly higher using colonoscopy as the initial diagnostic test to evaluate a Hemoccult positive stool. Unfortunately this study appeared to make several fallacious assumptions - no increase in the prevalence of cancers with advancing age, no malignant potential for polyps, no further surveillance for polyps found, etc. Allison et al (96) reported that analysis of Hemoccult screening in the Kaiser Permanente program demonstrated a net savings in medical care costs of $14,685 and a projected increase of 22 years in life expectancy. They estimated a marginal cost of $765 per year of life gained. They do not give enough specifics regarding procedural costs, etc to really analyze their data.

Barry et al (97) looked at the effect of different work-up strategies on the cost-effectiveness of screening with the FOBT for colorectal cancer. He found that the combination of flexible sigmoidoscopy and DCBE resulted in the prevention of 3.15 fatal cancers per 10,000 patients screened at a cost of $91,294 per life saved or $10,868 per life-year. Choosing

colonoscopy as the initial diagnostic test to evaluate a positive FOBT prevented 3.32 cancers per 10,000 screened at a slightly lesser cost. This was all determined for a 65 year old population in whom the prevalence of cancer would be considerably higher as would the positive predictive value of the FOBT.

Brandeau et al (98) evaluated the relative cost-effectiveness of 22 protocols for evaluating a hemoccult positive stool and concluded that initial colonoscopy would cost greater than $51,959 per year of life saved. To reiterate, all of these analyses make the tacit assumption that earlier Dukes' staging correlates directly with improved survival. This remains to be proven (99).

DIGITAL RECTAL EXAMINATION

The American Cancer Society currently recommends an annual digital rectal examination after the age of 40. Although this has been a common medical practice for many years, no formal studies of its effectiveness have been done (30). The average index finger is about 10cm long, and its effective insertion is estimated at 7.5cm (100). Thirty years ago up to 15% of all colorectal cancers were theoretically detectable by digital examinations, today only 10% (101). Nonetheless, the low risk and low cost of this procedure when performed in the context of a general physical examination has led to minimal controversy about its role as a screening method for colorectal cancer (102). Since it offers the additional opportunity to examine the prostate in men it is even more appropriate in that population (102), and a recent survey of physicians' practices in early cancer detection found it was utilized by 96% of the 1029 physicians surveyed (103).

SIGMOIDOSCOPY

Although rigid proctoscopy has been largely supplanted by flexible sigmoidoscopy, the only data available on reduction of mortality with endoscopic screening of the general population comes from studies using the former technique. Rigid proctoscopy has been in use since the late 1930s (102). Although the rigid proctoscope has a potential depth of insertion of 25cm the average depth of insertion is 16 to 20cm; only one-third of female and one-half of male patients can be examined for a depth greater than 20cm (104). While at one time up to 75% of colorectal carcinomas were detectable by rigid exam (101), recent estimates suggest that only 25-33% are currently within reach (102), because of the progressive shift to the right of colonic malignancies.

Five studies in the English literature have reported data on mortality or survival from screening proctosigmoidoscopy (37), and excellent critical reviews of this subject have been published by Neugent and Pita (102) and Ow et al (37). Only 3 of these will be discussed.

1) Minnesota Cancer Detection Center Study (13,37,102)

This is the major study on which the American Cancer Society recommendations for screening with sigmoidoscopy are based (102). Gilbertson et al (13) reported on the outcome of over 21,150 subjects over the age of 45 who underwent proctosigmoidoscopy and polyp removal as part of a program of annual multiphasic cancer screening. The study took place from 1948 through 1976 and an average of 5.4 examinations per participant were performed. Initial evaluations resulted in the detection of 27 carcinomas and follow-up examinations yielded 13.

They noted that the 5 year survival of 64% for patients found to have cancers on initial examination was twice the 31% reported for persons with the disease at that time, and further that all 13 cancers detected on follow-up examinations were confined to the bowel wall ($\leq$ B2) with 11 of 13 patients surviving over 5 years. Gilbertson also estimated from the annual incidence of rectal cancer reported for persons of similar ages in the population of Minnesota that 87-97 cancers should have been detected on follow-up examinations and concluded that the 85% reduction in anticipated cancers was secondary to screening and polypectomy.

The primary criticism of this study is the lack of a control group with patient selection bias likely to play a role in the favorable results as well as the problem of lead-time bias. Since no interval cases of colorectal cancer were diagnosed in the screened segment of the bowel, this suggests that length bias may not be an issue (37).

2) Strang Clinic Study (37,102,105)

Hertz et al (105) reported the results of annual screening digital rectal and proctosigmoidoscopic examinations in 26,126 subjects over the age of 45. A single guaiac test was also done on stools when sufficient material could be obtained at the time of the visit. A total of 47,091 examinations were performed and 58 cancers detected (1/450 examinees) (76.5% by sigmoidoscopy, 8% by positive FOBT). 81% of the cancers were confined to the bowel wall and the reported 5 year survival was 88%, much higher than typically expected.

Criticism of this study include selection bias, lead time bias and possible length bias (no mention of interval cases) (37).

3) Kaiser-Permanente Multiphasic Evaluation Study (37,102,106-108)

This trial began in 1964 and randomized 10,713 subjects between the ages of 35-54 years to routine follow-up within the Kaiser system or a special program where they were contacted annually and urged to have a multiphasic health check-up (MHC). The controls were free to arrange their own MHCs if they wished. MHCs for patients over 40 included digital rectal examination, blood studies for anemia and proctosigmoidoscopy (in addition to several other screening evaluations for other diseases).

The 16 year follow-up results reported in 1986 showed no difference in the overall mortality rate in the screened groups versus controls. When the 34 causes of death were looked at separately, however, the death rate from colorectal cancer was significantly lower in the screened group (2.3 vs 5.2 deaths/1000, $p<.02$) and this was generally interpreted as demonstrating the beneficial impact of screening proctosigmoidoscopy on colorectal cancer (37).

More recently, however, Selby et al (108) reanalyzed this data and determined that the results were inconclusive with respect to sigmoidoscopy for the following reasons:

1) Only a small difference in exposure to sigmoidoscopy existed between screened and control subjects (30 vs 25%).

2) A lower incidence of disease as opposed to better prognosis accounted for two-thirds of the total difference in mortality and this could not be attributed to polypectomy since no appreciable difference in removal of colorectal polyps was seen between groups.

To conclude then, each of the studies that provide a concrete basis for a recommendation of screening sigmoidoscopy has significant problems with the analysis or interpretation (102).

FLEXIBLE SIGMOIDOSCOPY

Rigid proctosigmoidoscopy never became a popular screening method with physicians or patients presumably because of the discomfort it produced (109). In the 1970s, introduction of the flexible sigmoidoscope increased the feasibility of such screening (110-112).

The 60cm flexible sigmoidoscope can examine the anus, rectum and sigmoid colon and should have a yield of at least 50% for all colorectal neoplasms, since current data suggest that 30% of all cancers are located in the rectum and an additional 35% in the sigmoid colon (67). Although the potential yield would thus be 65%, several studies have suggested that the average depth of insertion may only be 50cm (113-116). Flexible sigmoidoscopy can be performed without sedation after an enema preparation and the major complication is perforation (estimated incidence 1/10,000 procedures) (117). Complication rates rise with polypectomy and this should not be done unless the entire colon is adequately prepared to eliminate the risk of electrocautery-induced explosion (22).

The yield of invasive carcinomas has been estimated at 0.1 to 0.2% for newly examined patients over 40 (67), and approximately 10% for adenomas (10,19A). Rozen et al (118) looked at the yield of sigmoidoscopic screening in 1,176 asymptomatic subjects with simultaneous FOBTs and found that the FOBT detected only 18% of screenees with adenomas and 60% with invasive cancer vs 95% and 80% by flexible sigmoidoscopy. Further analysis demonstrated little

agreement between the two tests suggesting that they were diagnosing different neoplasia. Evaluation of expected gain in diagnosing neoplasia, by combining both tests, gave 18% for the FOBT and 94% for sigmoidoscopy.

The cost of the 35 and 60cm sigmoidoscopes is generally comparable although some have suggested that the former affords a more comfortable exam and requires less training to perform (3,67,114,115), while detecting up to 84% of the lesions found with the longer scope (114). It would seem however, that the longer scope may be superior since it is not significantly more expensive and affords the examiner the ability to detect more pathology given constraints of time, training and patient acceptance.

Rumans et al (119) estimated the cost of screening done by two community-based general internists in Oregon on 252 asymptomatic patients with negative FOBT to be $1,168 per patient found to have a polyp and $10,119 per patient with a malignancy. Gupta et al estimated a cost of detecting potentially curable carcinomas of $47,174 in FOBT negative patients, although the FOBT was performed on only a single specimen of stool (120).

To conclude, it is clear that flexible sigmoidoscopy can detect a number of carcinomas and adenomas, many not found by FOBT or digital rectal examination. No study has yet demonstrated a reduction in mortality from this procedure and estimates of cost and compliance if recommended to the general population have yet to be determined. It would seem however, that expenditures could be markedly reduced, if these examinations were included at cost as part of a general examination by a primary care physician or even physician-extender (nurse practitioner, physicians assistant, etc) (122).

COLONOSCOPY

While virtually no one recommends screening colonoscopy for the population at large (121), it has been suggested as the procedure of choice for higher risk individuals and as the initial procedure to evaluate a positive FOBT. Colonoscopy has become a routine outpatient procedure, particularly for asymptomatic patients, and less than 30 minutes is needed in most cases to adequately visualize the colon, although as mentioned previously, the cecum is not seen in 5-10% of procedures. The sedation used during the examination probably contributes to its greater patient acceptance versus barium enema (123). The major complication of colonoscopy is perforation and is estimated at 0.17% for diagnostic procedures (124) although increases with polypectomy (0.3 to 1.0%) (125-126). Bleeding is rare during diagnostic colonoscopy but occurs in about 2% of patients following polypectomy (124-125). Charges vary considerably between institutions but reasonable figures are $500 (diagnostic), $750 (with biopsy) and $860 (with polypectomy) (97), not including institutional charges (up to $500). Cost analyses by some investigators have determined initial colonoscopy to be less expensive than the combination of flexible sigmoidoscopy and DCBE in higher risk individuals (97).

SCREENING PROCEDURES FOR HIGHER RISK GROUPS

About 15% of patients with colorectal carcinoma belong to higher risk groups and the majority of these people have a family history of colorectal carcinoma in first-degree relatives (93B). Chronic inflammatory bowel disease, familial polyposis syndromes, and a history of prior colorectal carcinoma each account for 1-2% of the total (93B).

1) Familial Polyposis Syndromes

The specific syndromes of multiple colonic polyps were discussed in depth by Dr. John Dietschy in his Grand Rounds in 1988 (127). Briefly, the two major syndromes associated with a very high risk of carcinoma are Familial Colonic (Adenomatous) Polyposis and Gardner's Syndrome. Both are inherited as an autosomal dominant trait with over 90% penetrance. Specific probes demonstrate a deletion in the fifth chromosome that is responsible for both these syndromes, although at present genetic screening by restriction fragment length polymorphism analysis is only available at research centers such as the University of Utah (4). Such screening should allow us to determine the 50% of kindreds who will develop these syndromes with greater than 95% accuracy (4) and should thus modify the current recommendation for flexible sigmoidoscopy every 6 months - 2 years (27,35,93B) beginning from age 10-12 until the age of 50, unless polyps are found, an indication for total colectomy.

2) Family Cancer Syndromes (Hereditary Nonpolyposis Colorectal Cancer - Lynch Syndromes I and II)

These syndromes were recently reviewed by Dr. Graham Smith (4) and are generally associated with autosomal dominant inheritance without any evidence of diffuse polyposis. Characteristically, members of these families develop colorectal cancer at a relatively
early age (less than 50 years) and many of these tumors occur in the proximal large bowel. In a few families an increased risk of developing adenocarcinoma at multiple sites, including the breast, ovary, and more frequently the endometrium and colon has been documented. For these reasons, it is generally recommended that colonoscopic surveillance begin at age 20 and continue every 3-5 years (5,35,127) with annual

FOBTs. In females of families with cancers demonstrated at multiple sites, screening mammography, pelvic examinations, and endometrial biopsy are indicated at regular intervals. Lynch estimates that while 30% of the general population will have one first-degree relative with cancer, only 2.7% will have three or more and this should suggest a problem. He also recommends using genetic consultation if available (67,128).

3) Ureterosigmoidostomy

Patients who have undergone this procedure are at particularly high risk to develop neoplastic lesions at the ureterosigmoidostomy site (29%) (9). Adenomatous polyps and carcinomas have been found after latent periods as long as 4 decades, although the mean is 20 years and 26 years for adenomas and carcinomas respectively (9). Current recommendations from the American Gastroenterological Association include annual FOBTs and flexible sigmoidoscopy every 3-5 years indefinitely following the procedure (127).

4) Personal History of Breast or Genital Carcinoma

Epidemiologic studies have shown that women who have recovered from breast, endometrial or ovarian cancer have up to a two-fold increase in the risk of developing colorectal cancer (35,129-130). A prospective study of these patients by Rozen et al, using annual FOBTs and flexible sigmoidoscopy at 3 year intervals for screening found that adenomatous polyps and cancers were over 2.5 times more frequent in the study group as a whole, and 3 times more frequent in women with a past history of breast can cer (130). Current recommendations for screening generally include annual FOBTs and flexible sigmoidoscopy every 3-5

years, initiated at the time of diagnosis of genital or breast cancer (35,127,130).

5) Family History of Colorectal Cancer

The contribution of hereditary factors to the development of colorectal cancer in the population at large is not well understood. Retrospective epidemiologic studies have suggested that the risk of colorectal cancer is two to three-fold greater in first degree relatives of patients with colonic cancer (131) although such studies have been criticized for not necessarily excluding patients with the family cancer syndromes (5). Recent studies by Burt et al (132) and Cannon-Albright et al (133) of several kindreds with multiple cases of common colorectal cancer but no recognizable patterns of inheritance demonstrated a 21% incidence of adenomatous polyps in family members but only 9% in controls (spouses). Furthermore, likelihood analysis strongly suggested the dominant inheritance of a susceptibility to colorectal adenomas and cancers with a gene frequency of 19%. These investigators are currently studying relatives of single, randomly selected patients with colon cancer to confirm their hypothesis that an inherited susceptibility to adenomatous polyps is responsible for many cases of "sporadic" colon cancer. Since less than 20% of the population may be truly at risk from colon cancer, another implication of this study is that mapping the presumed susceptibiltiy locus to one of the numerous restriction fragment length polymorphisms now available could allow initial genetic screening with an 80% reduction in requirements for other strategies such as FOBTs, sigmoidoscopy, etc.

Currently, opinions on the appropriate screening of persons with one or more first degree relatives with colon cancer vary considerably. Bresalier and Kim (5) note that it remains to be determined if "patients

with a suggestive family history for example, one first-degree relative with colon cancer and one first-degree relative with breast cancer" should be "monitored in the same way as average-risk patients or be screened more rigorously". The American Gastroenterological Association (127) recommends annual FOBTs and flexible sigmoidoscopy every 3-5 years beginning at age 35-40 if there is one first degree relative with colon cancer and colonoscopy every 3-5 years if 2 or more relatives are involved.

Gryska et al (134) and Guillem et al (135) have determined from routine endoscopic screening programs of patients with one or more first-degree relatives with colon cancer that 20-30% of those with polyps had lesions not identifiable by flexible sigmoidoscopy and therefore feel colonoscopy is indicated. Grossman et al (136) suggest that colonoscopy is not an appropriate first step in screening persons with one affected first-degree relative as the prevalence of adenomas in this group, determined from colonoscopic examination, was no higher than might be expected in the general population. Rozen et al (137) found a 2-fold increased incidence of adenomatous polyps in first-degree relatives of those with colon cancer versus a control group when screened with FOBT and flexible sigmoidoscopy, and in a subsequent cost-analysis (138) calculated that initial colonoscopic screening became markedly (4-fold) more cost-effective if restricted to persons with two or more first-degree colon cancer relatives. In this group, initial colonoscopy significantly reduced the cost of screening. Eddy et al (139) applied a mathematical model to screening in this population (first-degree relative with colorectal cancer) and concluded that colonoscopy every 5 years or air-contrast barium enema every 5 years with an FOBT yearly, starting at age 40, were both highly efficacious strategies, the lower cost of the latter making it more cost-effective.

To conclude, since all these analyses were based on rather limited and conflicting data concerning the actual risk of colon cancer in these individuals, the previously outlined recommendations of the American Gastroenterological Association would seem a reasonable compromise.

6) Personal History of Colon Cancer

Since the frequency of synchronous or metachronous colorectal cancers is significant (1.6-7.6% and 1.4-10%, respectively) in persons diagnosed with one (139B), this group has been singled out for closer surveillance. Current recommendations include preoperative colonoscopy or colonoscopy during the first 6 months to "clear" the colon followed by repeat evaluation at 1 year and then at 3 year intervals (5,127).

Additional recommendations including periodic measurement of liver functions tests and CEA levels, as well as chest X-rays are controversial (5,127,140). Whether the frequency of colonoscopy may be decreased further after several negative examinations remains unclear (5).

7) History of Polyps - Adenomatous and Hyperplastic

Patients with a prior history of adenomatous polyps have a 20-40% chance of recurrence (24,25) and 25-40% of these patients may have a proximal lesion not detectable by flexible sigmoidoscopy (141,142). For these reasons, these patients are considered a high- risk group and complete surveillance of the colon is recommended. As discussed previously, initial colonoscopy is generally felt to be the procedure of choice (3,8,22,25) but only very limited data exist to demonstrate its diagnostic superiority to the combination of flexible sigmoidoscopy and

DCBE (94). Current recommendations by the American Gastroenterological Association include complete colonoscopy within one year of the index polypectomy (to "clear" the colon of missed synchronous lesions) followed by a repeat procedure at 3 year intervals with annual FOBTs (127). Boland et al (9) recommend dividing patients into low and high-risk groups at the time of polypectomy as follows:

RISK FACTORS FOR ADENOMA RECURRENCE

Low Risk	High Risk
Solitary adenoma	Multiple adenomas
Size <1 cm	Size ≥1 cm
Mild, moderate dysplasia	Severe dysplasia (carcinoma *in situ*)
Pedunculated	Sessile tubulovillous or villous
	Invasive carcinoma

All patients should then undergo a colonoscopy within 1 year and if the findings are negative, low-risk patients should receive colonoscopic surveillance at 3-5 year intervals, high-risk individuals at 2 year intervals. However, if the 1 year examination were to reveal additional adenomas, they recommend yearly colonoscopic surveillance until an adenoma-free colon is achieved. They also recommend annual FOBTs.

Bond, on the basis of preliminary data from the National Polyp Study (143) also recommends dividing patients into a low and high-risk group but with follow-up colonoscopy at 1 year and then every 3 years for high-risk patients and only every 3 years for the low risk group. He also advises increasing the surveillance interval to 5 years after 2 negative examinations and feels that DCBE combined with flexible sigmoidoscopy is a reasonable approach if colonoscopy is not feasible. He does not discuss the role of FOBTs in this setting. Data from the St. Mark's Neoplastic Polyp Follow-Up Study suggested that the sensitivity and

specificity of the FOBT was so poor in these patients that they have completely eliminated it from their follow-up protocol (93).

To conclude then, opinions vary as to the appropriate follow-up of adenomatous polyps, largely because of the limited information available about the growth and transformation rates of these lesions. Two large prospective studies are currently in progress in patients with adenomatous polyps - The National Polyp Study (143) and The St. Mark's Neoplastic Polyp Follow-Up Study (93) and should provide us with more concrete information on which to base our recommendations.

Hyperplastic polyps until recently were felt to be of no significance except for their nuisance value since several studies have demonstrated the endoscoper's inability to differentiate them from small adenomatous polyps except by biopsy (142). In 1985 however, a large multicenter autopsy study found a 3.5 - fold increase in the likelihood of finding hyperplastic polyps in patients with adenomas (144) and similar data was reported by Ansher et al (145) from colonoscopic evaluation of 845 patients. Moreover, they noted a 10 - fold increase in proximal adenomas in patients with hyperplastic polyps of the descending colon or rectosigmoid as opposed to those without. Provenzale et al (146) retrospectively reviewed 1588 consecutive colonoscopy reports and concluded the following:

1) patients with hyperplastic polyps had a prevalence of adenomatous polyps that was 26.4 times that of patients without hyperplastic polyps

2) patients with only hyperplastic polyps of the rectosigmoid (ie no distal adenomas) had greater than a 4 fold increased risk of proximal adenomas only detectable by evaluation of the entire colon.

Lieberman (142) notes that investigators from the National Polyp Study are not convinced of this relationship and report that of 300 patients with hyperplastic polyps, 50% had concurrent adenomas and 50% did not (147).

The potential implication of hyperplastic polyps being a marker for adenomas is enormous. Since the former have an estimated prevalence 10-times that of adenomas, colonoscopic surveillance of these patients would be burdensome, however could yield significant benefits. At present, the best approach to dealing with patients in whom isolated hyperplastic polyps are recognized is unknown.

8) Inflammatory Bowel Disease

Reliable data regarding the risk of cancer in patients with inflammatory bowel disease are difficult to come by, despite the fact that this association has been known for many years (148). A lengthy discussion of the pros and cons of surveillance in patients with ulcerative colitis and Crohn's disease is beyond the scope of these Grand Rounds but the reader is referred to two excellent reviews of this subject by Collins, Feldman and Fordtran
(149) and Glotzer (148).

Briefly, the American Gastroenterological Association currently recommends annual colonoscopy with multiple biopsies in patients with universal ulcerative colitis of 8-10 years duration and colectomy if severe dysplasia is found and confirmed (127). This is because they classify these patients as at extremely high risk for ultimately developing colon cancer. Patients with left-sided ulcerative colitis of 15-20 years duration are at "moderate risk" and colonoscopy every 1-2 years after this time with multiple biopsies and colectomy if severe dysplasia is found and

confirmed is recommended (127). Collins et al (149) argue that the degree of increased risk associated with extensive ulcerative colitis is unknown and that the studies on which the above recommendations are based are replete with biases and methodologic errors. They further assert that studies of dysplasia have similar problems and that surveillance programs have not been demonstrated to result in improved survival despite their inconvenience, risk and cost. They conclude that "screening of patients with ulcerative colitis with use of yearly colonoscopy is of even more questionable benefit than Hemoccult screening of the normal population." The risk is estimated to be much lower for patients with Crohn's disease and surveillance is not recommended by most (148).

Screening Recommendations for Colorectal Cancer In The Average Risk Population

Since the risk of colorectal cancer is only significant after the 4th decade of life but doubles with each decade thereafter (3), no one advocates screening asymptomatic individuals of average-risk before this time. Here, however, disagreement begins. The American Cancer Society, World Health Organization Center for the Prevention of Colorectal Cancer, National Cancer Institute and American Gastroenterological Association all recommend digital rectal examinations yearly beginning at age 40 with annual FOBTs beginning at age 50 and sigmoidoscopy every 3 to 5 years also beginning at this time (150). The Canadian Task Force, however, no longer recommends screening by means of FOBTs or sigmoidoscopy in these groups although agrees that the evidence is "insufficient to warrant stopping this practice where it already exists" (27). Frame recommends annual FOBTs but feels the evidence is insufficient to recommend flexible sigmoidoscopy (151).

On review of the literature I concur with the opinion of Winawer et al (150) that while the evidence is insufficient to support a recommendation for mass screening of the population at large, the guidelines outlined by the American Cancer Society can be justified in terms of "case-finding" that is the approach to the individual patient within an established practice. This is in fact the viewpoint of all major organizations recommending guidelines for the detection of colorectal cancer. Application of these guidelines to the population at large should require demonstration of improved survival and a clear understanding of the costs involved.

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