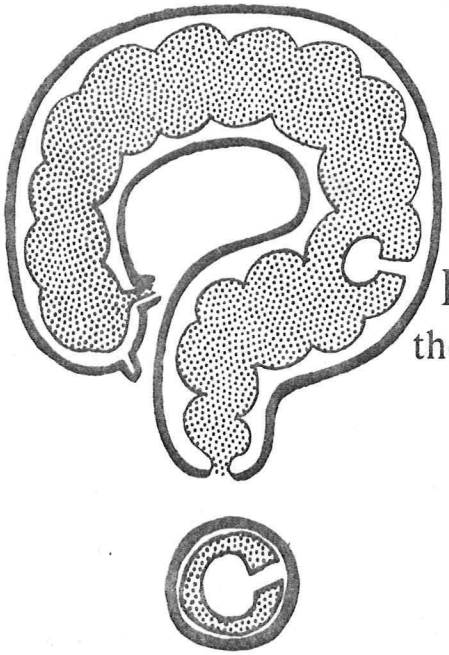
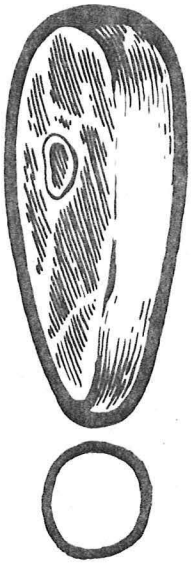
Medical Grand Rounds

University of Texas Southwestern Medical School

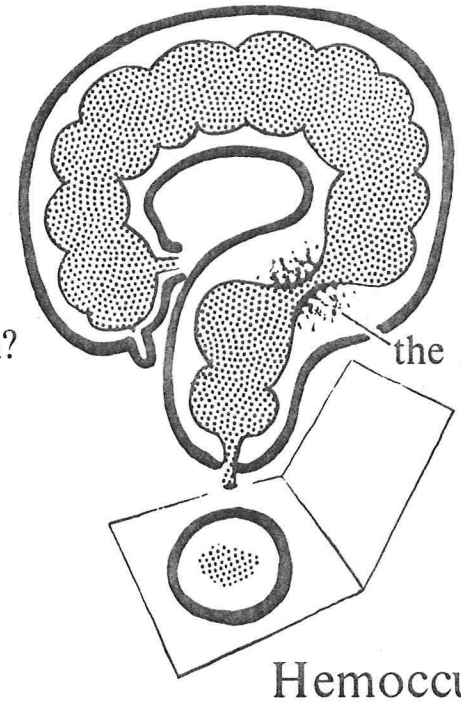
CURRENT CONCEPTS OF COLON CANCER



Polyps:
the Premalignant Lesion?



Red, Fat Meat:
the Causative Factor?



the Problem

Hemoccult®:
Early Diagnosis?

Walter Peterson, M.D.

17 August 1978

Introduction

The technique of electrocautery polypectomy via a flexible, fiberoptic colonoscope is believed by many to be a procedure that, if carried out universally in all patients with colon polyps, would essentially wipe out the entity of colorectal cancer. If, indeed, we have such a powerful tool at our disposal, it becomes important to review the topic of colon cancer in general and the prevention of colon cancer in particular. Although cancer of the colon and cancer of the rectum have several differing characteristics, these are becoming less noticeable. This discussion will deal with colorectal cancer as a single entity.

The Problem

Colorectal cancer is the most common internal cancer in the United States today, accounting for 15% of all cancers. This compares to an incidence of breast cancer of 14% and lung cancer of 13%. This year there will be some 100,000 new cases of colon cancer in the United States and at current rates, one of every 25 people will develop colorectal cancer during their lifetime. By the year 2000, about 140,000 new cases will be found per year.

The 5-year survival with colon cancer today is less than 50% and in 1978 about 50,000 people will die of the disease. This is one for every 5000 of our population. The death rate for colon cancer is second only to lung cancer and is greater than breast cancer (Table 1). Of note, survival has not improved over the past 20 years.

Table 1.

SURVIVAL WITH COLON CANCER

	% 5-YEAR SURVIVAL			
TYPE OF CANCER	1940-49	1950-59	1960-64	1965-69
LUNG	4%	8%	9%	9%
COLORECTAL	30%	40%	42%	42%
BREAST	53%	60%	62%	64%

Putting these figures in perspective, almost 600,000 person-years of life were lost to colon cancer in 1968. Colon cancer is a problem whose importance clearly outweighs the efforts expended in its investigation to date.

The male to female ratio is about 1:1 and the incidence is similar in caucasians and blacks. This is in contrast to previous years when men and caucasians experienced the disease more commonly. While the age range of colon cancer is 9 months and up, the vast majority of cases occur in individuals from 40-80 years (Figure 1). This is important in deciding at what age one should begin looking for colon cancer in the population.

Figure 1

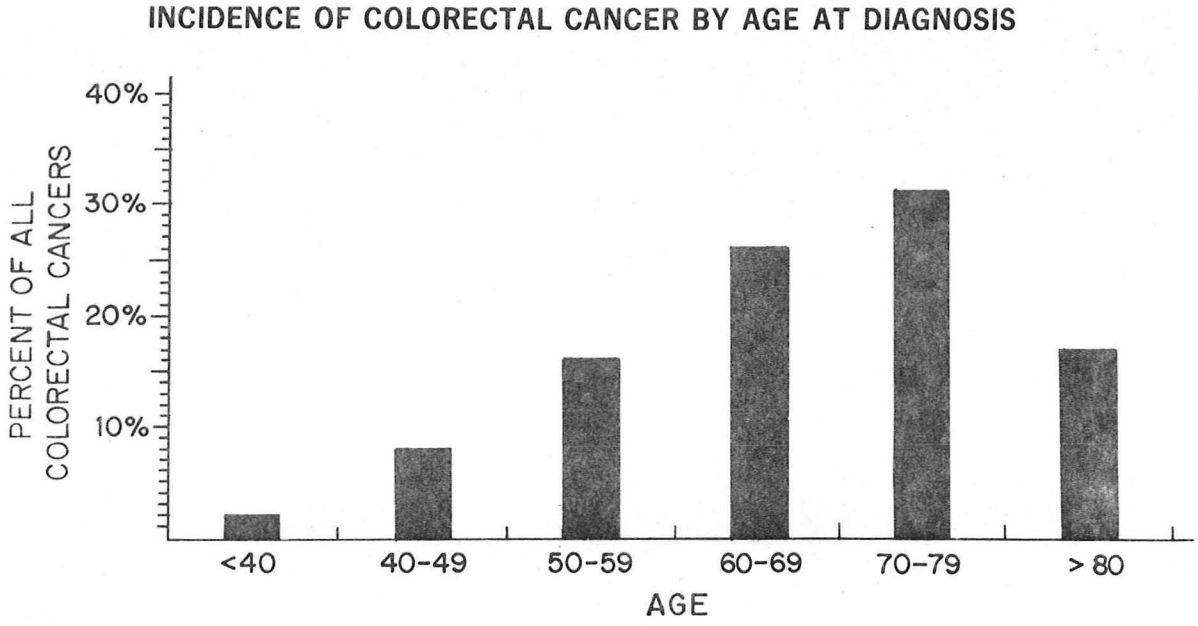
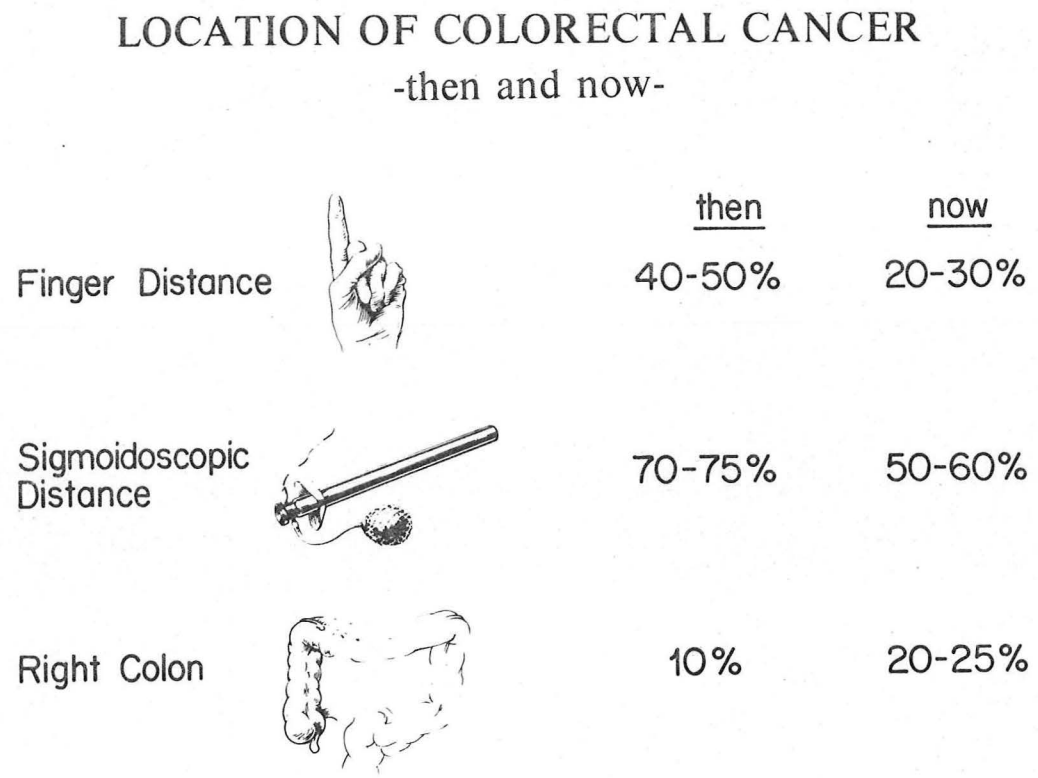


Figure 2

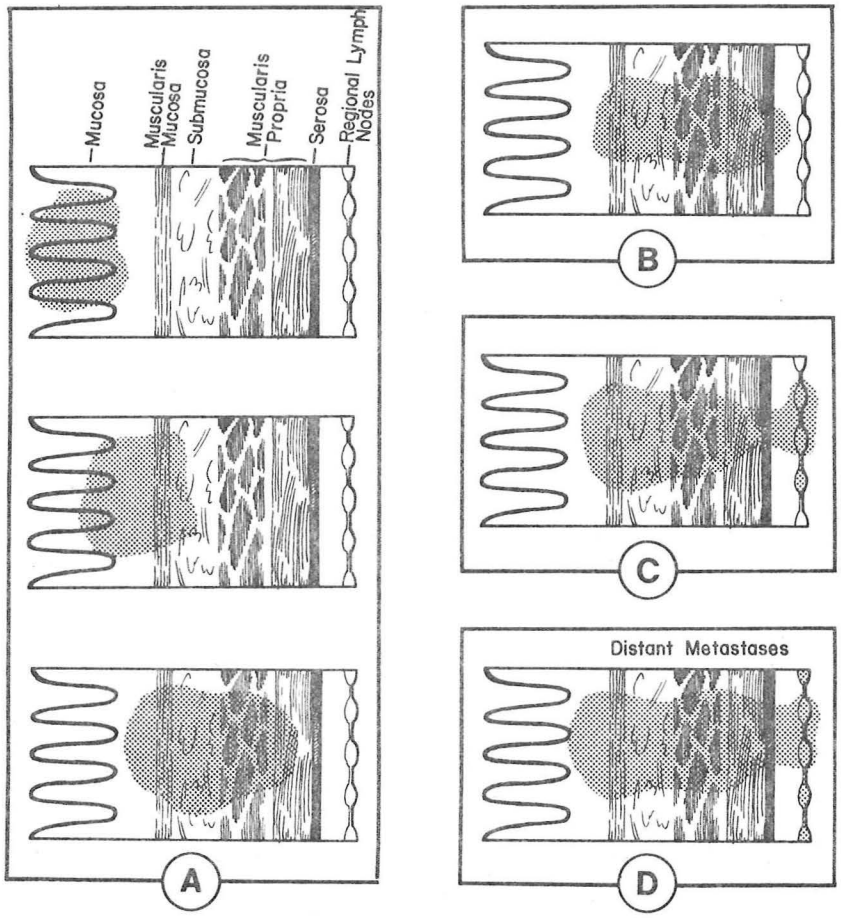


The location of cancer in the colon has changed over the past two decades (Figure 2). Whereas formerly almost one-half of cancers were within reach of the examining digit and almost three-fourths could be diagnosed by sigmoidoscopy, only 30% and 60% respectively are in such locations today. The increase in right-sided lesions is consistent with these changes. These observations, of course, have importance in terms of diagnostic approaches.

An important vital statistic of colon cancer is the cure rate in relation to the histologic invasiveness of the tumor. Figure 3 depicts current modifications of Cuthbert Duke's orginal classification of colon cancer.

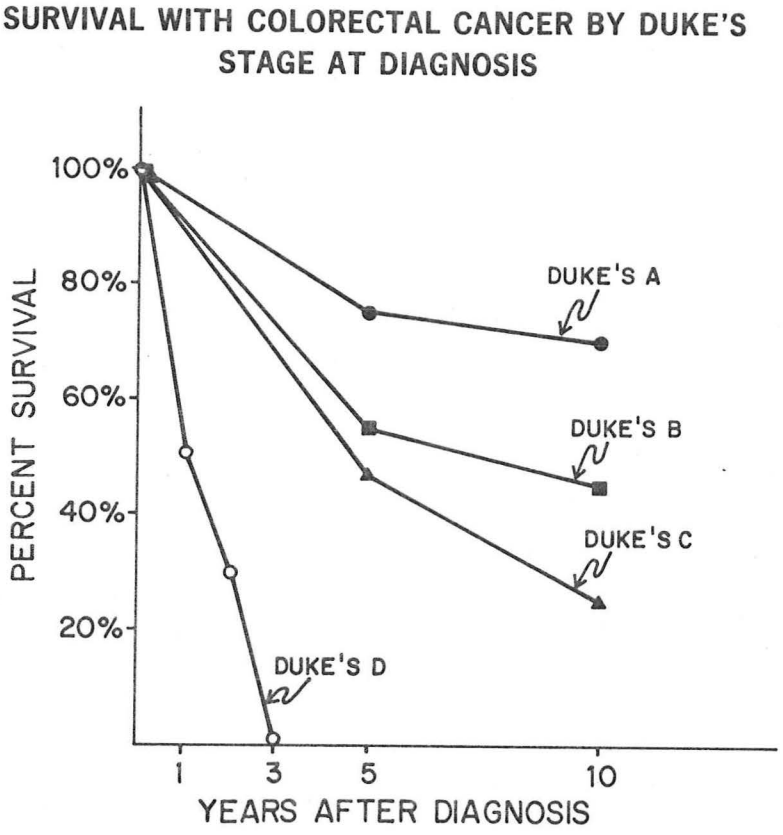
Figure 3.

DUKE'S STAGING OF COLON CANCER



Duke's A colon cancer involves varying levels within the bowel wall. Duke's B extends through the wall but not to any lymph nodes; Duke's C involves regional lymph nodes; and Duke's D is defined as distant metastasis. The survival curves for each of these stages is shown in Figure 4.

Figure 4.



It is clear from these figures that the hope for colon cancer lies in diagnosis at a point where the tumor is no more invasive than Duke's A or B.

If the cost, mortality, and suffering from colon cancer are to be reduced, three avenues are available:

1. DEFINE THE CAUSATIVE AND CONTRIBUTORY FACTORS
   - REMOVE THEM -

2. DEFINE ANY PREMALIGNANT LESIONS
   - REMOVE THEM -

3. DEVELOP EFFECTIVE SCREENING METHODS TO FIND EARLY OR PREMALIGNANT LESIONS
   - USE THEM -

In discussing these three pathways, one must keep in mind three reservations. First, most data concerning causation of colon cancer are based on tenous epidemiologic observations rather than solid experimental models. They are none-the-less provocative. Second, recommendations for early diagnosis and later follow-up have not withstood the scrutiny of "cost-effectiveness"or time. They are based on current logic and a desire for reasonable, high-quality patient care. Third, applying new knowledge to the general population may be altogether another issue. The attitudes of man are unpredictable and will confound our most well-intentioned goals.

Epidemiology

Geography

Investigation into the causation of colorectal cancer began with the observation that the incidence of this neoplasm varies markedly within different areas and countries of the world. While most records are far from exact and seldom age-standardized, some countries clearly have a high rate of colon cancer while others enjoy a very low rate (Table 2).

Table 2.

INCIDENCE OF COLORECTAL CANCER

IN SEVERAL COUNTRIES

HIGH		MODERATE	LOW
SCOTLAND	USA	HUNGARY	UGANDA
IRELAND	CANADA	POLAND	NIGERIA
ENGLAND	AUSTRALIA	ISRAEL	INDIA
AUSTRIA	NEW ZEALAND	GREECE	JAPAN
GERMANY	ARGENTINA	FINLAND	PANAMA
FRANCE	URUGUAY		COLOMBIA

Thus, high rates of cancer are found in Western European, North American, and Australian populations; moderate rates are found in Eastern Europe, Israel and the Iberian peninsula; and very low rates in Asian, African, Central and South American countries. There are, of course, exceptions to these generalizations (eg., Argentina has a very high rate; Finland a moderate rate) but the U.S., for example, has a rate close to 40 cases/100,000 population while Nigeria has a case rate of only 1/100,000. Interestingly, countries with high rates of colon cancer tend to have relatively lower rates of gastric cancer. The two possible explanations for these differences are variance in genetic factors or environmental factors.

Genetic Factors

With the exception of familial polyposis syndromes and cancer families, genetic variabilities appear to play small roles in differing rates of colon cancer. The bulk of the evidence for this statement rests on studies of migrant populations. For example, Jews who migrate to Israel from Yemen and North Africa have a lower rate of colorectal cancer than do those who migrate from Western Europe and North America. In turn, Jews in New York City have a much higher rate than Jews in Israel. Poles and Puerto Ricans migrating to the United States develop, over only a two decade span, an increased risk compared to that in their homelands.

The most carefully studied groups are the Japanese who move to Hawaii or the continental United States. Both first (Issei) and second (Neisei) generation Japanese in Hawaii and California have a much higher rate of colon cancer than their homeland counterparts. Interestingly, only the Neisei experience a commensurate reduction in the rate of stomach cancer. This implies that either the cause of stomach cancer takes longer to express itself or, more likely, the propensity to develop gastric cancer occurs early in life. Thus, the Issei were "set" while children in their homeland with a propensity to develop gastric cancer while their offspring, born in their new country, were not.

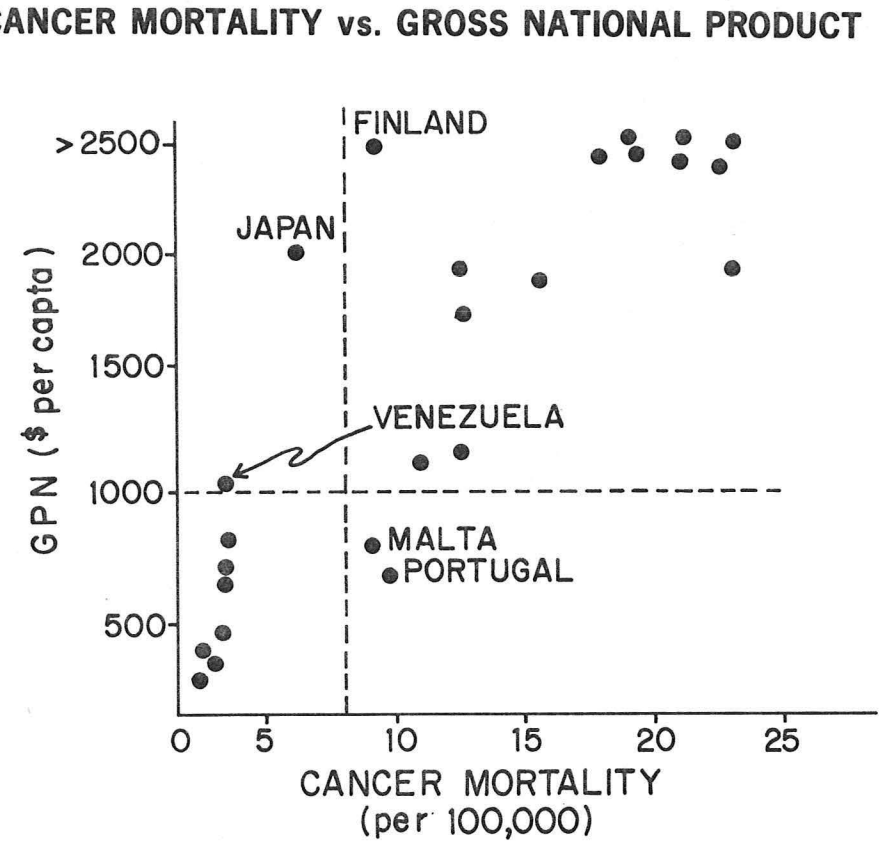
Finally, black Americans, who previously enjoyed a relatively low incidence of colon cancer, now have a cancer rate approching that of caucasians, much higher than their African counterparts. Clearly, the influence of the environment is paramount in promoting colorectal cancer.

Environmental Factors

One obvious difference between the countries experiencing high and low rates of colon cancer is the standard of living. A comparison of per capita gross national product (GNP) with mortality from colon cancer is shown in Figure 5 (From Kassira). There is reasonably good correlation between industrialization (GNP) and an increasing risk of colon cancer. Futher evidence of this association is found by analyzing the cancer mortality rates in various regions of the United States. As a rule there is increased risk of colon cancer in the more highly-industrialized Northeast and North Central areas. Certainly it is feasible that pollutants and chemicals which are inherent in highly industrialized areas and have ready access to the large bowel via inhalation, ingestion, or cutaneous absorption might have a carcinogenic potential in association with the colon.

There are several arguments against the industrialization theory. First, although in the past there was a slightly higher incidence of colon cancer in urban versus rural area, these differences are vanishing. Second, there are several prominent exceptions to the GNP-Colon Cancer Correlations. Japan and Venezuela have relatively high standards of living but low rates of cancer. Malta and Portugal have quite low GNP's but higher rates of cancer. Perhaps, then, variation in cancer rates is based on the adoption of a "Western" standard of living as opposed to only material abundance or economic success. This may explain world-wide differences as well as differences within individual countries. One very important difference between Western and Non-Western Societies is diet. Some have

Figure 5.



postulated that various chemical additives in food might be carcinogenic. However, Denmark has very stringent controls over the use of such additives and still exhibits a high incidence of colon cancer. Furthermore, alcohol and tobacco have been shown to bear no relationship to colon cancer. Thus, it is appropriate to investigate differences in the actual foodstuffs eaten by different peoples to detect any carcinogenic potentials. Such discussion must be prefaced by a cautionary note, however. Most dietary data in man are derived from broad assessments and are therefore circumstantial. It should also be remembered that cancer statistics probably reflect dietary habits existing many years before most correlations have been made.

Diet

The first popular diet theory was the "fiber-deficient" theory popularized by Denis Burkitt. He observed that rural blacks in Uganda (with a low rate of cancer) ate a diet consisting chiefly of raw fruits, vegetables, and unrefined grains whereas the English Whites (with a high rate of cancer) ate a diet consisting largely of processed and refined foods. He concluded that unabsorbable fiber was the most noticeable difference between Western and English diets. Stools of the Africans were larger; those of the English smaller. The low-bulk diet prolongs bowel transit time and allows potential carcinogens longer contact time with the bowel wall. Burkitt also speculated that this change in diet alters colonic bacterial flora, a possible factor in carcinogenesis. The rationale is based on the fact that cancer of the small bowel, where stool is liquid allowing rapid passage and the bacterial count is low, occurs very rarely. In the colon, stool is solid, passage is slower, and bacterial counts higher. Burkitt noted that the stools of African natives were odorless, implying a relative lack of bacterial putrefaction. These differences are summarized in Table 3.

Table 3.

	STOOL WEIGHT	BOWEL TRANSIT	STOOL ODOR?
AFRICANS	LARGE	RAPID	NO
ENGLISH	SMALL	SLOW	YES

A number of arguments have been marshalled against this theory being at least the sole cause of colon cancer. First, there is no relationship in a number of studies between constipation and colon cancer. Second, Glober has found that Japanese migrants have rapid bowel transit similar to native Japanese and Africans, yet much higher rates of colon cancer. Third, Seventh Day Adventists in California eat a low bulk, vegetarian diet and still have a relatively low incidence of colon cancer.

Kassira has compared the consumption of animal fat in countries with high and low mortality from colon cancer (Figure 6). There is a clear correlation between animal fat intake and colon cancer. Indeed, 12% of total calories eaten in Japan are derived from fat (mostly unsaturated) while in the U.S., almost 40% comes from fat (at least half of which is saturated). There is a strong correlation between international mortality rates from colon cancer and arteriosclerotic heart disease (ASHD) (Figure 7), a disease in which a connection to fat is more generally accepted. It is important, however, that within Western countries no correlation has been found between serum cholesterol concentrations and the later occurrence of colon cancer.

Figure 6.

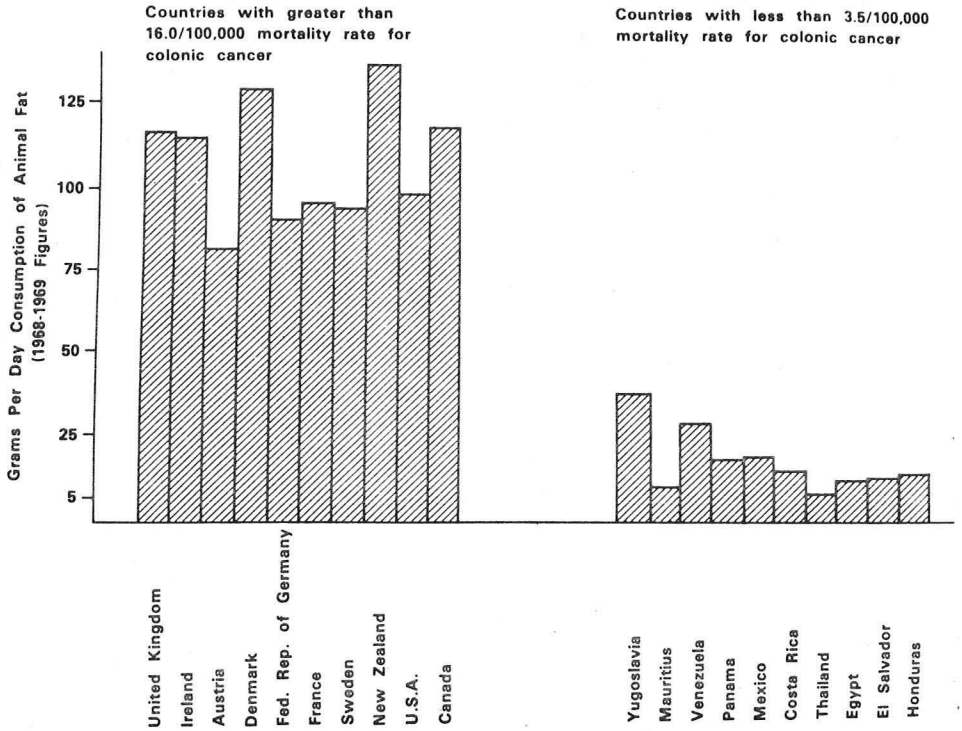
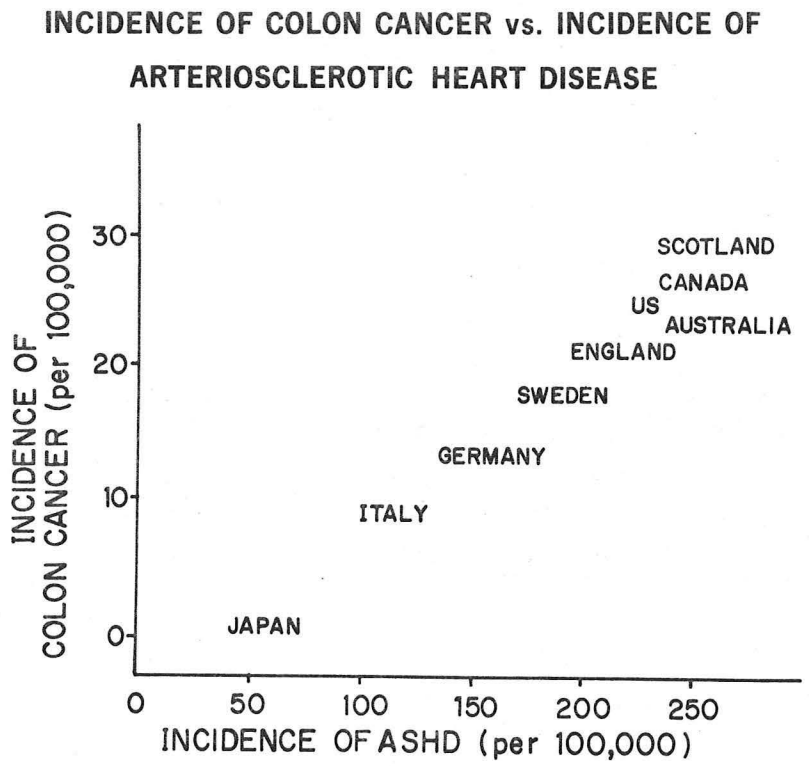
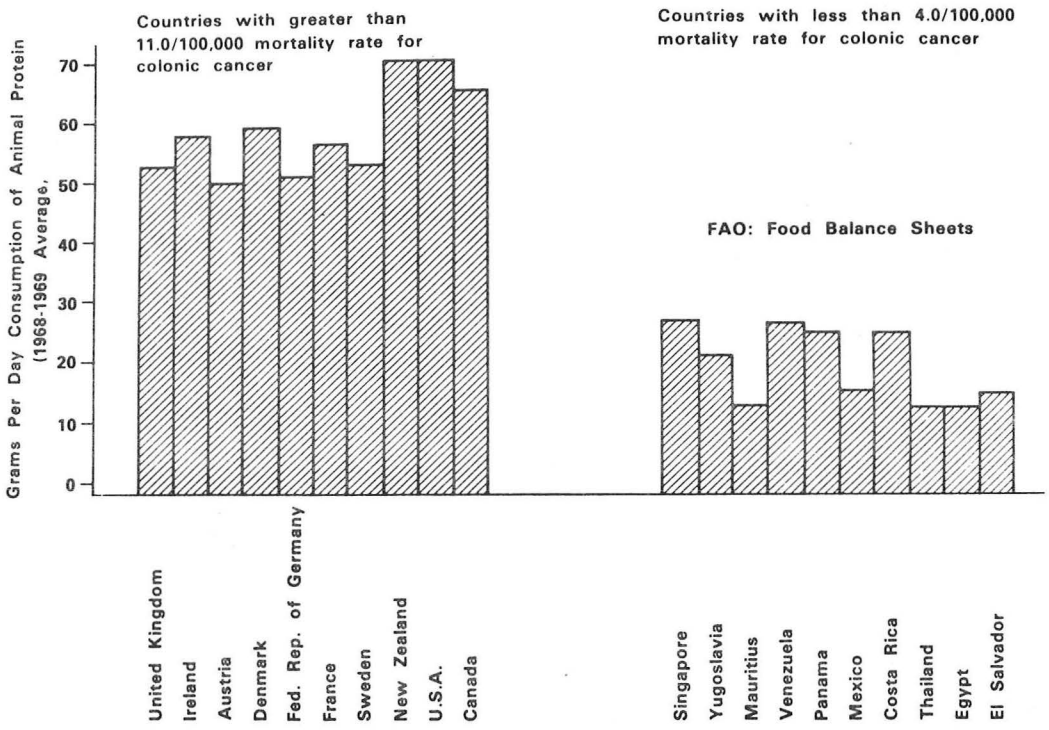


Figure 7.



Kassira has also plotted the consumption of animal protein with the mortality from colon cancer and, once again, there is a correlation (Figure 8).

Figure 8.

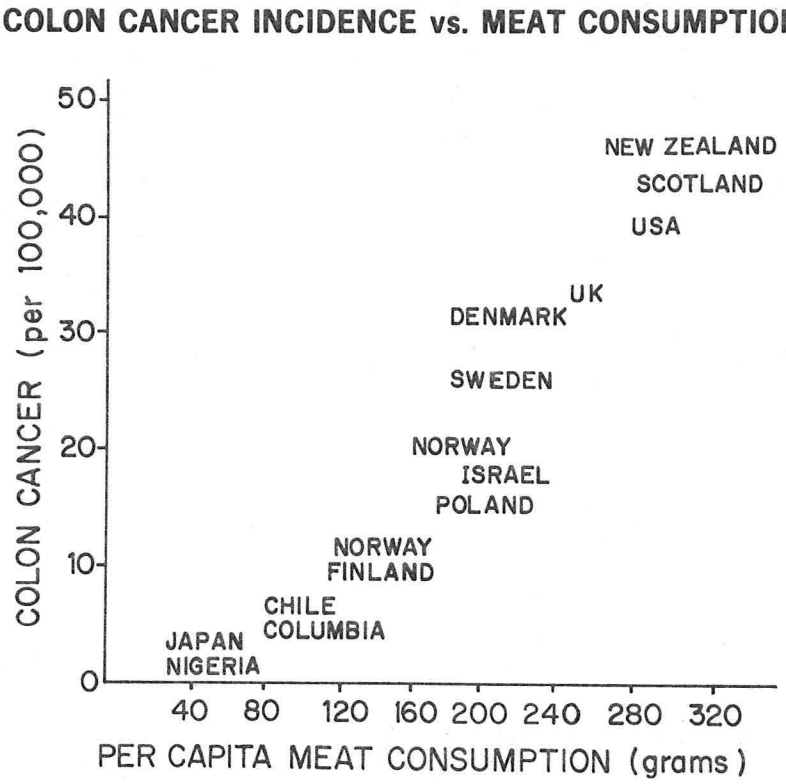


Haenszel originally indicted meat as a contributing factor to colon cancer from a case-control study of Japanese migrants to Hawaii. Patients with colon cancer ate more beef (and legumes) that did their counterparts who had not adopted a Western diet and who enjoyed a much lower rate of colon cancer. Armstrong and Doll conducted a careful food survey of 23 countries and found the incidence of colon cancer most closely correlated with the per capita daily meat consumption (Figure 9). While GNP and total fat intake also correlated, they could be accounted for by the meat consumption. They also noted no relationship of dietary fiber intake to colon cancer.

Several epidemiologic observations can thus be explained by the meat theory:

1. Argentina and Uruguay have quite high consumption rates of meat. Each has a relatively high rate of colon cancer despite a low GNP.

Figure 9.



2. Scotland has a very high rate of colon cancer, particulary in rural areas and especially Aberdeen and other beef-raising areas. Scots consume less meat overall but 19% more beef than English. Their mortality from colon cancer is 19% higher than that of the English.

3. Native Japanese eating a "Western" diet have a higher rate of cancer than those eating a "traditional" diet.

4. Seventh Day Adventists who consume an ovolacto-vegetarian diet have a relatively low rate of colon cancer.

5. Blacks formerly consumed greater amounts of maize and related fibrous substances and had one half the incidence of colon cancer that caucasians had. Now, eating a diet with more meat, their cancer risk is equal to caucasians.

6. There is no example of a population with high beef consumption and low rate of colon cancer.

Although the evidence presented is circumstantial and hampered by the fact the human diet does not consist of isolated foods, the best current theory is that most colon cancer is related to the increased intake of beef fat and protein while low bulk diets play only a minor role if any. Hard data are not yet forthcoming to prove these theories.

Proposed Mechanisms of Dietary Carcinogenesis

Important endogenous compounds that are related to the dietary fat in meat and are secreted into the gut include acid and neutral sterols. Dietary factors may also alter the intestinal microflora. The theory of dietary carcinogenesis, then, involves two aspects. First, a particular diet may affect the supply of substrate (eg., bile acids and neutral sterols) for carcinogen or co-carcinogen production. Second, there is a change in intestinal flora to act on these substrates.

Interest in bile acids (acid sterols) has stemmed from several lines of evidence:

1. The structure of bile acids is similar to carcinogenic polycyclic hydrocarbons.

2. Deoxycholic acid can be converted to 3-methyl cholanthrene, a carcinogen.

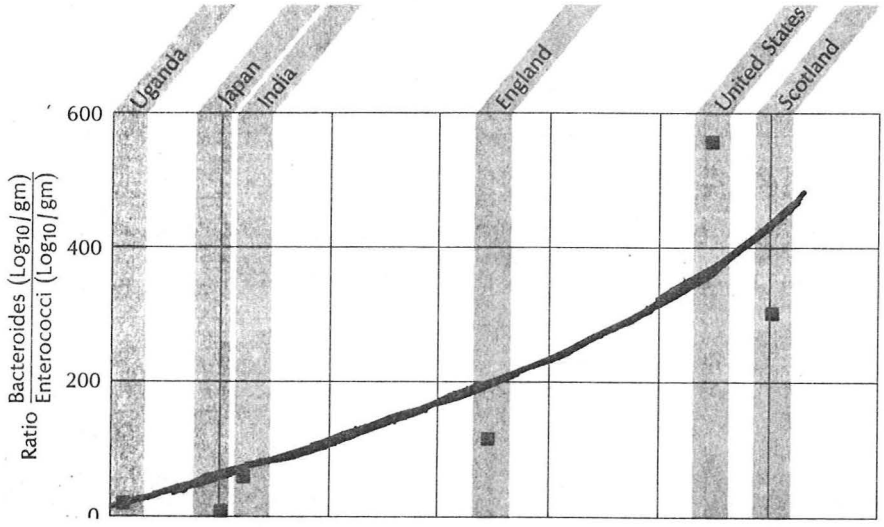
3. Aromatization of the bile acid nucleus can produce a carcinogen related to cyclopentenophenanthrene. Three of the four reactions necessary for the introduction of double bonds are carried out by anaerobic bacteria.

4. Bile acids enhance the action of carcinogens in experimental animals.

Hill's group compared the fecal flora of individuals from England, Scotland, and the U.S. to that of individuals from Uganda, Japan, and South India (Figure 10).

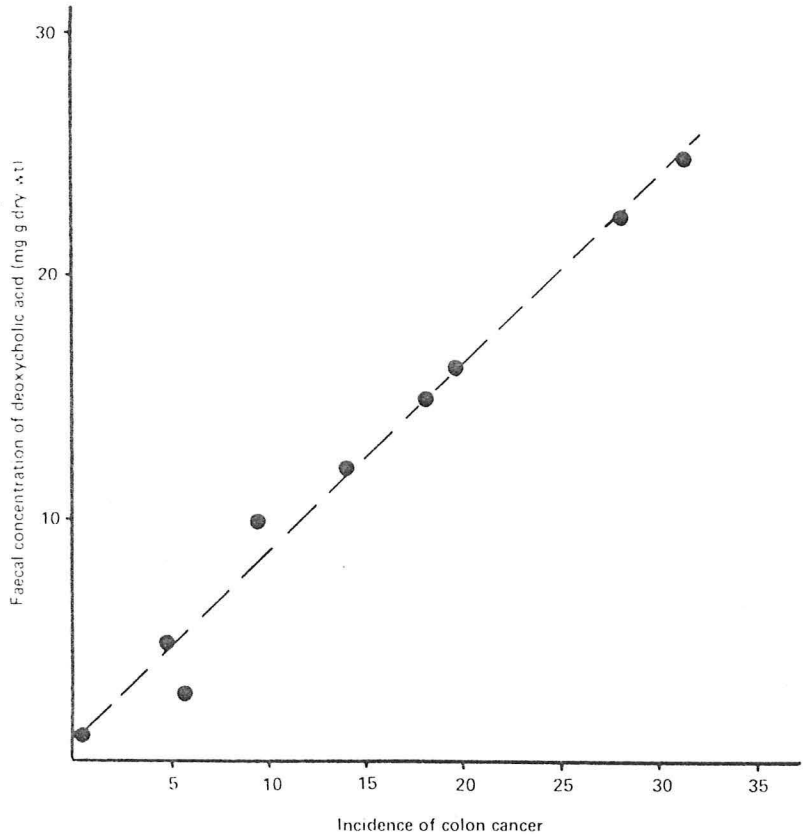
Figure 10.

Fecal Flora in Six Populations
(From Burdette)



The ratio of Bacteroides sp. to Enterococci is much higher in the stools of those from areas of high colon cancer risk. In addition, there is a correlation between fecal concentrations of neutral sterols (from cholesterol), acid sterols (from bile acids), and the incidence of colon cancer. Data with one bile acid, deoxycholic acid, are shown in figure 11.

Figure 11. Relationship of Fecal Deoxycholic Acid to Colon Cancer



Finally, Hill found that the number of bacteria producing 7 α-dehydroxylase (cholic → deoxycholic acid) is higher in the stools of subjects from high risk areas when compared to those from low risk areas. Dehydroxylation has been proposed as an early step in the formation of carcinogenic polycyclic aromatic compounds from bile acids.

Wynder and Reddy have confirmed these findings by comparing levels of neutral sterols and bile acids in the feces of 5 groups of people: Americans on a conventional mixed diet; American vegetarians; Seventh Day Adventists; Japanese Americans and Chinese Americans on a semi-vegetarian

diet. The results are shown in Figures 12A and B below.

Figure 12A.

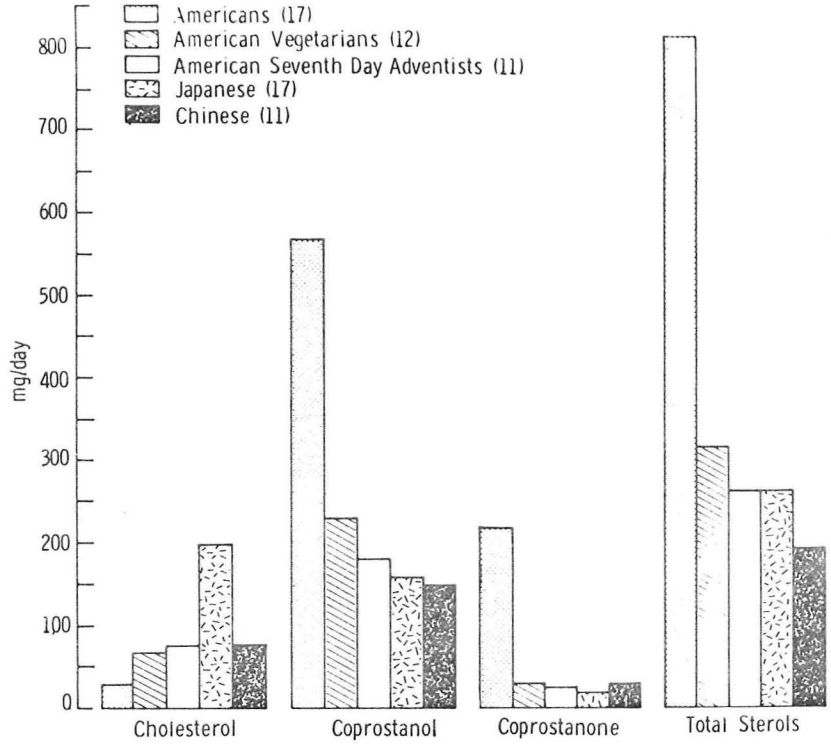
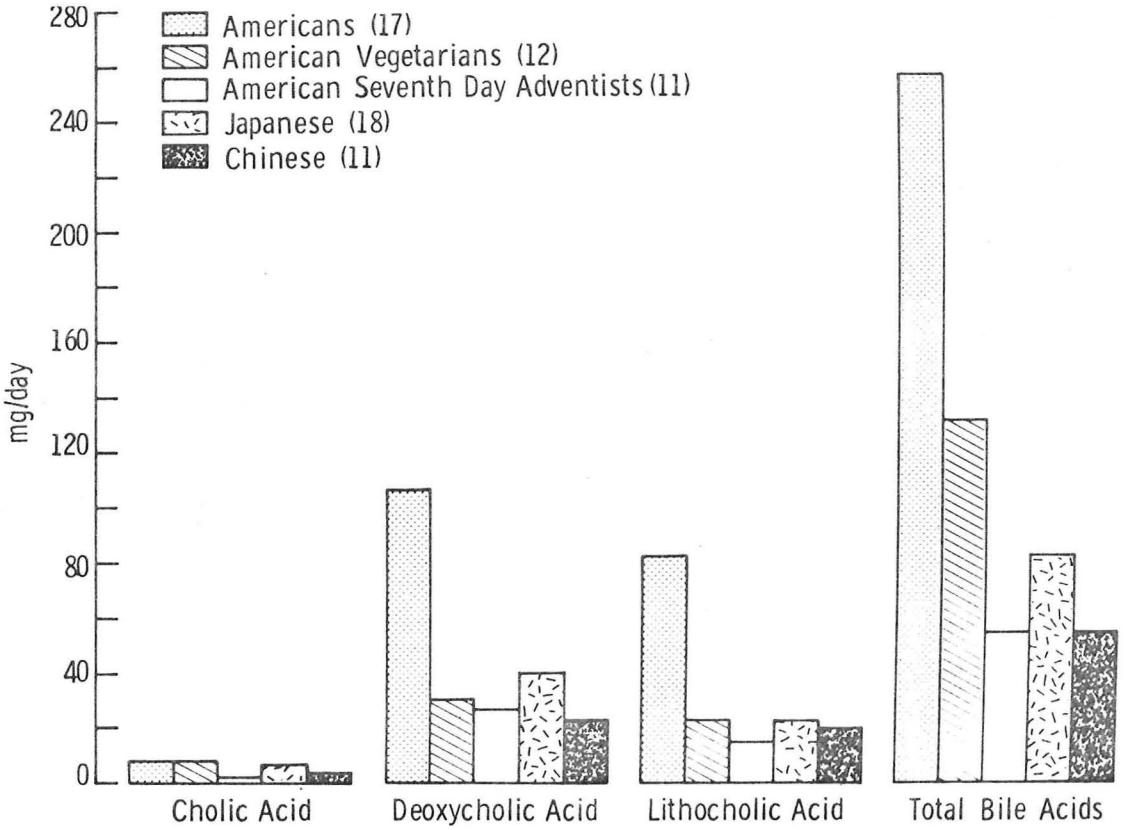


Figure 12B.



The average amount of neutral sterols was far higher in the stools of Americans on a conventional Western diet and the percentage present as unchanged cholesterol was much lower. Americans on a regular diet excreted more bile acids with a higher ratio of secondary to primary bile acids. Thus, not only does a Western diet appear to increase the fecal excretion of sterols, the gut flora is altered to enhance metabolism.

Proof that these changes induce cancer in man is not available. However, stools of patients with colon cancer have, when compared to controls, higher concentrations of neutral sterols, 7 α-dehydroxylase, deoxy- and litho- cholic acids (secondary bile acids). Concentrations of primary bile acids are not different. Whether these changes are cause or effect is problematic.

Other Enzymes

In addition to 7 α-dehydroxylase, the importance of which has been discussed, 3 other enzymes may play roles in this scheme of carcinogenesis. These include β-glucuronidase, bacterial nitroreductase, and bacterial azoreductase. The latter two are particularly important in relationship to the generation of aromatic amines which have been considered potentially carcinogenic compounds.

β-Glucuronidase has been found in greater concentration in the stools of Americans on a mixed-Western diet when compared to vegetarians or Japanese and Chinese Americans. Glucuronide conjugation may somehow be protective and the activity of β-glucuronidase may abrogate this protection. Finally, Goldin and Gorbach compared the fecal enzyme activities in omnivores eating 32 oz red meat/week with those in lacto-ovo-vegetarians. β-glucuronidase, nitroreductase, and 7 α-dehydroxylase were all elevated in those consuming a Western diet.

Effect of Dietary Manipulations

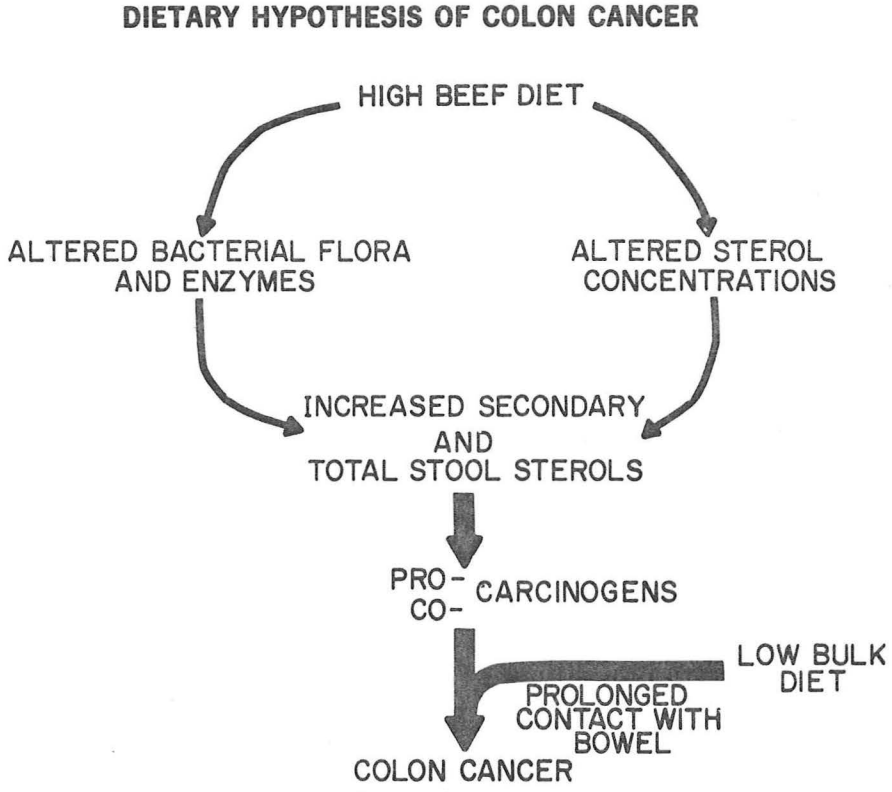
Rats fed grain and fiber diets have relatively low levels of β-glucuronidase, nitroreductase, and azoreductase. When shifted to a beef diet, there is a 2-2 1/2 fold increase in enzyme activities. Wynder and Reddy took 8 normal subjects who consumed a typical high meat, high fat diet and collected stools for 4 days. The subjects then were transferred to a non-meat, balanced diet. After 4 weeks on such a regimen, stools were again collected for 4 days. The high meat diet resulted in elevated levels of secondary bile salts and cholesterol metabolites; increased bacterial β-glucuronidase activity; and more total anaerobic bacteria.

In a similar study, Maier manipulated only the meat and not the fat content of the diets. There was no significant change in the fecal bacteria.

Finally, some mention should be made of the effect of bulk on the fecal excretion of sterols, bile acids, and enzymes. Goldin and Gorbach gave their volunteer subjects eating the omnivore diet liberal amounts of bran for 5 weeks. There were no differences in β-glucuronidase, nitroreductase and azoreductase. Only 7 α-dehydroxylase declined significantly. Since fiber probably binds bile salts, the substrate for bacterial flora is decreased and may eventuate in lower levels of 7 α-dehydroxylase.

Figure 13 summarizes the current dietary hypothesis of colon cancer. Even if correct, it does not preclude the contribution of environmental factors such as air pollutants in highly industrialized areas or other potential carcinogens.

Figure 13.



Dietary Recommendations

Data are not presently sufficient to justify wholesale modifications in dietary patterns in the hope of preventing colon cancer. Although it may well be beneficial in terms of general health to reduce total calorie intake and reduce fat intake, it is not likely this could be accomplished. Hope must rest instead on the removal of premalignant lesions if colon cancer is to be prevented.

The Premalignant lesion

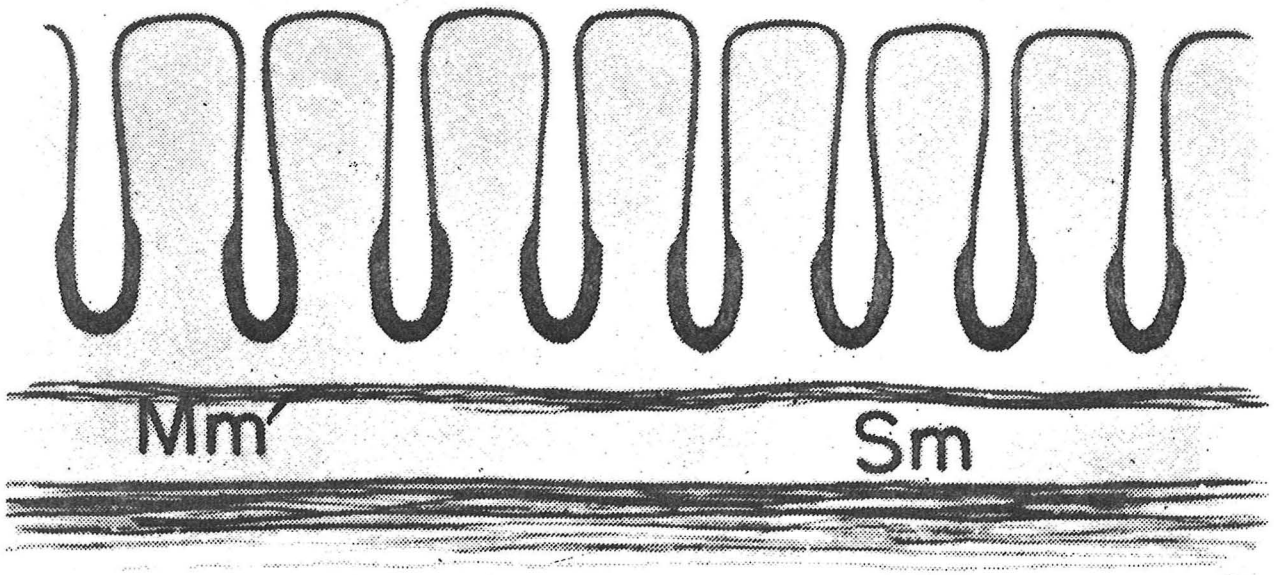
There is an expanding literature on cellular abnormalities in the colonic mucosa of patients with colorectal cancer. Investigation of groups with a high incidence of colon cancer (eg., ulcerative colitis, familial polyposis, and certain high risk families) has led to a model of abnormal cell differentiation as the premalignant phenomenon in colonic neoplasm. Normally, DNA synthesis ceases in colonic mucosal cells as they move from the crypts to the surface. Using tritiated thymidine as a label, Deschner and Lipkin in particular, have found that the surface mucosal cells of patients with the above conditions as well as those with cancer or isolated adenomatous polyps, continue to undergo mitosis and synthesize DNA. At a cytologic level, Morson has noted abnormalities in the mucosa of patients with ulcerative colitis which he believes are premalignant and forecast the presence or development of colon cancer. Similar changes are found in adenomatous polyps. The remainder of this discussion, then, will focus on polyps as the premalignant lesion of colon cancer. References are provided for those who wish to read more of Deschner's, Lipkin's, and others work.

The topic of polyps as premalignant entities is not new and debate continues in the literature. We will summarize this controversy with the understanding that a definitive answer may never be forthcoming.

Classification of Polyps

Normal cell division is restricted to the deepest 1/3 of colonic crypts of Lieberkühn. The cells migrate upward and differentiate into mature goblet and absorptive cells. Such cell division and migration is perfectly balanced by exfoliation of cells from the free mucosal surface (Figure 14).

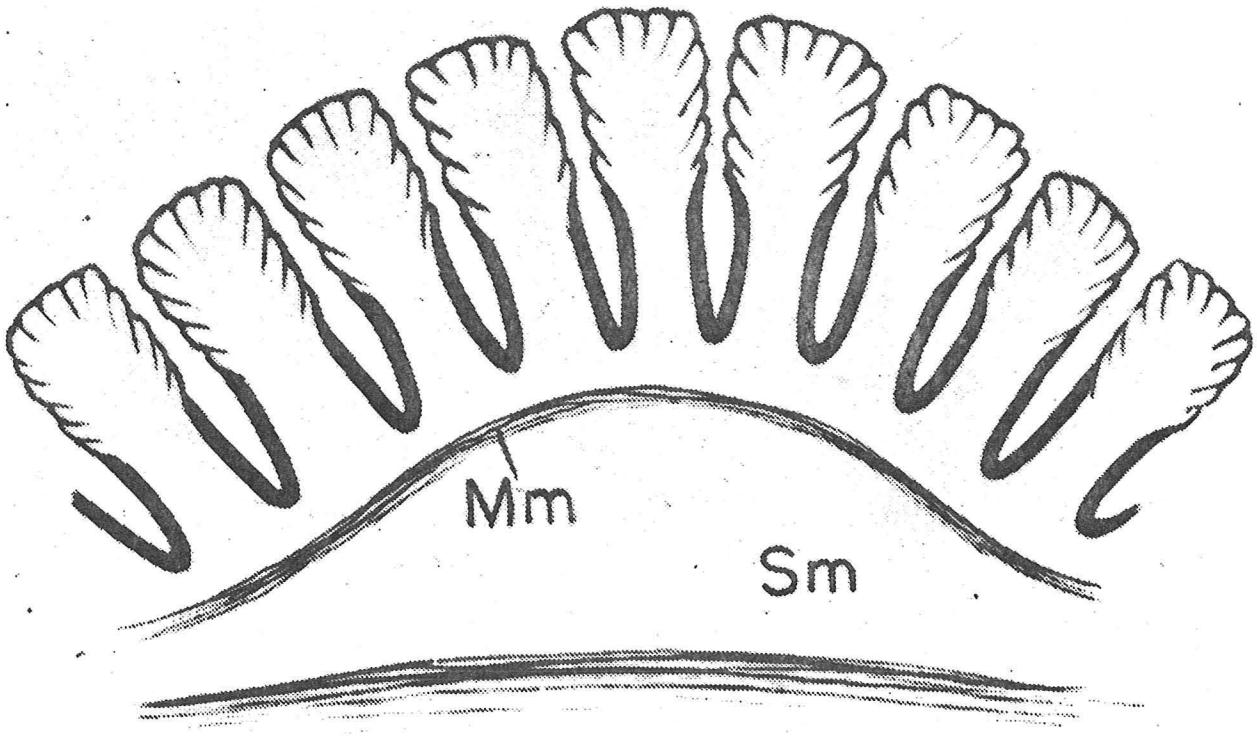
Figure 14. Normal Cell Division (Fenoglio and Lane)



If this balance is shifted toward cell division, a protrusion or polyp may result. A polyp is thus defined as any visible protrusion on the mucous membrane. Although juvenile polyps and Peutz-Jegher polyps (both hamartomas), inflammatory pseudopolyps, lymphoid masses, leiomyomas, and lipomas may be "polypoid", they will not be considered.

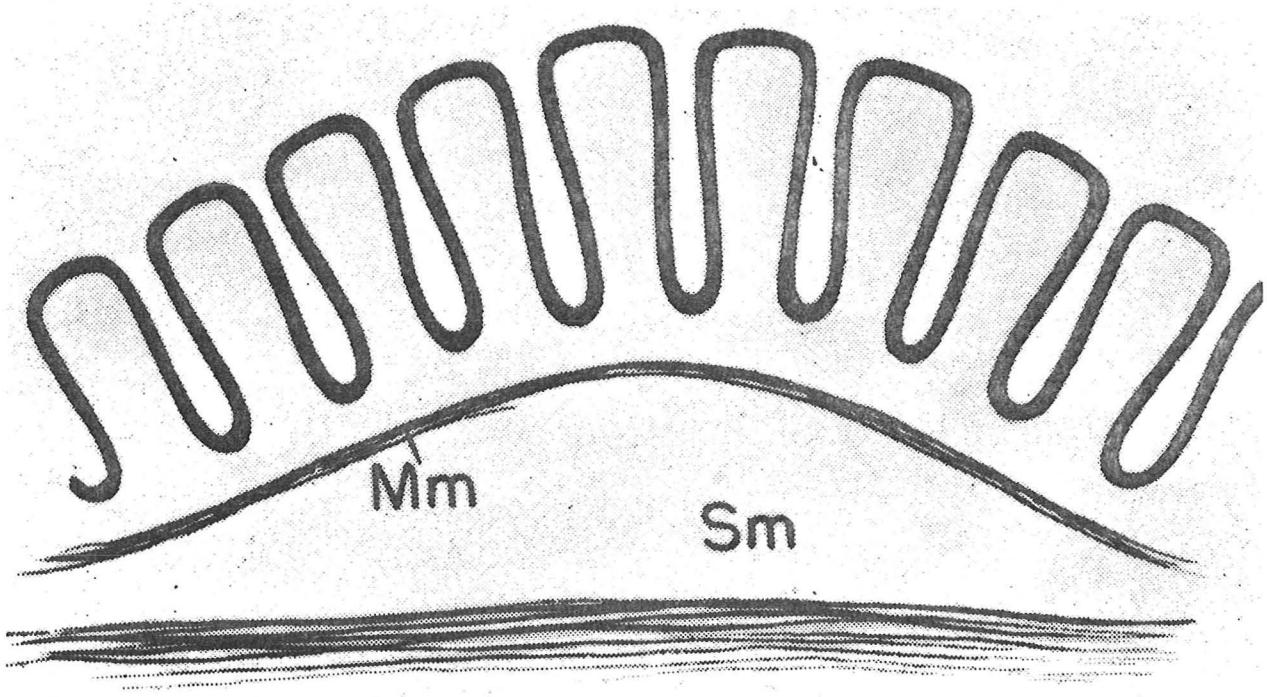
There are 2 basic types of mucosal proliferation. Hyperplastic polyps (Figure 15) are discrete, tiny elevations of little consequence, accounting for 90% of all polyps. There is a slight expansion in the zone of cell division but complete differentiation into goblet and absorptive cells is maintained. Cell division is restricted to the lower portions of the crypts, an important characteristic of non-neoplastic tissue.

Figure 15. Hyperplastic Polyp



The other type of mucosal proliferation forms adenomas (Figure 16). Here, cell division is unrestricted so mitotic activity is seen at all levels of the tissue. The unrestricted replication plus failure to differentiate into mature goblet and absorptive cells is indicative of the neoplastic nature of this process.

Figure 16. Adenomatous Polyp



The gross appearance of an adenomatous polyp may be either sessile or pedunculated (Figure 17) and histologically they may be divided into 3 categories (Table 4 and Figure 18):

Figure 17. Sessile and Pedunculated Polyps (From Welin)

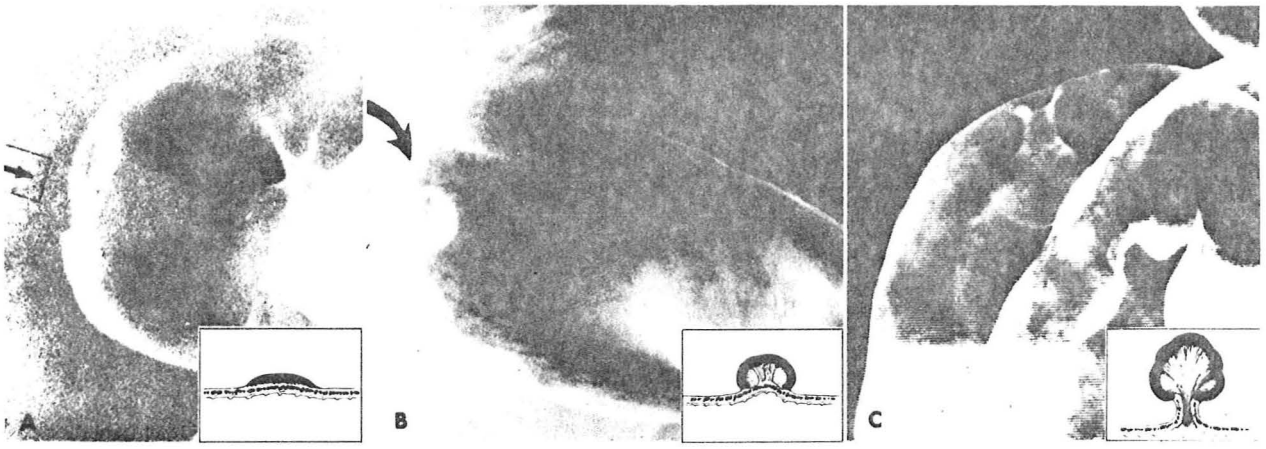
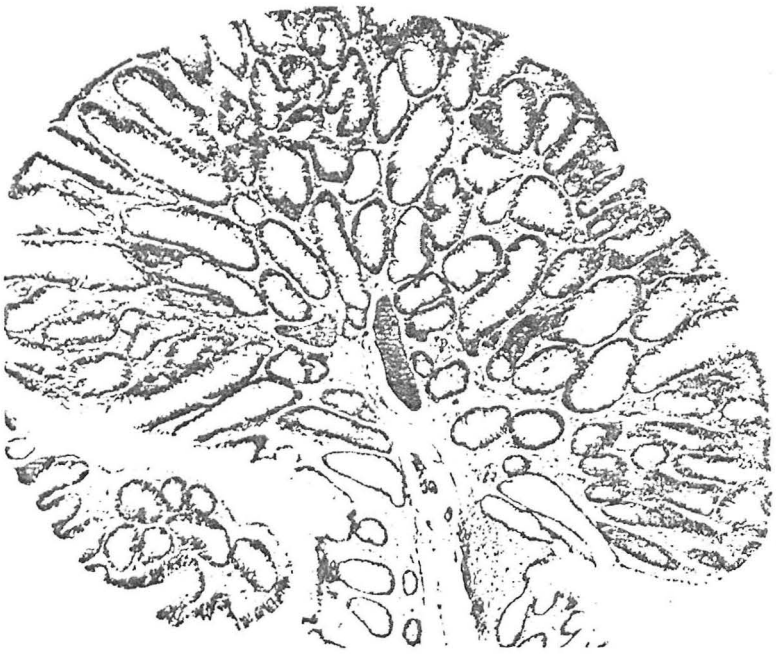


Table 4 TYPES OF ADENOMAS

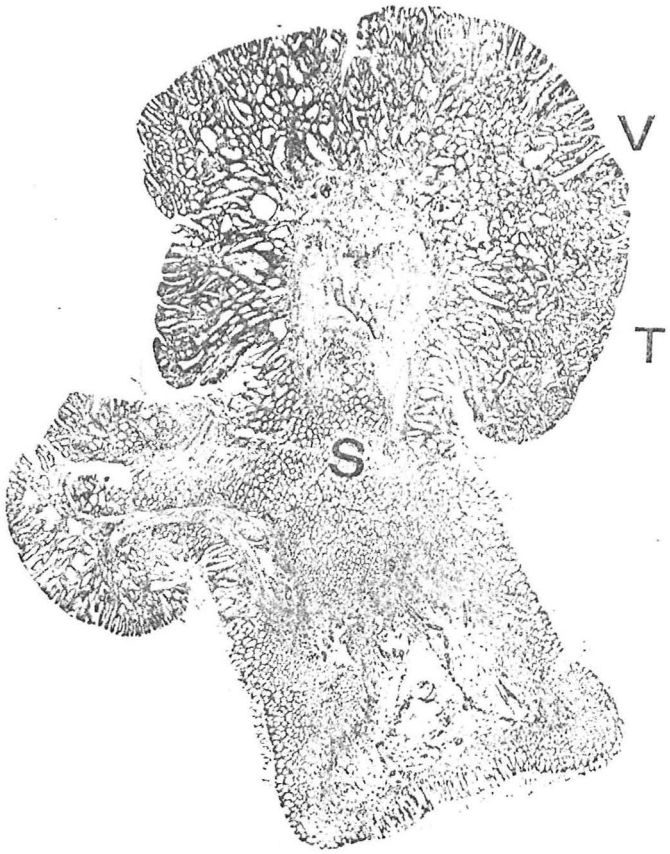
HISTOLOGIC TYPE	% OF ALL ADENOMAS	% WITH CANCER
TUBULAR	75%	5%
TUBULAR-VILLOUS	15%	20%
VILLOUS	10%	40%

Figure 18.

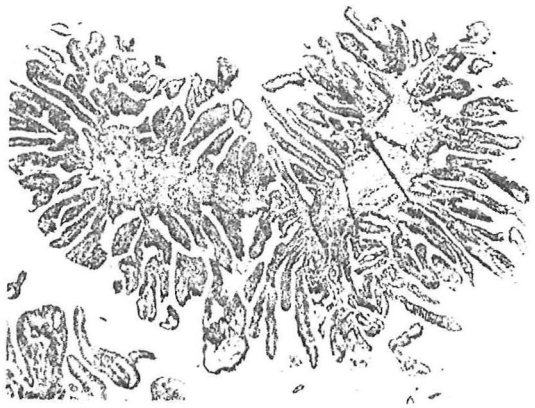
Types of Adenomas



Tubular Adenoma



Tubular-Villous Adenoma
(Tubular area T; villous area V.) Stalk
(S) is covered by normal mucosa.



Villous Adenoma

1. Tubular Adenomas (adenomatous polyps, polypoid adenoma) - normal mucosal architecture is lost but muscularis mucosa is smoothly continuous and usually uninvolved in the structure of the polyp. They are usually pedunculated and some 5% will have a focus of cancer, either in situ or invasive.

2. Tubular-Villous Adenomas (villoglandular polyp) - features of tubular and villous adenomas both grossly and microscopically. Cancer is found in close to 20% of such tumors.

3. Villous Adenomas (papillary adenoma) - larger tumors, shaggy, soft and usually sessile. The lesion appears to arise from mucosal surface, exhibits long, frond-like villous processes and tends to spread. No glands are present and cells have little or no mucus. Malignancy is frequent (40% and up).

Incidence of Adenomatous Polyps

The incidence of adenomas varies according to the type of survey made (sigmoidoscopy, surgery for colon cancer, or autopsy); the size regarded as important; and the age of the population. Although careful autopsy studies using a hand lens will find polyps in up to 70% of cases, most of these are very small and probably not even adenomas. Most authors accept an incidence of 5-10%, a figure that as we shall see, is much lower than in patients with cancer. The incidence of polyps increases impressively with age.

Size of Polyps

Most polyps are small. The importance of polyp size is in relation to the percent with cancerous changes (Table 5).

Table 5. SIZE OF POLYPS IN RELATION TO CANCER

HISTOLOGIC TYPE	PERCENT CANCER IN EACH SIZE RANGE		
	< 1 cm	1-2 cm	> 2 cm
TUBULAR	1%	10%	30% +
VILLOUS	-	30%	50% +

Growth Rate of Polyps

Spratt and Ackerman reported in 1961 a patient with colon cancer who refused surgery and in whom 9 barium enemas were performed over a 7 1/2 year period. They found a doubling time of 636 days. Welin, in an incredible study, followed 20 patients with cancer, 23 with villous and tubular-villous adenomas, and 69 with tubular adenomas with serial barium enemas. The plotted the growth rates in mm/day for each tumor type. The mean doubling time for cancers was 620 days. As shown in Figure 19, most cancers had a rapid growth rate and most tubular adenomas a slow one. Villous adenomas were in-between. Using the data from the fastest growing group of tumors, Welin calculated the number of days for a tumor of one gland to reach 10 mm and for a 10 mm polyp to reach 60 mm in size (Table 6).

Figure 19.

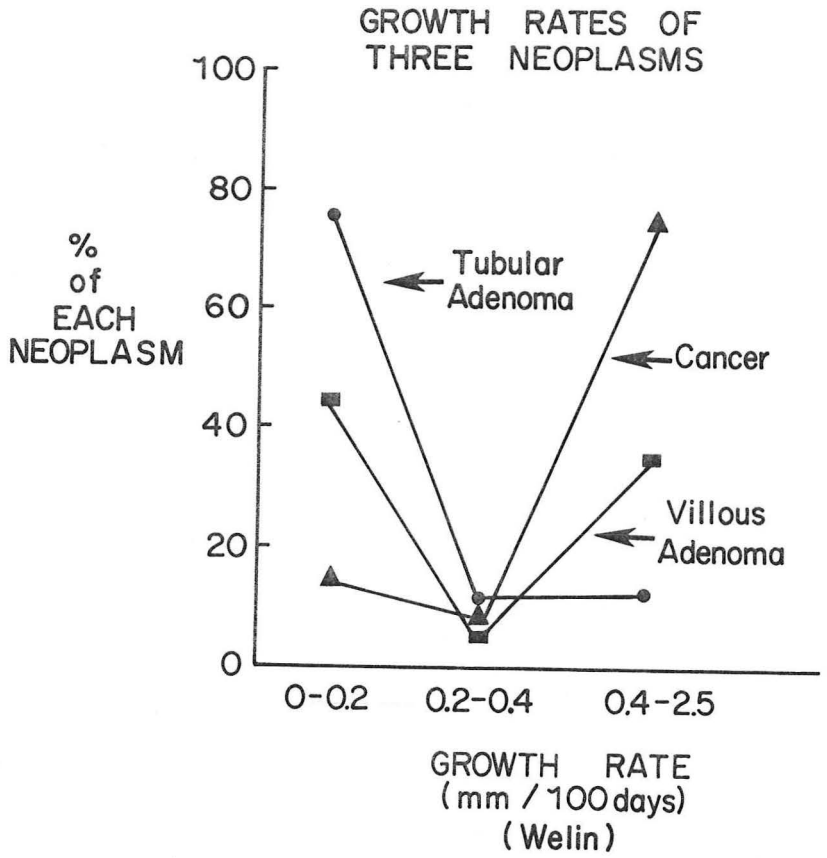


Table 6 GROWTH TIME OF FAST-GROWING TUMORS

	No. OF DAYS
ONE GLAND → 10 mm	2,000 - 12,500
10 mm → 60 mm	400 - 2,500

It would require 6-8 years for a tumor of glandular size to grow to 60 mm. Today, we do not use growth rates to determine treatment, but we can be reassured that follow up exams need not be done more than every 3-5 years under normal circumstances.

Adenoma-Cancer Controversy

With this background, let us now address the issue of the adenoma-carcinoma controversy. Specifically, the discussion will center on tubular adenomas, for there is virtually no dissenting opinion that villous adenomas are premalignant lesions. The questions to be asked are:

1. Is there a correlation between tubular adenomas and colorectal cancer?

2. Do benign adenomas become cancers?

There is clearly a correlation between adenomas and colon cancer. If followed long enough, subjects with polyps have an increased cancer risk, said to be 5-10 times greater than those without polyps. Subjects with cancer have 2-3 times the normal incidence of colon polyps. The incidence is even higher in those patients with metachronous (second) colon cancers or synchronous (simultaneous multiple) cancers. Finally, Reddy and Wynder have noted stool sterol and 7 α-dehydroxylase activities to be similar in patients with adenomatous polyps and colon cancer, both higher than normal controls. Such correlations could, of course, reflect nothing more than a propensity in some subjects to develop neoplasms, be they adenomas or carcinomas.

The presence of carcinoma *in situ* or carcinoma in the head and neck of an otherwise benign polyp is well accepted. But are these the lesions that progress to classic infiltrating cancer of the colon? Prior to the 1960's, it was almost universally believed that such was the case. However, Spratt and Ackerman as well as Castleman and Krickstein have led a challenge to this concept and several lines of argument are available. First, the incidence of adenomas in various populations does not correlate with the incidence of cancer. Second, the location of polyps is more widespread throughout the colon than are cancers. Third, many pathologists have been unable to find unequivocal remnants of benign adenomatous tissue in specimens of frank colon cancer.

Proponents of the adenoma-cancer sequence retaliate with data that the presence of benign adenomatous tissue in cancer is related to the invasiveness of the cancer (Table 7).

Table 7.

PERCENT CANCERS WITH
BENIGN ADENOMATOUS TISSUE
(MORSON)

DUKES A (SUBMUCOSAL) = 57%

DUKES A (MUSCULARIS) = 18%

DUKES B = 8%

To find residual benign adenomatous tissue, one must look at less invasive cancer. Furthermore, a number of patients have developed cancer at the site of an unremoved polyp. Finally, experienced colonoscopists and surgeons (Waye, Rittenhouse) find small (< 5 mm) invasive cancers only in the heads of polyps. Waye proposes a sequence of 5 stages from benign adenomatous polyp to colon cancer. The vast majority of polyps stay at stage 0 (benign), but some progress through stages 1 (carcinoma in situ), 2 (invasion), and 3 (proliferation) to stage 4, penetrating colon cancer. This requires an average of ten years but villous adenomas will progress at a more rapid rate.

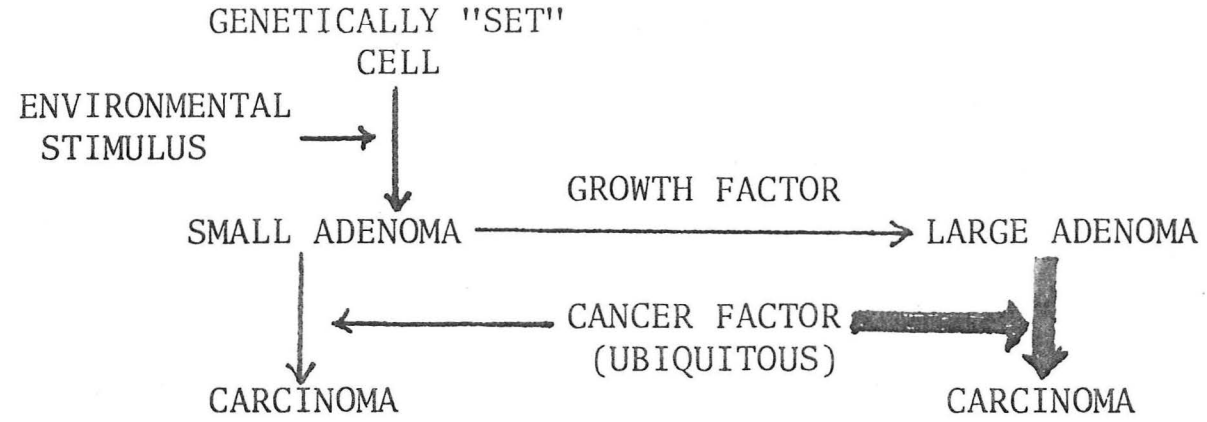
From the preceding discussion, it is clear that unless a "polyp" can be removed, sectioned and found free of invasive cancer, replaced in the colon, and followed for several years, the answer will never be firmly at hand. As regards management of patients, however, such an answer may be immaterial.

An interesting hypothesis for the development of cancer from an adenoma has been proposed (but of course unproven) by Morson. This sequence (Figure 20) is based on 3 lines of reasoning:

Figure 20.

PROGRESSION FROM ADENOMA
TO CARCINOMA

(MORSON)



1. Since the frequency and location of adenomas differ from those of cancer, then the agent causing adenomas may differ from that causing cancer. This agent, an environmental stimulus, may act on genetically "set" cells to form small adenomas.

2. The strongest correlation between polyps and the rate of cancer in various countries is with large polyps. Morson postulates a factor in countries with high cancer risk that promotes growth of small to large adenomas.

3. The chance of a large polyp being malignant is the same in countries with high or low cancer incidence. Thus, there is an ubiquitous cancer factor that facilitates the progression of adenomas to cancer. This occurs much more frequently with large polyps but could account for the rare cancer occurring from small polyps also.

In his scheme, the major factor is that which causes small adenomas to become large. Again, science is desperately needed to sort out such unfounded speculation.

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CASE PRESENTATIONS

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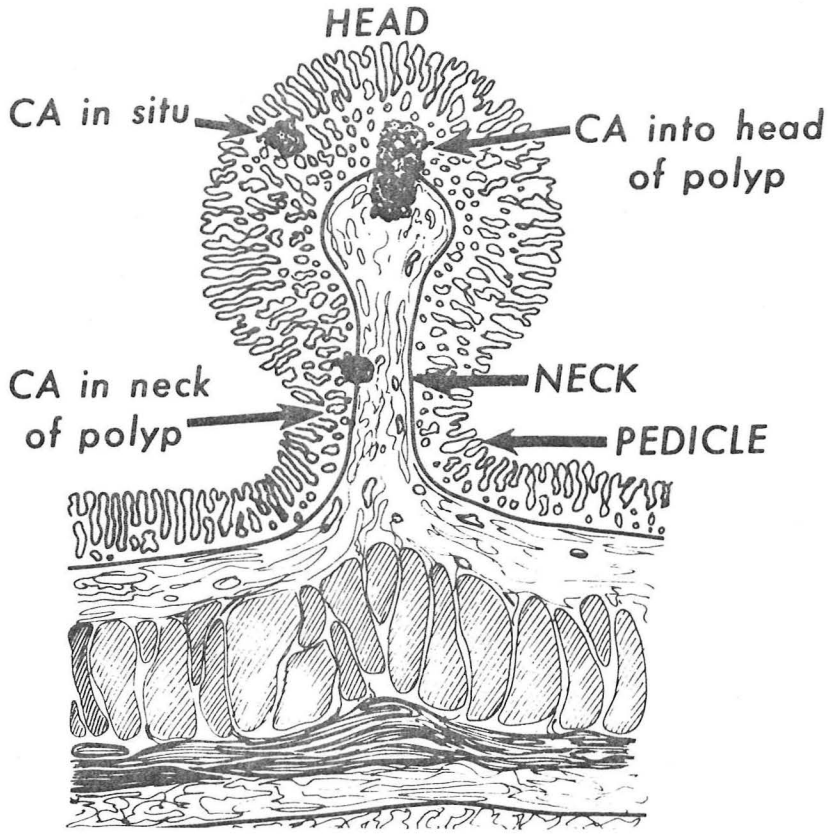
Treatment of Colon Polyps

Once a polyp has been found, the approach is straightforward. The entire colon should be examined by colonoscopy because of the high frequency of synchronous neoplasms. All lesions on a stalk are removed "in-toto" with cautery polypectomy and sent for histologic evaluation. Removal of sessile lesions depends on the size of the polyp and the experience of the colonoscopist. Ulcerated sessile polyps are almost always cancerous. These and other unremoved polyps must be measured and biopsied. The need for further surgical intervention will depend on the patients's age and operative risk, size of the lesion, and histology. For example, most villous adenomas should be removed.

The Stalk As A Safety Factor

Figure 21 displays a typical adenomatous polyp on a stalk with varying degrees of invasive cancer.

Figure 21.

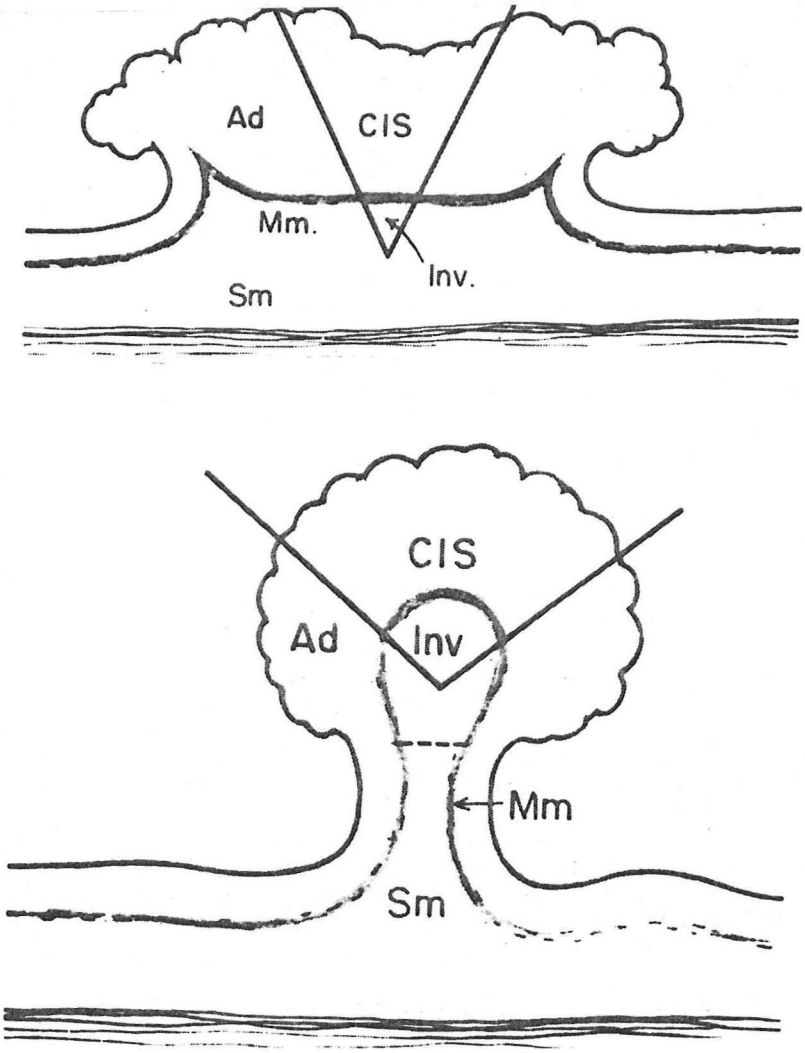


In such polyps, all cancers above the muscularis mucosa are considered "cured" following their removal. This is true whether the focus is epithelial or subepithelial. Numerous series, including those of Okike and Shatney report no metastses from such lesions. The reason for such good results is that lymphatics extend up to, but not through the muscularis mucosa.

If the focus of malignancy has invaded the muscularis mucosa, the vast majority are still considered "cured" if they remain in the head. Figure 22 demonstrates the rationale for such a statement. Two adenomas (Ad) are depicted. One is sessile, the other pedunculated. In both, a

Figure 22.

Invasive Cancer in A Sessile and Stalk Polyp (From Fenoflio and Lane)



focus of cancer has penetrated the muscularis mucosa (Mm). In the sessile lesion (top panel), the cancer will already have reached the submucosa of the bowel wall proper. In the pedunculated lesion (bottom panel), the focus is still separated from bowel wall proper and although lymphatics are present, metastases are very uncommon. In Shatney's series, no patient with such a lesion was found to have metastases. Wolff and Shinya have confirmed this and list 3 reasons to proceed with surgical resection in polyps with cancer invading the muscularis mucosa but still confined to the head: 1) cancer cells penetrate close to the plane of resection; 2) cancer cells are in lymphatics; and 3) the cancer is highly undifferentiated. Focal cancers in the neck of the polyp or below should be followed with elective surgery.

The procedure with sessile polyps is similar. All cancers above the muscularis mucosa are considered cured and all cancers below should be followed with surgery.

The benefit of such "prophylactic polypectomies" is given support by data from Gilbertsen's group in Minneapolis. Over a 25 year period, 18,000 asmyptomatic patients underwent 104,000 proctoscopies at which time all polyps were removed. Only 11 cancers were found in 85,000 patient years of experience while it was expected they would find 75-80. Furthermore, all cancers found were Dukes A or B.

Summary

1. There is a direct correlation between epithelial polyps and colorectal cancer.

2. While the presence of polyps may at the lease herald only a generalized mucosal derangement allowing a propensity to the development of cancer, some, and perhaps all, cancers begin as polyps.

3. Despite the fact that most will remain benign, discovered polyps should be removed if possible:

   a. That one polyp may be the one progressing to cancer.
   b. A polyp may already harbor carcinoma in situ.
   c. The polypoid lesion may be a cancer already and fractional biopsies of such are misleading.
   d. Colonoscopy is readily available and polypectomy relatively safe (0.02% mortality).

4. If not removed, the polyp should be extensively biopsied and carefully measured. Further surgical therapy depends on histology, size, and a patient's overall status.

5. Scrupulous follow-up should be maintained because of the increased risk of future polyps and/or cancer.

Diagnosis of Colorectal Cancer

Symptomatic Individual

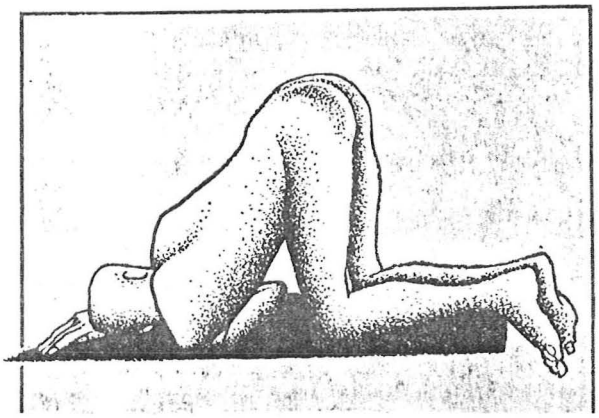
The diagnostic approach to patients having symptoms compatible with colon cancer is straightforward. Because 5-year survival decreases with increasing duration of symptoms before diagnosis, there must be no delay in evaluating the patient once he presents himself. The work-up should include: digital rectal exam and stool guaiac; sigmoidoscopy; barium enema; and colonoscopy.

Digital Rectal Exam

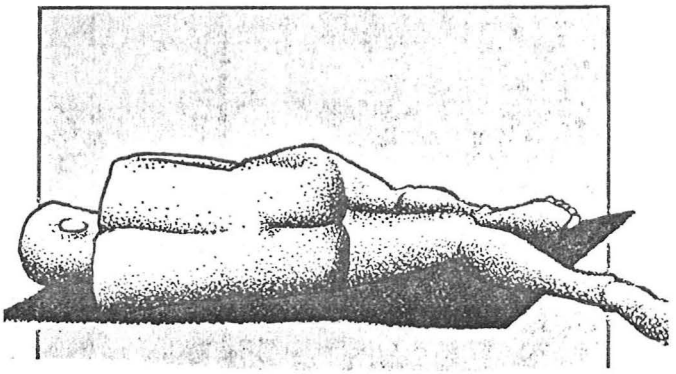
Digital rectal exam is, of course, an essential aspect of every physical examination and is mandatory in a patient with colonic symptoms. The proper technique is depicted in Figure 23.

Digital Rectal Exam

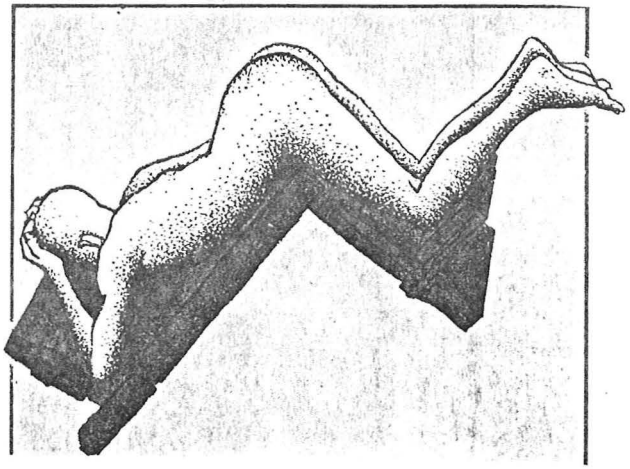
Figure 23.



Shoulder-Knee Position

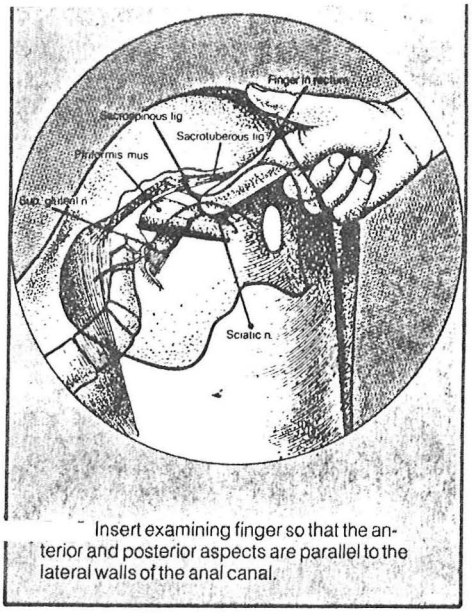


Sim's Position



Procto Position

. Retract the edges of the anal orifice to inspect the anal region.



Insert examining finger so that the anterior and posterior aspects are parallel to the lateral walls of the anal canal.

Digital exam will disclose fewer tumors today than in the past but can still be expected to detect 20-30% of colorectal tumors.

Sigmoidoscopy

Sigmoidoscopy will detect 50-60% of all colorectal cancers. This is lower than the 75% reported in the past and reflects the changing pattern of colon cancer. If the results of sigmoidoscopy are negative, further workup is necessary. If a lesion is found, a search for synchronous lesions above the sigmoid colon should be undertaken. In either case, one must turn to barium enema or colonoscopy.

Barium Enema and Colonoscopy

Barium enema examination of the colon will diagnosis most advanced lesions but only 50-70% of early cancers and fewer polyps. The air contrast technique will improve this yield but still misses the smaller polyps. Colonoscopy, on the other hand, has become the gold standard of colonic diagnosis. It is safe, allows biopsy or removal of lesions, and is said to be more accurate than barium enema. In my opinion, however, too much has been made of the relative advantages and disadvantages of these two techniques. Dodds, Stewart, and Hogan have detailed the problems inherent in most studies comparing barium enema and colonoscopy. These include:

1. Techniques for cleansing the colon are often different.

2. The expertise of the radiologist and colonoscopist often differ.

3. There is no true arbiter of false-negativity.

4. The colonoscopist is ofter aware of the x-ray findings while the radiologist is usually unaware of colonoscopy results.

5. In many studies, polyps <5 mm in diameter are considered "significant" lesions. Barium enema rarely discloses lesions this small. Such lesions are rarely of clinical importance.

Because barium enema occasionally detects lesions missed by colonoscopy, especially in colonoscopic "blind-spots" (eg., rectosigmoid, the flexures, and cecum), it should be considered complementary to colonoscopy.

* * * * *

Case Histories

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If workup discloses frank cancer, it is treated as usual with surgery depending on the presence of distant metastases. If polyp(s) are found, they are removed and sent for histologic examination or at least biopsied and measured. As discussed previously, the need for further intervention depends on the size, histology, invasiveness, and the patient's operative risk. The key point to remember is that a thorough, rapid evaluation is necessary for maximal survival.

Asymptomatic Individuals

More than half of all patients found to have colorectal cancer are symptomatic at the time. Because relatively few have localized disease (Table 8), the survival is poor. On the other hand, if the lesion is diagnosed before symptoms occur, it is usually localized (Duke's A or B) and the chance for cure is excellent.

Table 8.

Rationale For Detection of Colorectal Cancer in the Asymptomatic Individual

Lesion Diagnosed when:	Pathologic Stage	5-Year Survival
Symptomatic	Invasive	40%
Asymptomatic	Localized	>90%

Whatever else is true in this discussion, one cannot deny the fact that early diagnosis is helpful. It is helpful with cancers, of course, but also with polyps because they a) may already harbor malignancy or b) may develop into cancer. Clearly, then, the emphasis on diagnosis should be in the asymptomatic person.

The goals of screening asymptomatic subjects, then, are two-fold: 1) detect non-invasive, "early" cancer and 2) discover and remove polyps. These goals are especially important in those individuals with higher than normal risk of developing colorectal cancer. These include subjects with: 1) age over 40 years; 2) previous colorectal neoplasm; 3) ulcerative colitis; 4) hereditary polyposis syndromes; and 5) family cancer.

Models for cancer screening include gastric cancer in Japan and breast cancer in New York. Surveys in Japan using mobile-vans and technicians performing gastroscopy resulted in increased detection of very early lesions involving only mucosa and submucosa. Thus derived the term "early gastric cancer". These cancers had increased resectability and a cure rate as high as 90%. In a randomized controlled trial in New York, repetitive screening for breast cancer using both clinical examination and mammography led to a 1/3 reduction in deaths from breast cancer overall, and almost 1/2 reduction in those age 50-60.

The standards for any screening program vary depending upon the circumstances. In those subjects with increased risk, any screening program must have high sensitivity. For those with normal risk in a general office practice, high sensitivity is not quite as important, but the program must be safe and acceptable to the patient. Finally, for mass screening of the population at large, the key standards are inexpense and rapidity. Currently, colonoscopy and barium enema are the most sensitive and should be used in patients with high risk. On the other hand, because of their invasiveness, poor patient acceptance, time, and expense, they are not suited to screening either the general office practice or especially the population at large. Instead, patients must be selected on the basis of other, simpler tests to undergo

barium enema and colonoscopy. The two candidates for such screening are sigmoidoscopy and fecal occult blood testing.

Sigmoidoscopy

Proctosigmoidoscopy with the rigid, 25 cm scope has been used for over 200 years and is often part of the "executive physical". Rozieri in the 18th Century first used a tube with a candle at the end as a light source. Almost a hundred years later, in 1899, Pennington recommended air insufflation and Laws suggested a distal light source.

If one performs sigmoidoscopy as a screening procedure in asymptomatic subjects over 40 years of age, one can expect a yield of cancer of about 1.5-3.0 per thousand. Ward has summarized a number of studies and I have added those of Powers and Corman (Table 9).

Table 9.

Yield of Sigmoidoscopy: A Survey of the Literature

Author	No. Patients	No. Ad. Polyps	No. Cancers
Bolt	477	____	1
Cameron	1886	60	9
Corman	2500	25	6
Crumpacker	14921	433	19
Hertz	47091	____	58
Knoernschild	21564	1121	151
Moertel	1020	76	0
O'Grady	14298	357	57
Portes	50000	3600	18
Powers	694	76	2
Strode	21000	1575	105
Ward	363	24	1
Weiss	1000	33	4
	176,814	7380 (5.7%)	431 (0.24%)

There is marked variabilty in the results obtained but, overall, cancer was found in about 2.5/1000 and polyps in 57/1000. The reasons for the discrepancies include the strictness of definition of "asymptomatic" and the definition of "polyp". Some studies counted only polyps > 0.5 cm while some studies counted every polypoid excrescence. Whatever, comment was frequently made that the cancers detected in this manner were of a lower invasiveness than customary. In this regard, three studies are of particular interest.

Hertz reported in 1960 results obtained at the Strang Clinic and Memorial Sloan-Kettering Cancer Center from 1946-1954. Some 26,000 patients ("mostly asymptomatic") underwent 47,091 proctosigmoidoscopic exams. A total of 58 patients (1/450) were found to have colon cancer, almost 75% of which were diagnosed at the initial visit. Analysis of these 58 cases (0.22% of the group), disclosed that 16% were rectal, 43% recto-sigmoid, and 41% higher in the right and left colon. Only 1/2 of the rectal lesions were found by digital exam but almost 60% were found directly by sigmoidoscopy. Another 15% higher in the colon were found by barium enema performed because of another abnormality found on sigmoidoscopy.

All 58 patients went to surgery and 56 underwent curative surgery. Only 15% had nodal involvement compared to 50% expected. After a 5 year-followup, almost 90% of these patients were still alive in 1959 and, after 15 years, the figure is maintained. Interestingly, 4 of these 58 patients had their cancer at the site of a previously diagnosed polyp (2 of which had been biopsied disclosing adenomatous polyp). All 4 had refused excision of the polyp.

Similar results were obtained by Gilbertsen's group who found 11 cancers in their 18,000 patients who underwent 100,000 protoscopies over a 25 year period. Of 10 patients followed for 5 or more years, 8 were still alive.

The value of annual sigmoidoscopy as part of a yearly multiphasic health checkup was evaluated by the Kaiser-Permanente Group in Northern California (Dales). This checkup consisted of a history questionaire, screening laboratory tests, sigmoidoscopy, and a physician follow-up visit. One group was urged to take this annual check-up and another group did so only on their own volition. Patients were between 35-54 years of age on admission. The results are summarized in Table 10.

Table 10.

RESULTS FROM KAISER-PERMANENTE

	SCREENED GROUP	CONTROL GROUP
NUMBER ENROLLED	5156	5577
YEARLY EXAM URGED	YES	NO
UNDERWENT YEARLY EXAM	60-70%	20-25%
STILL ENROLLED AT 7 YEARS	78%	76%
DEATH FROM COLON CANCER	2	10

While more individuals in the screened group were found to have benign rectal polyps (which were removed), fewer died of colon cancer. This reduction in colon cancer contributed to the significantly lower overall mortality rate in the screened patients age 45-54.

Despite such data, there are dissenting opinions. Moertel, in his own study, found only one carcinoma in situ, no cancers, and 75 polyps. He believes that only if removing benign polyps is truly prophylactic will the cost of screening sigmoidoscopy be justified. Bolt found one cancer in 477 patients, a rate of 2 per 1000 examinations. In 10,000 examinations, 20 cancers would be found. If the 5 year survival is 90% with early detection, 18 would be alive after 5 years compared to 10 of 20 (50% survival) if early-detection were not accomplished. Thus, 8 extra 5-year survivals would accrue with every 10,000 examinations. Bolt notes that if each exam costs $50, the cost for each extra 5-year survival would be about $60,000. Even so, this may be a bargain when compared to costs of hospitalizations for cancer and loss of earnings. Indeed, both Ward and Gilbertsen marshall arguments for the economic benefits of routine proctosigmoidoscopy. Bolt concludes "this analysis, if it serves no other purpose, should make it apparent that routine sigmoidoscopy is, by no means, the final answer to cancer of the rectosigmoid.

In assessing the value of sigmoidoscopy, one must also consider the morbidity/mortality of the procedure. The only complication of sigmoidoscopy worthy of consideration is perforation of the colon. In three studies reviewed by Bolt, 10 perforations occured in 177,000 examinations or only 1/20,000 and no deaths occurred. The procedure is safe.

Finally, is annual examination necessary and at what age should it begin? Based on Spratt's studies of growth rates of polyps, most patients who are deemed free of polyps can forgo examination more than every third to fifth year. While Corman recommends beginning exams at age 50, most others suggest 40 as the critical age.

Summary (Sigmoidoscopy):

1. When compared to barium enema and colonoscopy, sigmoidoscopy is cheaper, safer, less time-consuming and more aceptable to patients.

2. Routine screening will detect 2 cancers and about 60 polyps per 1,000 exams in asymptomatic subjects.

3. As performed today, sigmoidoscopy falls short as an annual procedure or screening technique. The expense is formidable, patient acceptance still unenthusiastic, and lesions above 20-25 cm will be missed.

4. Suggestions to lower the cost of sigmoidoscopy include less frequent exams and the use of proctotechnicians.

5. Other means must be employed to screen for early cancer.

Fecal Occult Blood Testing

Fecal occult blood testing with guaiac (Figure 24) has been employed for years, but usually only with single, random stool specimens. The detection rate has been unacceptably low (high false negative) and the spurious positive rate too high (false positive). Countless unwarranted workups have been performed. The problems with occult blood testing are summarized in Table 11.

Figure 24. GUAIAC REACTION

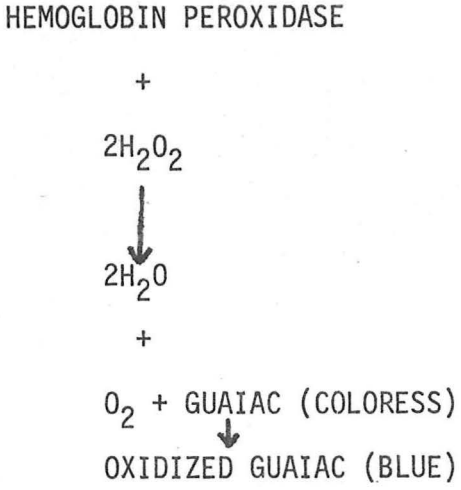


Table 11.

PROBLEMS WITH OCCULT BLOOD TESTING

SITUATION	RESULT	SOLUTION
1. UNRELIABLE REAGENTS	FALSE(+) AND (-)	QUALITY CONTROL
2. LESION BLEEDS INTER-MITTENTLY	FALSE (-)	MULTIPLE SPECIMENS
3. LESION DOES NOT BLEED	FALSE (-)	IRRITATE LESION
4. REAGENT REACTS WITH NON-HEMOGLOBIN PEROXIDASE	FALSE (+)	DIETARY PRECAUTIONS

The development of guaiac-impregnated filter paper slides on a commercial basis (Hemoccult, SK&F) plus a stabilized reagent promised a more reliable test. The physician to take up the banner of Hemoccult screening was David Greegor. In 1966, Dr. Greegor analyzed his patients with colon cancer and found one common denominator - positive stools for occult blood. Using 2 Hemoccult cards for each stool on three consecutive days (6 cards) he then screened 128 patients. Two cancers were found but there was a very high false positivity rate (20%). He altered his approach by restricting meat from the diet (to decrease false positive). Because he had noted some patients with known colon lesions to stop bleeding on a bland diet, he also added bulk to the diet to "promote bleeding" (to decrease false negatives). Patients consumed the diet for 4 days and sampled stools on days 2,3, & 4.

In his next 278 asymptomatic patients, 3 cancers were found and only 8% were false positive. All cancers were Dukes A. In a further uncontrolled experiment he enlisted the aid of 2000 other physicians. They found 139 cases of colon cancer during a 6 month period. The number of patients screened is

not known. Of these 139, 47 were asymptomatic and 85% were Dukes A or B. Only 4 of 47 were in sigmoidoscopic range.

Glober confirmed these results in screening 1530 patients without dietary restriction. Four hundred (400) were positive on at least one card, a positivity rate of 25%. Of 344 retested on a meat-free diet, 53 (or 3% of the original group) remained positive. He noted that the more positive the initial test, the more likely one was to remain positive on the meat-free diet. Thirty-two of these 53 were evaluated and 3 were found to have colorectal cancer.

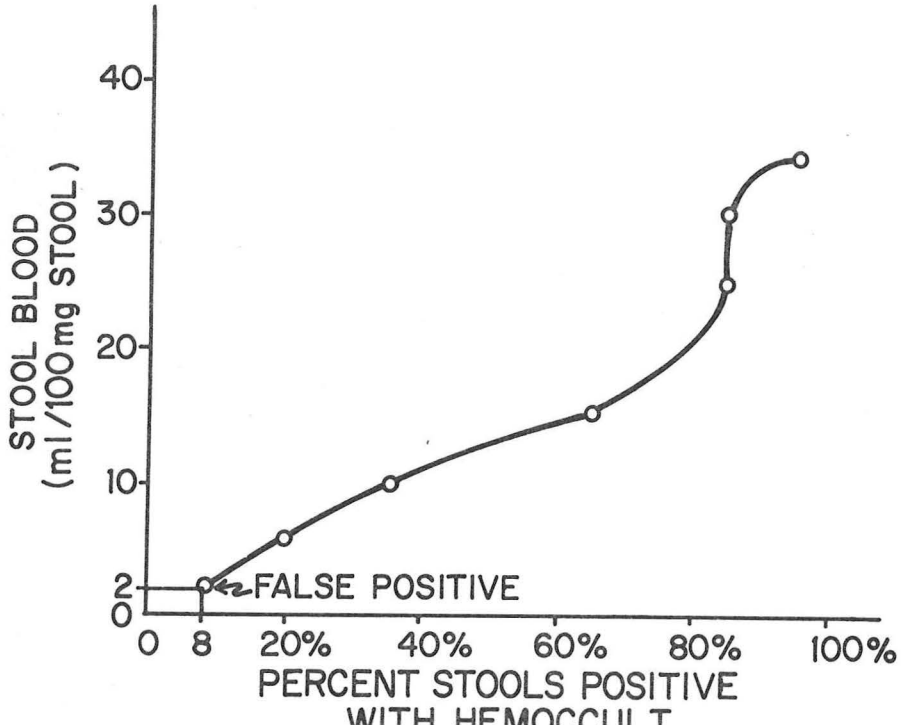
Hastings conducted Cancer Detection Day in Mercer County, New Jersey. One percent (3450 people) of the population came and were offered a rectal exam and a Hemoccult kit to take home. Fifteen percent refused the rectal exam but all took the kits home with dietary instructions. Of 2625 returned, 159 were positive. Evaluation in 51 disclosed 5 cancers. Two years later, one more cancer was found in the Hemoccult positive group and one in the Hemoccult negative group.

With this early evidence that Hemocult screening of asymptomatic subjects might play a role in detecting colon cancer, 2 groups evaluated the Hemoccult test using Cr^{51} labled red cells as the gold-standard of blood loss in patients with suspected GI bleeding. No diet was given . Companion papers were published in the October, 1976 issue of the American Journal of Digestive Diseases by Stroehlein et al and Morris et al. Results of these studies were summarized in an editorial by Sidney Winawer:

1. Relationship of stool blood concentration and Hemoccult.
   Stroehlein measured the stool blood concentration by Cr^{51} labeled red cell loss (ml blood/100ml stool) and noted the Hemoccult positivity (Figure 25)

Figure 25.

CORRELATION OF HEMOCCULT WITH ACTUAL STOOL BLOOD LOSS



In the normal range of blood loss, approximately 0-2 ml, 8% of the Hemoccult tests were positive. Morris found a false positivity of 12% so we can conclude there is about a 10% false positive rate. This was considerably lower than a 70% false positive rate with regular bench guaiac reagent or Hematest tablets. There is clearly a significant rate of false negativity also when individual stools were analyzed. Multiple stools must be checked.

2. Importance of the single (1 of 6) positive stool

A single positive test, even if weakly so, is important. In Morris' study, every patient who passed at least 3 stools containing over 2 ml blood had at least one positive Hemoccult. The intermittent nature of bleeding emphasizes the importance of multiple stool exams. Winawer also points out that only a blue color is considered positive.

3. Effects of iron, barium, and laxatives

There was no effect on positivity in patients having barium exams. Patients on iron or laxatives actually experienced lower false positive and negative reactions. Theroretically, laxatives will produce dilution of non-hemoglobin peroxidase to reduce false positives. At the same time, a laxative may irritate potentially bleeding lesions. While not mentioned here, Vitamin C has been shown to produce false-negative reactions.

4. Conversion of Reactions

Initial negative hemoccult reactions rarely, if ever, become positive with storage but positive reactions may turn negative after 2-3 days. Attempts at rehydrating the slides before adding reagent will restore positivity but may also create extra false positive reactions.

Three more large studies have recently been published evaluating Hemoccult screening (Bond and Gilbertsen; Winawer; and Gnauer). Two of these merit brief descriptions (Table 12).

Table 12.

RESULTS OF MASS SCREENING WITH HEMOCCULT

		WINAWER	
	BOND	SIGMOID + HEMOCCULT	SIGMOIDOSCOPY
NUMBER SCREENED	23,500	11,505	7,325
NUMBER (+) HEMOCCULT	525(2.2%)	115 (1%)	- - -
NUMBER CANCERS	43(0.2%)	10 (0.1%)	9
NUMBER MISSED	--	2	- - -
PERCENT DUKES A OR B	80%	90%	55%

Bond and Gilbertsen divided 47,000 asymptomatic volunteers between 50-80 years into a control group and a screened group. Of the 23,500 screened, 2.2% had at least one of six Hemoccult cards positive. Upon evaluation of these 525, 10% had cancer and another 35% large polyps.Most of the cancers were Dukes A or B. Patients in both groups will be followed 10 years.

In Winawer's study, 18,380 asymptomatic patients were divided into 11,505 who received Hemoccult screening (6 cards) plus sigmoidoscopy and 7,325 who had sigmoidoscopy only. Occult blood testing was performed while the subjects consumed a no-meat, high-bulk diet. Ten of the twelve cancers found in the first group were detected by Hemoccult and eleven were Dukes A or B. Nine subjects in the second group were found by sigmoidoscopy alone to have cancer - 55% of these were Duke's A or B. In analyzing the group with a positive Hemoccult test, it was noted that both specimens from a single stool were positive less than 20% of the time - further evidence that multiple specimens are necessary.

If all 5 studies of Hemoccult screening are combined, one finds a yield of 104 cancers (0.21%) and 258 large polyps (0.51%) in 50,000 subjects.

The cost of Hemoccult screening has not been well evaluated. Let us assume screening could be carried out for $3 per 6 slides. This is, of course, contingent on a drastic reduction in the cost of Hemoccult slides. Let us assume that sigmoidoscopy, barium enema, and colonoscopy in Hemoccult positive patients would cost $350. Finally, assume a 2% overall Hemoccult positive rate and a 0.2% cancer detection rate.

10,000 screened at the cost of $3	=	$30,000
200 Hemoccult positive screened at the cost of $350	=	$70,000
0.2% cancer = 20 Cancers	=	$100,000

If we use Bolt's approach, 18 of these 20 would live 5 years compared to 10 of 20 if the cancer were detected at a later stage. The cost of each extra 5 year survival is $100,000 divided by 8 or $12,500.

In Summary:

1. The proper manner of conducting Hemoccult screening is to collect 2 specimens from each of 3 daily stools while the patient is consuming a meat-free, high-bulk diet.

2. If at least one positive stool is considered significant, then 1-2% of all cards will be positive.

3. When patients with positive Hemoccult screens are fully evaluated, the

following can be expected:
a) 50% will have significant lesions (10% cancer; 40% large polyps)
b) 40% will have benign bleeding lesions.
c) 10% will have no lesion.

4. False positives may result from other peroxidases.

5. False negative reactions may occur because of:

a) nonbleeding lesion
b) intermittent bleeding
c) Vitamin C
d) Sampling errors
e) Conversion of positive to negative with storage

A comparison of sigmoidoscopy and Hemoccult testing in screening for colon cancer is shown in Table 13.

Table 13.

COMPARISON OF SIGMOIDOSCOPY AND HEMOCCULT TESTING TO SCREEN FOR COLON CANCER

	DETECTION RATE		
	CANCER	POLYPS	COST PER EXTRA 5 YR SURVIVAL
SIGMOIDOSCOPY	0.24%	5.7%	$60,000
HEMOCCULT	0.22%	0.5%	$12,500

As a screening test, the true positivity is probably higher with hemoccult, but the false negativity is also higher making the overall cancer detection rates comparable with the two procedures. Sigmoidoscopy obviously has lower false positive rate and detects many more polyps. This is reasonable in light of the fact that polyps bleed less often than cancer.

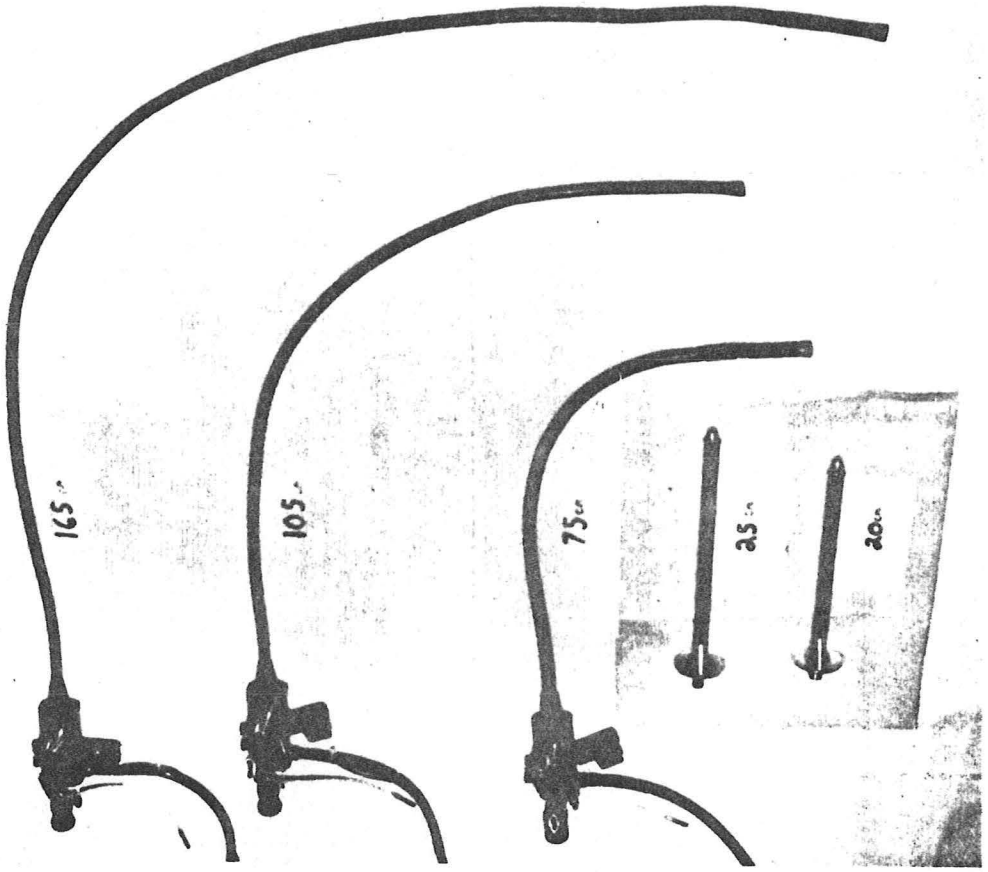
Diagnostic tests Currently but not Readily Available

Flexible Fiberoptic Sigmoidoscopy

Because the rigid, 25 cm sigmoidosocpe is uncomfortable, examines varying distances < 25 cm, and misses at least some lesions, a flexible fiberoptic sigmoidoscope of 60 cm length was developed (Figure 26). When compared to rigid sigmoidoscopy, flexible sigmoidoscopy takes longer, reaches greater distances but is generally preferred by the patients.

Figure 26.

FLEXIBLE SIGMOIDOSCOPE COMPARED
WITH RIGID SCOPE AND COLONOSCOPES



Bohlman examined 139 patients with both rigid and flexible sigmoidoscopes and found 36 neoplastic lesions. Only 1/2 were below 20 cm. The flexible scope was superior at all distances above 11 cm from the anus and no lesion seen by the rigid scope was missed by the flexible one. Winawer examined 91 patients over 40 years of age with positive Hemoccult tests. The number of symptomatic individuals is not known. His results with rigid and flexible sigmoidoscopy are shown below (Table 14) in comparison to barium enema and colonoscopy. The flexible sigmoidoscope is superior to the rigid one but whether the increased yield is adequate to justify the expense of such a scope, especially when pan-colonoscopy is superior yet, must be further evaluated.

Biopsy and Lavage

While the biopsy of discrete lesions is of obvious value and is readily available with sigmoidoscopy or colonoscopy, there are some who believe cytological evaluation of random tissue may detect individuals with a propensity to malignant changes. Morson believes that careful cytology in patients with ulcerative colitis, for example, can alert the physician to impending or early cancer formation and signal the need for colectomy before malignancy becomes invasive. This is also speculated for those individuals with familial polyposis. Methods of obtaining tissue include biopsy, brush cytology, or colonic lavage through a standard sigmoidoscope or colonoscope. Lavage is accomplished using a Water-Pik irrigating machine. The key here, and what limits this technique

Table 14.

DIAGNOSITC ACCURACY WITH
4 MODALITIES IN 91 PATIENTS
WITH POSITIVE HEMOCCULT

(Winawer)

	PERCENT OF EACH DIAGNOSED		
	POLYPS < 5 mm (N=55)	POLYPS > 5 mm (N=81)	CANCERS (N=22)
RIGID SIGMOIDOSCOPY	10%	20%	40%
FLEXIBLE SIGMOIDOSCOPY	35%	48%	71%
BARIUM ENEMA	26%	47%	80%
COLONOSCOPY	90%	96%	95%

to a few centers, is scrupulous preparation of the cytologic material and an experienced cytologist. This technique may also be used to provide cells for determination of DNA synthesis, an abnormal occurrence in surface muosal cells.

These procedures remain experimental, limited, and applicable only to those individuals with diffuse abnormalities of colonic mucosa such as ulcerative colitis and familial polyposis. Widespread use remains to be evaluated.

Other Diagnostic Tests

CEA

Carcinoembryonic antigen was first identified in 1965 in the serum of patients with colorectal cancer and was heralded as the ultimate screening method. Unfortunately, many problems have come to light with CEA. These include:

1) CEA is elevated in less than 60% of patients whose disease is localized (Table 15)

Table 15.

CEA AT VARIOUS DUKE'S STAGES
OF COLON CANCER

DUKES STAGE	% POSITIVE CEA
A	20%
B	40%
C	50-65%
D	100%

The discovery of an elevated CEA in someone with advanced disease helps little.

2) CEA is elevated in patients with other neoplasms (eg., pancreatic cancer).

3) CEA is elevated in patients with non-neoplastic diseases (eg., ulcerative colitis).

4) CEA is elevated in smokers with no disease.

5) CEA adds little in the evaluation of recurrent colon cancer after surgical resection.

It may be that measurement of CEA in other fluids (eg., colonic lavage) will be more helpful but this is conjectural.

Other Tumor Markers (See Schwartz)

Arylsulfatase B
Sialyltransferase
Galactosyltransferase
Polyamines

If these markers are to be helpful, they must meet the following criteria: 1) be organ specific; and 2) detect 75% of all cancer when 90% have not undergone metastasis.

Recommendations For Individual Screening in Office Practice

Hereditary Polyposis Syndromes

1. Sigmoidoscopy with lavage (where available) every six months.

2. Colonoscopy with lavage every year

3. Screening should be carried out until age 40. If polyps are discovered, total colectomy is indicated.

Ulcerative Colitis

1. The indications for prophylactic colectomy to prevent cancer in patients with ulcerative colitis have not been delineated.

2. If surveillance is chosen, frequent sigmoidoscopy and colonoscopy (again, with lavage and biopsy where available) may disclose premalignant changes prompting colectomy.

Patients with Previous Colon Cancer or Polyps
(Figure 27)

Asymptomatic Individuals

1. Begin at age 40 or, if there is a family history of cancer, at a younger age.

2. Sigmoidoscopy every 3-5 years.

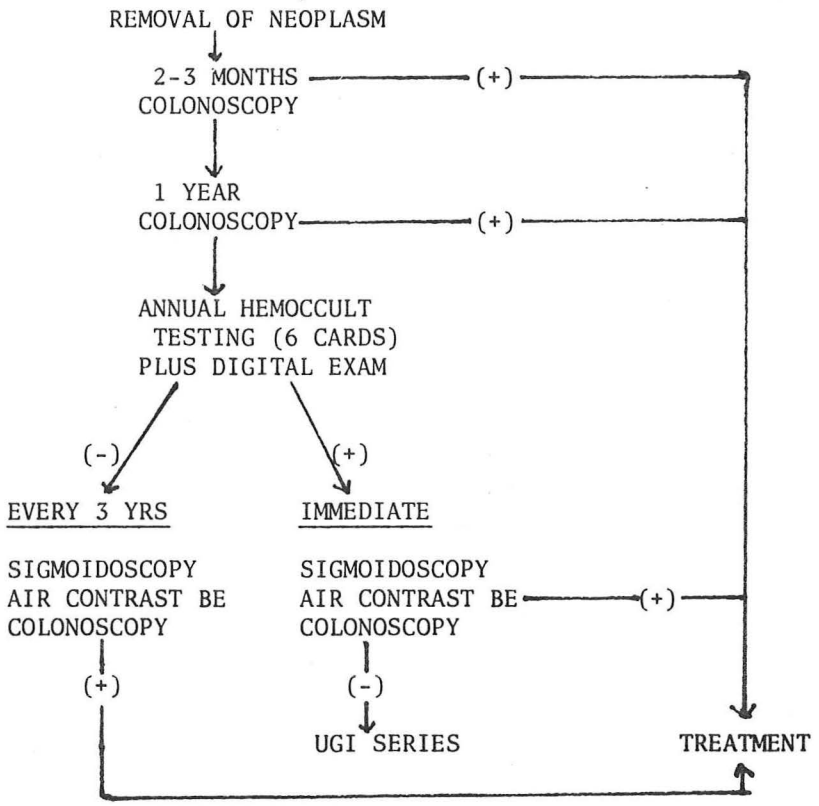
3. Annual Hemoccult testing (6 cards) and digital rectal exam.

4. If Hemoccult is positive, perform sigmoidoscopy, air contrast barium enema, and colonoscopy.

5. If workup is positive, treat. If workup is negative, do an UGI series.

Figure 27.

SCREENING OF PATIENTS WITH
PRIOR POLYP OR CANCER



Recommendations For Mass Screening

Hemoccult Testing

Hemoccult testing best meets the criteria for mass screening although public acceptance would be a problem. There is a general disdain of discussions concerning the bowels and a long-standing "fear of finding" cancer. Additionally, some may be unwilling to stay on a 4 day diet; others will fear the discomfort of the preparations for follow up procedures not to mention the procedures themselves. Until the public embraces mass screening of stools as beneficial, nothing can be accomplished.

Other Suggestions

Possible means of enhancing detection of colon cancer include over-the-counter sale of Hemoccult Kits and a national Colon Cancer Screening Week. Proctotechnicians in mobile vans could further evaluate those with positive tests. One company is working on an occult blood test that consists of dropping a tablet in the toilet bowl after a bowel movement. Blood leached into the water from the stool would turn the tablet blue (?Tidy Bowel?). A final suggestion (Lehrer) that, in my opinion, stands no chance of acceptance today is digital self-rectal examination.

Summary

1. Colon cancer appears to be an environmental disease, perhaps related to diet.

2. Adenomatous polyps may be important in the development of colon cancer.

3. Current hope for increased survival with colon cancer lies with early detection.

Perspective

Most diseases producing early death result from varying degrees of genetic predisposition coupled with environmental factors. Some diseases, such as familial hypercholesterolemia, require relatively little environmental stimulus. Others, such as brochogenic carcinoma, chronic lung disease, most arteriosclerotic disease, cirrhosis, and obesity result predominantly from environmental excesses. Perhaps colon cancer can be added to this list. While some colon cancers occur in patients with genetic predisposition, the majority of cases result from some environmental factor, possibly dietary in nature. The difference between colon cancer and the others mentioned above, is that cure or prevention can be effected without relying on the patient's self-restraint from smoking, "improper" diet, or excess alcohol imbibation. It is for this reason that enhanced emphasis must be placed on the early diagnosis of colon cancer.

Conclusion

As of this moment, 4½ million of our citizens who are alive today will succumb to colorectal cancer. Many will die years before their productive, enjoyable period has ended constituting millions of wasted years. The tools appear to be at hand to reduce markedly this awesome toll. Few would argue the merits of the recommendations listed for patients followed on a regular basis in one's office practice. Many, however, would question the wisdom of mass-screening the general population. Would false-positive Hemoccult tests provoke undue anxiety in the population? Would cancer-phobia become rampant? Would negative exams promote false senses of security and keep people away from their physicians? Such questions await answers. At the least, we must: 1) continue research into causes and early detection of colon cancer and 2) elicit the cooperation of all primary care physicians to screen their patients for early cancer and polyps. If further research validates the utility of mass screening we must 3) educate the public away from "cancer-phobia" toward an attitude of self-help in the detection of early or premalignant colonic neoplasms.

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