Recognition and Treatment of Patients with Hereditary Nonpolyposis Colon Cancer (Lynch Syndromes I and II)

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Primary genetic factors are etiologic in at least 5–10% of patients with colon cancer. The polyposis syndromes (FPC) are easily identified examples because of the spectacular number of polyps. The hereditary nonpolyposis syndromes (HNPCC), although five times more common than FPC, are usually not recognized because they do not have such a distinctive clinical, premonitory genetic marker. Colorectal cancer expression was surveyed in 10 extended, thoroughly documented HNPCC kindreds. One hundred sixteen patients were found to have 183 colorectal cancers. Despite the striking family history, less than 5% were correctly treated by subtotal colectomy. This provided a unique opportunity to study the natural history. Five findings differed significantly ($p < 0.05$) from patients with sporadic colon cancer: (1) mean age of initial colon cancer diagnosed was 45.6 years; (2) 69.1% of first colon cancers were located proximal to the splenic flexure of the colon; (3) 18.1% had synchronous colon cancer; (4) 24.2% had metachronous colon cancer develop with life table analysis showing the risk for a metachronous lesion at 10 years to be 40%; and (5) only 23.3% of cancers were located in the sigmoid colon or rectum. Based on this data, it is recommended that the family history of all patients with a newly diagnosed colon cancer be evaluated for evidence of this syndrome. If an autosomal dominant inheritance pattern emerges, an in-depth genetic investigation is indicated. When HNPCC is confirmed, the following recommendations apply: a subtotal abdominal colectomy is indicated at the time of the initial colon cancer because of the risk of synchronous and metachronous lesions. The rectum should be spared in favor of careful lifetime surveillance because of the proclivity for proximal colon cancer involvement. As yet unaffected members of a newly diagnosed HNPCC kindred who are in the "direct genetic line" should be cautioned that they are at 50% risk and must begin an intensive surveillance program beginning in the third decade with careful attention to the right colon. Patients from newly diagnosed HNPCC families who have had a previous conventional colectomy for colon cancer should, at the very least, enter an intensive surveillance program; a prophylactic completion subtotal colectomy should be considered for patients who are less than totally compliant.

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IT IS ESTIMATED that colorectal cancer will develop in 145,000 patients in the United States in 1987. Sixty thousand individuals will die of the disease.[1] Five to ten per cent of these malignancies are now recognized as being hereditary.[2] A fraction of these patients from this hereditary subset are members of families with familial polyposis coli (FPC) or a related syndrome and are thereby easily recognized because of the distinctive clinical marker of multiple adenomatous polyps. Unfortunately, hereditary *nonpolyposis* colon cancer (HNPCC), which is more than five times as common as FPC, does not have such a distinctive clinical marker.[3] Thus, a patient with a newly diagnosed colon cancer who is a member of an HNPCC kindred may not be recognized as such and is inappropriately treated with a conventional colectomy as one would recommend for sporadic colon cancer.

The purpose of this paper is to make recommendations concerning first, the recognition of patients with HNPCC by simple analysis of the family history and second, management strategy that is distinctly different from FPC or sporadic colon cancer. These recommendations are based on an in-depth analysis of 10 HNPCC kindreds to determine the natural history of the condition.

Methods and Materials

The study population consists of 10 kindreds followed at the Creighton University Hereditary Cancer Institute. The index patient was referred by either a physician or a

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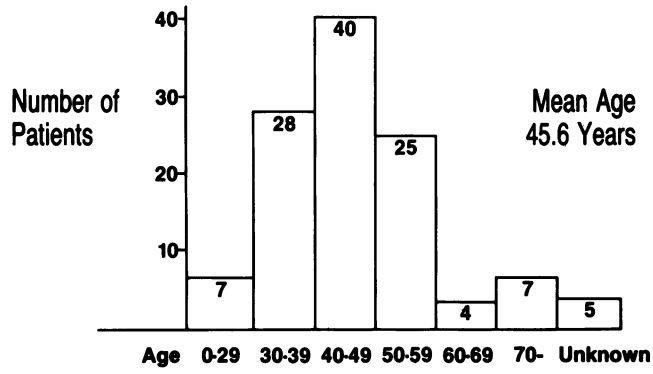

FIG. 1. Age distribution at the time of initial colon cancer diagnosis.

member of the family because of a perception of an inordinately high incidence of cancer. The patients with colon cancer in these families were uniquely suited for study of the natural history of HNPCC because less than 5% were treated appropriately by subtotal colectomy at the time of initial diagnosis. Extensive pedigree analysis through multiple generations disclosed that these 10 families fulfilled previously defined criteria of HNPCC.[4] Verification of family reports of cancer was accomplished whenever possible by primary medical document review including medical records, operative notes, pathological reports, and autopsy and death records.

Statistical Methods

Descriptive statistical methods were used in the analysis of these data. Categorical variables were described

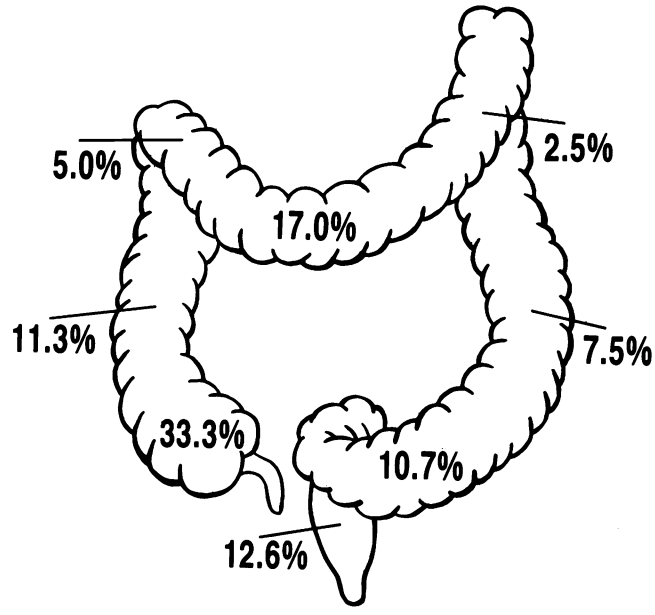

FIG. 2. Location of the first colon cancer in 113 patients. Three patients are not included because the site could not be unequivocally documented.

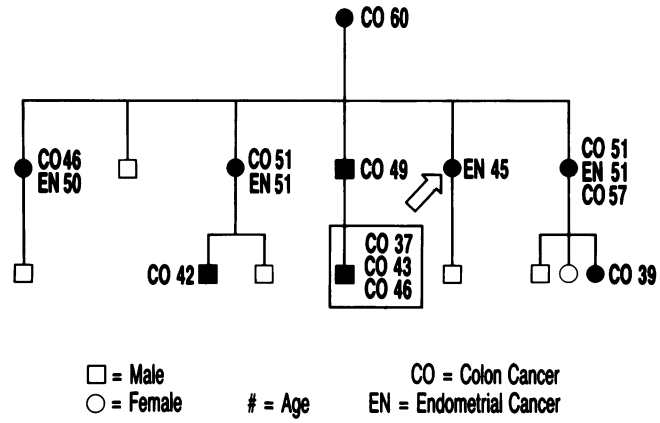

FIG. 3. A partial family pedigree of one of the HNPCC kindreds in this study. The patients highlighted by the box and the arrow are discussed in the text.

with frequency distributions and proportions; continuous variables (*i.e.*, age) were described additionally in terms of means and standard deviations. Inferences about differences from the unselected population of colon cancer cases were made by establishing 95% confidence intervals and comparing these with the closest comparable values found in the general population literature.[1,5-7] The incidence of metachronous colorectal cancer was also described using life table analysis, taking the initial colorectal diagnosis as the start of observation and calculating risk over a specified interval as cumulative proportion surviving through that interval subtracted from one.

Results

One hundred sixteen individuals were identified with 183 histologically confirmed colorectal cancers. There were 52 females and 64 males. Mean age of colon cancer onset was 45.6 years. The age distribution is depicted in Figure 1. The location of the first colon cancer was unequivocally documented in 113 of the 116 patients. The distribution is shown in Figure 2; 69.1% were located proximal to the splenic flexure and only 23.3% involved the sigmoid colon or rectum. Synchronous colon cancer was defined as any additional colon cancer occurring within 1 year of another. Thirty-three colon cancers in 21 patients fit this description for a synchronous colon cancer rate of 18.1%. If a colon cancer was diagnosed more than 1 year after a preceding colon malignancy, it was considered metachronous. This was found in 34 colon cancers in 28 patients for a metachronous colon cancer rate of 24.2%. Life table analysis disclosed the cumulative incidence of metachronous colon cancer to be 40% by 10 years. Colon cancer incidence was consistent with an autosomal dominant inheritance pattern in all 10 families, and representative pedigrees are depicted in Figures 3 and 4. Extracolonic cancers were found in

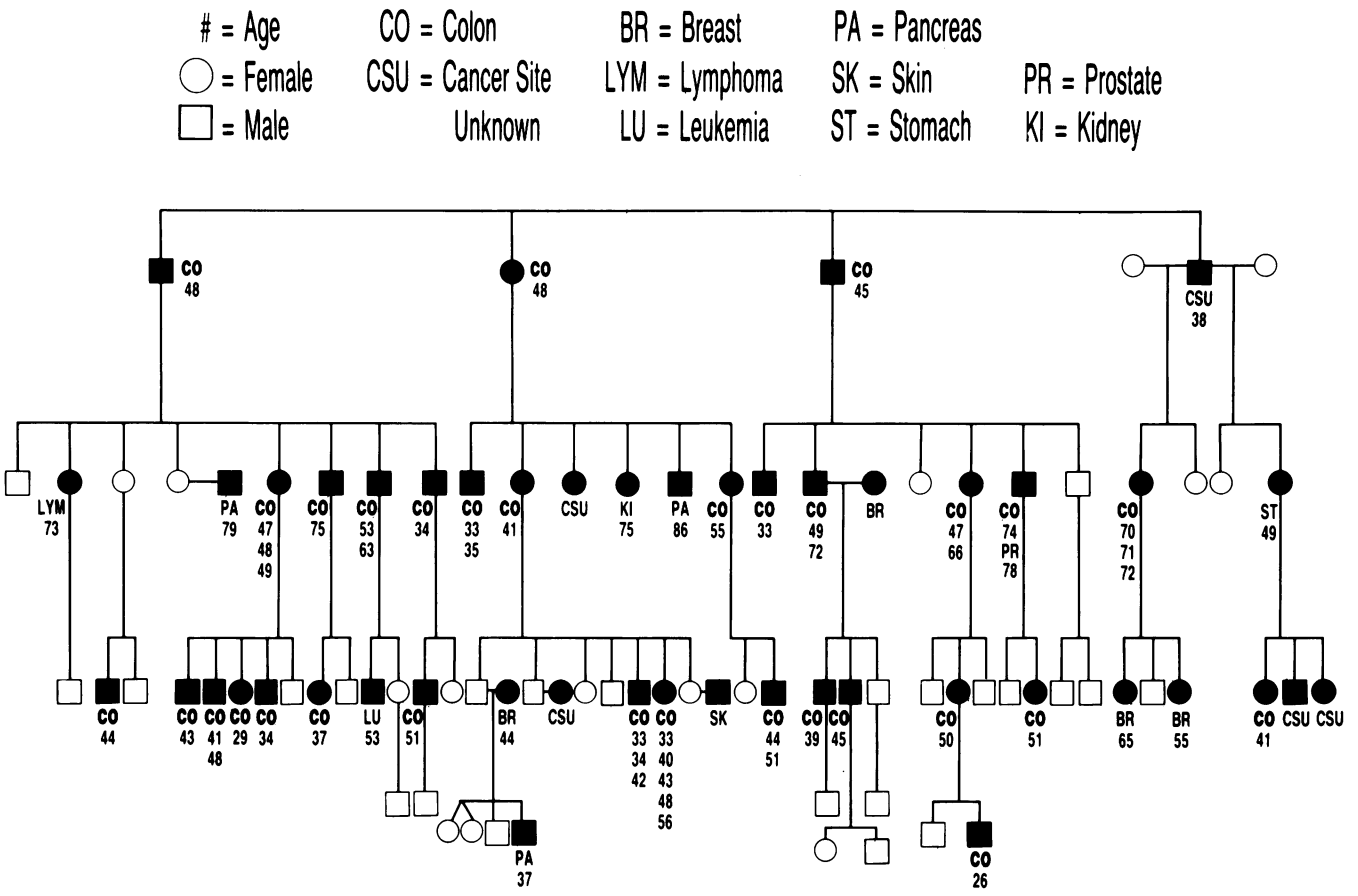

FIG. 4. A partial family pedigree of another family in this study. The multiple operative procedures necessitated by the synchronous and metachronous colon cancers could have been avoided if the presence of the syndrome was appreciated at the initial diagnosis.

151 members of the 10 families with an unusually high incidence of female genital tract lesions, *e.g.*, 32 endometrial cancers. Table 1 reflects the distribution of all cancers. The findings of early age of onset, proximal colon involvement, relative sparing of the sigmoid colon and rectum, and the high incidence of synchronous and metachronous colon lesions differed significantly at the $p < 0.05$ level when compared with representative published reports dealing with sporadic colon cancer[5-7] (see Table 2).

TABLE 1. *Comparison of Distribution of Cancers with the General Population*

Site (No.)	HNPCC Patients (%)	1987 Estimate for General Population[1] (%)
Colon and rectum (183)	55	15
Female genital tract (45)	14	7
Skin (19)	6	3
Lymphoma, leukemia (9)	3	5
Breast (17)	5	14
Stomach (13)	4	2
Urinary tract (17)	5	18
Pancreas (4)	1	3
Lung (1)*		15
Miscellaneous (11)	3	18
Cancer site unknown (15)	4	
Total (334)	100	100

* The curiously low incidence is currently under investigation.

Discussion

HNPCC is a syndrome that affects a significant percentage of the total colon cancer population but is not

TABLE 2. *Significantly Different Findings ($p < 0.05$) Between the Patients in this Study and Sporadic Colon Cancer Patients*

Finding	HNPCC Patients	Sporadic Colon Cancer Patients*
Age of first colon cancer diagnosis	45.6	63.0
Location proximal to the splenic flexure of the colon	69.1%	28.6%
Location in the rectum or sigmoid colon	23.3%	66.3%
Synchronous colon cancer	18.1%	4.8%
Metachronous colon cancer	24.2%	7.7%

* From representative published reports dealing with sporadic colon cancer.[5-7]

easily recognized because it lacks a distinctive clinical marker such as multiple polyps. It is important that physicians caring for patients with colon cancer appreciate its subtle presentation because the treatment for affected individuals is different than sporadic colon cancer and its autosomal dominant inheritance pattern allows the use of Mendelian genetics to make accurate predictions concerning risk for other members of the family. The incidence can be appreciated best if one divides the total colon cancer burden into four types: (1) sporadic, 70–80%; (2) familial, which represents those patients who have at least two first-degree relatives with a history of colon cancer without a clearly definable genetic inheritance pattern, 10–20% (3) hereditary colon cancer of the polyposis variety (FPC), slightly less than 1%; and (4) HNPCC, 5–6%.[4]

The natural history of HNPCC delineated by the data in this study suggests several cardinal features: (1) proximal colonic cancer involvement, (2) increased incidence of synchronous and metachronous colon lesions, (3) early age of onset, and (4) autosomal dominant genetic transmission. Extracolonic adenocarcinomas are associated in some of the families. The relationship is best understood if HNPCC kindreds are divided into two syndromes: (1) Lynch Syndrome I (Hereditary Site Specific Colon Cancer), which is characterized by an increased incidence of colon cancer, only, and (2) Lynch Syndrome II (the Cancer Family Syndrome), which is the same as Lynch Syndrome I with respect to colon cancer but is also associated with an increased risk for selected extracolonic adenocarcinomas that develop at a relatively early age and are inherited integrally (*i.e.*, on the same gene) with the colon cancer. The endometrial cancer in the family depicted in Figure 3 serves as an example. In this study, only female genital cancers were inherited in this fashion. However, breast, pancreas, and other cancers have been reported to act the same way in other families.[4] Once the cardinal features of HNPCC, as well as the relationship to extracolonic carcinomas, are appreciated, it is possible to recognize patients who are members of an affected family and then make appropriate treatment recommendations which, for the colon, are different than one would make for the same patient with a sporadic or familial colon cancer or hereditary colon cancer of the polyposis variety.

Recognition of Patients with Hereditary Nonpolyposis Colon Cancer

A surgeon faced with a patient who is a member of an HNPCC kindred with a newly diagnosed colon cancer will not make a correct management decision regarding the appropriate operative procedure unless the presence of the syndrome is appreciated. Unfortunately, no specific biomarkers are available for screening. Thus, the physician must depend entirely on the patient's family history. A relatively young patient with a proximal colon lesion is the first clue that should arouse suspicion. The next step is to inquire about the family history with specific attention to the presence of an autosomal dominant inheritance pattern and the presence of synchronous and metachronous lesions. An example is provided by examining the pedigree of one of the families in the data base of the current study (Fig. 3). Let us assume that the surgeon is asked to see the patient indicated by the box. He is a 46-year-old man with a newly diagnosed colon cancer. He has a past medical history of two previous colon cancers, one at age 37 and another at age 43. Inquiry concerning his family history reveals that his father and his paternal grandfather both had colon cancer. In addition, colon cancer has developed in three aunts and one uncle on his father's side. Finally, two of his paternal cousins have been affected. The autosomal dominant inheritance pattern is obvious. More detailed questioning will confirm the presence of frequent metachronous lesions, relatively early age of onset, and a proclivity for proximal colon involvement. No other measures are necessary to confirm that this patient is a member of an HNPCC kindred.

Figure 3 also illustrates another important consideration in evaluating patients for the presence of HNPCC. The family is an example of Lynch Syndrome II, which is determined by the inheritance of the endometrial cancer in concert with the colon cancer. Endometrial cancer developed in the patient's aunt (see arrow Fig. 3) at age 45. The chance of this being a random event is small because the incidence of endometrial cancer in the general population is only 3.6%.[1] This, coupled with her relatively young age for the development of endometrial cancer, makes it likely that she harbors the deleterious gene that contains both cancers. Thus, she is at great risk for the development of colon cancer if she lives long enough. It is simply a matter of the endometrial cancer phenotype being expressed before the colonic. For the same reasons, the patient's niece, who developed colon cancer at age 39, is at great risk for endometrial cancer.

Therapy of HNPCC

Treatment considerations for patients who are members of HNPCC kindreds should be divided into three clinical situations: (1) treatment of the patient with a newly diagnosed colon cancer, (2) recommendations for family members as yet unaffected by colon cancer, and (3) recommendations for patients who have had a previous conventional colectomy that is now known to have been inadequate therapy because the HNPCC syndrome has just been identified (see Table 3).

Treatment of a Newly Diagnosed Colon Cancer Patient

On the basis of our data on synchronous and metachronous colon cancer, we recommend a subtotal co-

TABLE 3. *Summary of the Treatment and Surveillance Recommendations for an Individual Known to be a Member of an HNPCC Family*

I. A patient with a newly diagnosed colon cancer:
  (1) Lynch I and II patients:
    A. Subtotal colectomy with ileorectal anastomosis.
    B. Biannual endoscopic evaluation of the remaining rectum.
  (2) Lynch II patients only:
    A. Female genital tract cancers: consider prophylactic TAHBSO at the time of the colectomy. Otherwise, biannual pelvic examination and yearly endometrial aspiration biopsy. ? Ovarian ultrasound.
    B. Individualized surveillance program as determined by the pedigree if the extracolonic cancer is also extragenital.
II. A patient as yet unaffected by cancer:
  (1) Lynch I and II patients:
    A. Biannual occult fecal blood testing beginning at age 20.
    B. Yearly colonoscopy beginning 5 years earlier than the age of onset of the earliest colon cancer in the family.
    C. Prophylactic subtotal colectomy with ileorectal anastomosis for obligate gene carriers.* Biannual endoscopic evaluation of the remaining rectum.
  (2) Lynch II patients only:
    A. Female genital tract cancers: biannual pelvic examination and yearly endometrial aspiration biopsy. ? Ovarian ultrasound.
    B. Individualized surveillance program as determined by the pedigree if the extracolonic cancer is also extragenital.
III. A patient treated by partial colectomy before being recognized as an HNPCC family member:
  (1) Lynch I and II patients:
    A. Biannual occult fecal blood testing.
    B. Yearly colonoscopy.
    C. A completion subtotal colectomy if not totally compliant.*
  (2) Lynch II patients only:
    A. Female genital tract cancers: biannual pelvic examination and yearly endometrial aspiration biopsy. ? Ovarian ultrasound.
    B. Individualized surveillance program as determined by the pedigree if the extracolonic cancer is also extragenital.

* An opinion from a clinical geneticist is urged before proceeding with therapy.

lectomy with ileorectal anastomosis. Because of the propensity of these cancers to involve the proximal colon, sacrifice of the rectum would not be routinely performed. Even the less mutilating mucosal proctectomy, pouch-anal procedures are not believed to be indicated because the incidence of rectal cancer does not justify the added morbidity when compared with ileorectal anastomosis.[8] Of some concern, however, is the concept that by transferring the effluent of the distal ileum from the right colon to the rectum, one might establish the same environment in the genetically susceptible mucosa of the rectum that had previously existed in the right colon. This could result in a high incidence of cancer in the retained rectum.[9] As yet, no data are available to address this question because so few patients are treated correctly with a subtotal colectomy when the initial colon cancer is diagnosed. Since the majority of patients we are now following for HNPCC are being treated with a subtotal colectomy at diagnosis of the first colon cancer, mature data should be available in several years.[10] Currently, frequent endoscopic evaluation of the remaining rectum is all that is recommended.

Patients from Lynch Syndrome II families must also have consideration given to integrally inherited extracolonic cancers. In this study, all of these cancers involved the female genital tract. Therefore, hysterectomy and bilateral salpingo-oophorectomy is recommended at the time of the colectomy. A difficult problem exists in the younger patient, perhaps in her early 30s. Factors such as childbearing desires, osteoporosis, psychological considerations, and the carcinogenic effects of prolonged estrogen replacement therapy complicate the management recommendations. A decision concerning removal of these organs must be individualized for each patient. If hysterectomy and oophorectomy are not performed, a screening program consisting of biannual pelvic examinations with attention to the ovaries and yearly endometrial suction curettage as an office procedure should be begun. The role of screening ovarian ultrasound is currently under investigation.[11]

If the extracolonic cancer is also extragenital, the pedigree must be examined on an individual basis and recommendations made to the family concerning risk. Prophylactic treatment of these organs is usually not practical but an effective surveillance program should be outlined. An opinion from a geneticist in these uncommon families may be in their best interest.

Recommendations for Other Members of the Family as Yet Unaffected by Colon Cancer

The autosomal dominant inheritance pattern of this condition dictates that only 50% of the first-degree relatives in an HNPCC kindred have the cancer gene. In general, prophylactic colectomy is not recommended. It is imperative that an effective surveillance program be established. Our recommendations include biannual fecal occult blood testing and yearly colonoscopy beginning 5 years earlier than the youngest colon cancer occurring in the family, *i.e.*, age 25–30. It is our belief that yearly endoscopy is mandatory because the widely accepted polyp cancer sequence in sporadic cancer may not be applicable to this hereditary cancer syndrome. So called "flat mucosal" cancers have been suggested by patients who have had thorough colon examinations,

both operatively and endoscopically, only to present with invasive colon cancer in a period of just a few months.[2]

There are some situations in which the risk for developing cancer approaches 100% and therefore prophylactic surgery is indicated. An example would be a patient from an HNPCC family who relates a history of a parent and a son or daughter who has developed colon cancer. Mendelian genetics dictates that an autosomal dominant gene could not have been passed from the parent to a grandson or granddaughter without being present in the "middle" person (obligate gene carrier). This assumes that the gene was not present in the opposite side of the family and that the development of colon cancer in the parent, grandson, or granddaughter was not a random event. Since the gene has a high degree of penetrance (89%), the risk of developing colon cancer is extremely high.[10] Prophylactic subtotal colectomy with ileorectal anastomosis is recommended in this situation.

In Lynch Syndrome II patients, a surveillance program must also be outlined for selected extracolonic cancer as determined by the individual pedigree. For families with integrally inherited female genital tract cancer, we are currently recommending biannual pelvic examinations and yearly endometrial suction biopsies beginning at the same age as the endoscopy.

Recommendations for Those Individuals Affected by Colon Cancer but Treated before being Recognized as a Member of an HNPCC Family

It is not unusual to see a patient who has had a conventional partial resection for colon cancer in which the significance of the family history was not appreciated. Our data suggest that the risk of developing metachronous colon cancer is 40% by 10 years. At the very least, an aggressive screening program for the remaining colon and the appropriate extracolonic organ(s) (Lynch Syndrome II patients only) must be recommended. Examination of an individual pedigree sometimes discloses a higher rate of metachronous colon cancer than average. In these patients we recommend conversion to subtotal colectomy. This recommendation is also made in any patient who will not be totally compliant with an effective surveillance program.

Conclusion

Construction of a nuclear pedigree in patients with colon cancer allows the use of basic genetic principles to ascertain an autosomal dominant inheritance pattern. HNPCC is confirmed when the autosomal dominant inheritance pattern is found to be coincident with the cardinal clinical features for the colon cancer, namely, early age of onset, proximal involvement, and frequent synchronous and metachronous lesions. Subtotal colectomy with ileorectal anastomosis is the treatment of choice for a patient with a newly diagnosed colon cancer who is a member of an HNPCC kindred. Extracolonic adenocarcinomas are common in some of these families (Lynch Syndrome II), and thereby dictate the need for prophylactic extirpative surgery or at least an intensive surveillance program directed at the specific organs suggested by the pedigree. Members of the kindred who are as yet unaffected by cancer are at a 50% or greater risk, (*i.e.*, obligate gene carriers approach 100% risk). An intensive surveillance program is begun at a young age. Prophylactic surgery is recommended in selective cases. Finally, patients treated for colon cancer with a partial colectomy before it was discovered that they were members of an HNPCC kindred should have their follow-up treatment considered in the light of a 40% chance of metachronous colon cancer developing by 10 years. These treatment recommendations are summarized in Table 3.

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Discussion

DR. CLAUDE H. ORGAN, JR. (Oklahoma City, Oklahoma): I rise to congratulate Dr. Fitzgibbons and his associates for identifying a distinctive subset of colonic neoplasms that have as their characteristics an early age of onset, an autosomal dominant mode of transmission, an excess proximal concentration of these lesions, increasing numbers of synchronous and metachronous lesions, and the possibility of an improved survival.

C. P. Snow has suggested that we are suffering from two coexistent but inadequately communicating cultures: the culture of the clinician and the culture of the basic science investigator (JAMA 1973; 225:617–621).

What is clearly needed for the most effective translation from dis-