Hereditary Cancer: Ascertainment and Management

Henry T. Lynch, M.D., Patrick M. Lynch, J.D., William A. Albano, M.D., John Edney, M.D., Claude H. Organ, M.D. and Jane F. Lynch, R.N.

Generalities in Family Cancer

Virtually all hereditary cancers and precancerous diseases show the following characteristics: (1) early age of cancer onset, the identical histologic variety often occurring 20 or more years earlier than in the general population. For example, while only four percent of all colorectal cancers occur before age 45, in genetically predisposed families with or without polyposis, the mean age at onset is 45 years. (2) a marked excess of bilateral cancer occurrence in paired organs, e.g., breasts, adrenal (pheochromocytomas) and thyroid glands, carotid body, kidney (Wilms' tumor), acoustic neurinoma; (3) in nonpaired organs, multiple primary or multicentric cancer occurs with a frequency many times greater than otherwise expected. Tumor registry data have shown that the risk of other cancer in patients with certain histologic varieties is significantly higher than in cancer-free patients of the same age. While these studies did not evaluate specific etiologies, many of the most frequently occurring multiple primary tumor associations in cancer registry data were considered consistent with a genetic etiology; (4) although there are well established autosomal recessive, sex-linked, and cytogenetic cancer and precancerous disorders, in many cases vertical transmission in consecutive generations of families has been identified with segregation patterns consistent with autosomal dominant inheritance.

These characteristics can be utilized as familial cancer selection criteria when identified in isolated patients and nuclear family cancer clusters, with or without an immediate impression as to the specific hereditary cancer or precancer syn-
drome that may be involved. As seen in the "nuclear components" of Fig. 1 (the breast cancer-prone family), when a patient presents with breast cancer at an early age (below age 45) and has a sister or mother similarly affected early in life, the physician should immediately consider the possibility of a hereditary breast cancer syndrome. When bilateral disease and/or associated malignant neoplasms (such as carcinoma of the ovary) are observed, the likelihood of a hereditary cancer syndrome is greater and should provide a basis for extending the family history to include second degree relatives. When these uncommon features continue to be expressed in collateral branches of the same family, the initial impression of a familial/genetic predisposition should be regarded as essentially confirmed. At this point, the developed pedigree can be formally compared with known cancer genetic syndromes or previously reported familial tumor aggregations. In certain circumstances, cutaneous signs of one of the more than 50 cancer-associated genodermatoses might be identified, thereby providing useful clues to hereditary cancer syndrome identification.9

Important Elements in Compiling Family Cancer History
The ready accessibility, patent simplicity, and predictive capability of the family cancer history could reduce cancer morbidity and mortality perhaps more effectively than some of our most sophisticated and expensive diagnostic tools. In our Oncology Clinic, nurses with an orientation in cancer genetic theory and interview techniques have assumed full responsibility for the compilation of cancer family histories.10 Family history interviews taken by them have focused on first degree relatives and, in young patients, on second degree relatives.

In the Clinic, pedigree schematics have helped structure the initial family history interview. The patient, by seeing the pedigree relationships, is better able to recall a more complete genealogy and medical history of his relatives. When, as is often the case, the patient is accompanied by other relatives, they are asked to participate in the history collection since they may be able to provide more detailed genealogic and medical facts about the family. Patients are encouraged to discuss these historical matters with other relatives and to bring any of this information, including available vital documents, to the Clinic at the time of their next appointment.

In evaluating family history for the presence of adult onset, autosomal dominant inherited disorders, certain second and third degree relatives, because of their older ages, may be more "genetically informative" than the patient's relatively young children, siblings, and perhaps even parents.

Our efforts have enabled Clinic physicians to devote more of their attention to the evaluation of the pedigrees. A decision to pursue the history in greater detail involves referral to the familial cancer registry of the Institute for Familial Cancer Management and Control (2500 California, Omaha, Nebraska 68178). As syndromes are determined to exist in a particular family, appropriate management protocols for the patient and his/her high-risk relatives are either instituted or recommended.10

In following up a family history, the patient's report that a given relative had cancer focuses critical attention on specific issues: age at onset; target organ involved; the presence of significant non-genetic risk factors. Age and associated risk factors (smoking history, occupation) may be fairly well known to the patient. The critical factors of organ and cell type are subject to extraordinary inaccuracy, requiring documentation through primary pathologic records whenever possible.

Among the first 300 cancer patients evaluated in our Oncology Clinic, approximately 10 percent have already reported striking familial aggregations of cancer that on further inspection fulfilled more rigorous criteria for hereditary cancer syndromes.10
Familial Cancer Registries

It is not possible for the busy practitioner alone to devote the resources necessary to elucidate the subtleties of cancer expression in an extended cancer-prone family, involving perhaps 100 to 500 or more members. One possibility for the centralized handling of cancer in genetically predisposed extended families—alogous to health department responsibilities in monitoring communicable disease—would be more routine referral to highly visible centers charged with the duties of evaluating such disorders and counselling patients at high risk of or suffering from the disease. Non-compulsory referrals by concerned patients and/or their physicians should minimize the potential for invasions of privacy, breaches of confidentiality, or improper use of the information gathered.

Integrated familial cancer registry systems could pool data on suspected cancer-prone families. Registry staff could provide information on hereditary cancer syndromes to physicians caring for high-risk relatives. In addition to risk figures pertaining to cancers of specific anatomic sites, the most current methods of surveillance for and management of a particular disorder could be rapidly disseminated to these physicians in a manner similar to that of most health departments that keep physicians informed of control methods for communicable disease in their communities (Table 1).

Familial Cancer Diagnosis and Management

Familial Polyposis Coli

Familial multiple adenomatous polyposis of the colon (FPC), is frequently cited as the classical prototype of a hereditary cancer-predisposing disorder. This is due to its supposed unvarying progression from isolated to diffuse colonic polyps to cancer of the colon, and because its genetic segregation clearly follows a Mendelian inheritance pattern, autosomal dominant.12 Table 2 provides a cursory sketch of the chronology of FPC and of the clinical and basic research into its natural history, pathogenesis, and treatment.

Estimates of the frequency of the polyposis gene range from approximately one in 700013 to one in 24,00014 livebirths (applied to the population of the United States this would mean that between 150 and 500 newborns would be affected each year). Because this disease has been so extensively investigated, its surgical management (Table 2) is perhaps the most familiar and generally accepted cancer prophylaxis known in hereditary precancerous disease.15 Recent evidence of heterogeneity in its expression and advances made in its management and control warrant review.

Families have been observed in which apparent carriers of the FPC gene (i.e., patients having both a parent and children with the classical phenotype) have developed colon cancer despite having no more than a few isolated polyps by age 20-3016 (Fig. 2). Because of this heterogeneity, the traditionally accepted rule of thumb—that at least 100 polyps are required to establish the diagnosis,17—occasionally may not apply; thus, failure by offspring of affected parents to manifest multiple polyposis of the colon by age 20 or 30 should not result in relaxed surveillance, nor should it be supposed that such offspring cannot themselves have children affected with the “complete” phenotype.

The traditional distinctions between classical FPC and the related, but allegedly discrete (genotypically) polyposis syndromes18-21 (Table 2) have been blurred by the meticulous clinical studies of several investigators.22,23 For example, occult osteomatous and cutaneous changes have been observed in FPC families thought to lack the stigmata generally associated with Gardner's syndrome.22 The notion that the adenomatous polyposis in FPC is limited to the colon has been criticized by clinicians who have identified adenomatous or hyperplastic polyps in the small bowel and stomach.23,24 The earlier views are at-
Fig. 1 An extended breast cancer-prone family showing the following: "nuclear-family components," transmission through unaffected males, early age at onset, and association with ovarian carcinoma.
| Disorder | Screening of Patients at Risk* | Management of Affected Patients |
|----------|--------------------------------|--------------------------------|
| MEA-I [50-53] (pituitary, adrenal cortical, parathyroid, pancreatic cell neoplasia) | (1) Annual serum gastrin (ages 10-65)  
(2) Emphasis on signs/symptoms associated with MEA-I (see text)  
(3) Positive findings mandate complete, appropriate workup of involved systems | (1) Non-beta cell tumor diagnosed:  
(a) Total gastrectomy  
(b) Removal of solitary pancreatic lesions when possible  
(2) Beta-cell pancreatic tumor diagnosed  
(a) Explore and remove solitary lesions  
(b) Biopsy pancreatic tail; 80% distal pancreatectomy, if adenomatosis found  
(c) If no tumor found, 80% distal pancreatectomy  
(3) Evaluate for parathyroid disease with annual CA++ and phosphorous and/or PTH, and treat accordingly.  
(4) Removal of symptomatic pituitary, thyroid, or adrenal tumors |
| MEA-II [50, 54-61] (Sipple’s syndrome) Medullary thyroid cancer, pheochromocytoma, parathyroid neoplasia | (1) Annual serum calcitonin  
(2) Annual PTH and CA++ (PTH $\neq$ may precede calcitonin $\neq$)  
(3) Emphasis on signs/symptoms associated with MEA-II (see text)  
(4) Calcitonin elevation pathognomonic of familial medullary thyroid carcinoma | (1) If calcitonin $\neq$, exclude pheochromocytoma (Pheo) prior to neck exploration  
(a) If pheo identified chemically, bilateral adrenalectomy  
(b) Lifetime surveillance mandatory if pheo not identified  
(2) Evaluate for parathyroid disease and treat accordingly  
(3) Near total thyroidectomy with neck dissection if metastases suspected  
(4) Routine post-op calcitonin determination |
| MEA-III [50, 54-61] (multiple mucosal neuroma syndrome) Shows same clinical characteristics as MEA-II but in addition may show multiple mucosal neuromas, Marfanoid habitus and intestinal gangliomatosis; parathyroid neoplasia uncommon | | |
CANCER FAMILY SYNDROME (CFS)\textsuperscript{2}, 7, 29–38, 72

(a) Excess adenocarcinoma, particularly of colon (proximal location predominates) and endometrium; less frequently, ovary, stomach, and breast
(b) Early age of cancer onset (x \(\cong 45\))
(c) Significant multiple primary cancer excess (> 40%)
(d) Vertical transmission of cancer compatible with autosomal dominance
(e) In certain families, risk appears limited to colonic cancer\textsuperscript{33, 35, 39, 71, 73}

Beginning at age 20:

1. Annual screening for occult fecal blood
2. Every 3 years either procto and B.E. or colonoscopy
3. Annual pelvic exam with endometrial biopsy every 3 years
4. In selected families, patients should be screened for breast, ovarian, or gastric neoplasms

A) CFS status established at time of initial therapy

1. Complete evaluation to exclude other primary cancers
2. Treat primary cancer in standard fashion; however, the scope of surgery should be extended to include a total abdominal colectomy and total hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO). Informed consent critical.

B) CFS status established subsequently
(Patients having undergone standard resection and having no evidence of metastatic disease)

1. Consider elective completion of abdominal colectomy and TAH-BSO
2. If further surgery contraindicated on medical, social, or personal grounds, annual screening mandatory

HEREDOFAMILIAL BREAST CANCER\textsuperscript{3, 5, 46}

Early onset of breast cancer; frequent bilaterality; possible transmission through unaffected males; association in many females with early onset ovarian cancer

Beginning at age 20 years:

1. Monthly breast self exam (BSE)
2. Mammography every 3 years
3. Biopsy or aspirate all dominant or suspicious lesions
4. Prophylactic bilateral subcutaneous mastectomies with implants for highly selected patients

(1) Perform standard therapy for initial breast cancer; evaluation of contralateral breast by mammography; biopsy. Standard therapy for synchronous cancer identified in contralateral breast
(2) Consider contralateral prophylactic mastectomy with reconstruction
(3) If prophylactic surgery contraindicated on medical, personal, or social grounds, meticulous followup is mandatory

A) Cowden's disease\textsuperscript{78}
Multiple hamartomas associated with carcinoma of the breast, occasional colonic polyps and thyroid lesions

(1) Observe for expression of phenotype-cutaneous hamartomas
(2) Follow as for heredo-familial breast cancer

(1) When phenotype is manifested, patients should undergo bilateral total mastectomy by age 20 (subsequent reconstruction should be considered)
(2) Bilateral subcutaneous mastectomy with implant may be considered, though incidence of cancer in remaining breast tissue may be high

\textsuperscript{*}Annual H&P required in all patients.
| Disorder | Screening of Patients at Risk* | Management of Affected Patients |
|----------|-------------------------------|---------------------------------|
| HEREDOFAMILIAL BREAST CANCER (cont') B) Breast\textsuperscript{42} and ovarian cancer: Pre to peri-menopausal adenocarcinoma of breast and/or ovary, genetic transmission and multiple primary risk otherwise akin to heredo-familial breast cancer | Same as for heredo-familial breast cancer, plus annual pelvic exam. Laparoscopy/laparotomy for abnormally enlarged ovaries/pelvic mass. | Same as for heredo-familial breast cancer: Consider prophylactic oophorectomy Annual pelvic exam in patients in whom oophorectomy is contraindicated because of medical, social, or personal reasons Laparoscopy/laparotomy for abnormally enlarged ovaries/pelvic mass |
| C) Breast\textsuperscript{30} and GI tract cancer (predominantly colon) | Screening and treatment for breast cancer as in heredo-familial breast cancer; screening and treatment for colon cancer as in CFS | |
| D) SBLA\textsuperscript{43} (Sarcoma, Leukemia, Brain tumors, Breast, Lung, Laryngeal, and Adrenal cortical carcinoma) Syndrome | Annual H&P exam directed toward organs and systems potentially at risk | Upon detection of primary cancer, carefully evaluate all other organs at risk with thorough annual followup |
| E) Breast\textsuperscript{3} cancer and malignant melanomas | Screening and treatment of breast cancer as in heredo-familial breast cancer | |
| FAMILIAL ATYPICAL MULTIPLE MOLE-MELANOMA SYNDROME (FAMMM Syndrome) | (1) Avoidance of excessive sunlight (2) Examination of entire skin at least 4 times per year (3) Biopsy of any suspicious lesions (4) Extensive patient education as to early signs of cutaneous malignant melanoma | (1) If melanoma identified, standard therapy based on level/depth of invasion (2) Intensive skin surveillance at least every 3 months with biopsy when indicated |

*Annual H&P required in all patients
tributed primarily to a failure to routinely explore the upper gastrointestinal tract. However, the malignant potential of extra-colonic polyps in affected patients appears not to be as great as for polyps of the colon proper.24

In a remarkable kindred reported by Binder et al.25 medulloblastoma characteristic of Turcot's syndrome (more descriptively called the polyposis-glioma syndrome and believed to be autosomal recessively inherited) was reported in a patient whose relatives manifested sebaceous cysts and gastric polyps compatible with Gardner's syndrome. Thus, features of several supposedly distinct syndromes were witnessed in a single family unit.

Screening Patients with Unexpressed FPC Phenotype

Management of FPC has heretofore consisted primarily of proctoscopic screening of patients until polyps appeared in sufficient numbers, at which time either subtotal colectomy with ileorectal anastomosis or total proctocolectomy with ileostomy was performed. The now apparent heterogeneity in this disorder requires, and advances in diagnostic and treatment techniques allow, a more flexible approach to its management.

Screening for polyps should be commenced at age 10 in high-risk patients (those with one or more affected first degree relatives) or earlier if there are symptoms or signs, such as rectal bleeding or cutaneous and/or osseous manifestations of Gardner's syndrome. The difficulty of performing adequate proctosigmoidoscopy in youngsters coupled with frequent noncompliance, necessitates biannual screening for occult fecal blood. Hemoccult screening should be continued biannually through age 45, and annually thereafter.

In asymptomatic patients, a baseline barium enema with air contrast is performed at age 20. In symptomatic patients or those with a positive Hemoccult test, double air contrast barium studies of the lower gastrointestinal tract should be performed. Proctosigmoidoscopy is begun on a routine basis at age 15 if it can be accomplished easily and effectively. This is continued on an annual basis until age 45 and repeated at one to two year intervals as long as the patient remains asymptomatic.

Treatment

In patients with more than 100 polyps, total proctocolectomy remains the treatment of choice. Utilization of a continent ileostomy or performance of sphincter-preserving procedures warrant careful consideration. While such techniques have led to an acceptable continence rate, patients contemplating these procedures must be told that an ileostomy may eventually be required.26,27

The frequently employed and more conservative total abdominal colectomy with ileorectal anastomosis requires diligent evaluation for and fulguration of rectal polyps on a three-month basis for life (though the possibility exists of polyp regression due to the action of "ileal contents"). Because of the magnitude of cancer risk to the rectal stump in patients with rectal polyps (59 percent at 23 years)24 elective proctectomy at 10 years postresection must be considered; the development of retroperitoneal fibrosis following total abdominal colectomy in Gardner's syndrome may make subsequent proctectomy technically difficult. Follow-up must include screening for polyps of the upper gastrointestinal tract (see Table 2).

In FPC families, in patients having 10 to 100 polyps and in whom the rectum is not extensively involved (six to 10 polyps), a total abdominal colectomy with ileorectal anastomosis and fulguration of subsequent rectal polyps on a three-month basis for life is the procedure of choice. In those patients whose rectum is extensively involved, total coloproctectomy should be performed with consideration for a continent ileostomy or pull-through procedure.

In patients with fewer than 10 polyps, biannual colonoscopic removal of all polyps may be accomplished. If the
| Year | Investigator | Discovery | Implications |
|------|--------------|-----------|--------------|
| 1847-93 | (Couvisant\textsuperscript{62} and others\textsuperscript{63,64}) | Polyposis phenotype | Baseline clinical observation stimulating further research (below) |
| 1882 | (Cripps\textsuperscript{65}) | Recognition of familial clustering | Basis for evaluating other family members |
| 1890 | (Handford\textsuperscript{66}) | Demonstration of colon CA association | Early CA detection when phenotype observed |
| 1925 | (Lockhart-Mummery\textsuperscript{67}) | Specific mode of inheritance determined to be autosomal dominant | Basis for differentially focusing attention on certain family members |
| 1925-50 | (Lockhart-Mummery, Duker\textsuperscript{68}) | Temporal sequence of isolated polyp-diffuse polyp-cancer progression reported | Diagnosis earlier in life (isolated polyp stage of disease; rationale for prophylactic colectomy) |
| 1952-78 | (Wool\textsuperscript{71}, Smith\textsuperscript{72}, Lynch\textsuperscript{73}) | Hereditary isolated polyps, associated with colon CA | Underscores potential for variation in FPC phenotype (some large families have been observed in which no colon cancer patients manifested diffuse polyposis; in other kindreds, some patients exhibit diffuse polyposis and close relatives manifest isolated polyps only, but with equal cancer proclivity) |
| 1957 | (Hubbard\textsuperscript{69}) | Spontaneous regression of rectal polyps in certain patients | Opportunity to perform ileo-rectal anastomosis in preference to ileostomy |
| 1960 | (Watte, 1977\textsuperscript{20}) | Failure of polyps to regress following subtotal colectomy in many patients, leading to cancer in rectal stump | Rectal mucosal stripping, leaving intact muscularis, enhancing bowel function while removing high risk tissue |
| 1963 | (Cole & McKalen\textsuperscript{70}) | Ascorbic acid for polyp regression in rectal stump | In certain cases, potential for avoiding proctectomy |
|      |              | Abnormal proliferation patterns in mucosal crypts | Potential for identification of gene carriers prior to expression of polypos (not reliable enough for routine use) |
polyps cannot be removed via the colonoscope or the frequency of recurrence appears to be increasing, total abdominal colectomy with ileorectal anastomosis followed by proctoscopic fulguration of polyps should be considered. Factors such as the age of the patient (polyps at an early age are more likely genetic) and a history of colon cancer in relatives with isolated polyps may aid in distinguishing the hereditary (colectomy required) from sporadic (polypectomy adequate) nature of the isolated polyps that are encountered.

The Cancer Family Syndrome
Criteria for the Cancer Family Syndrome (CFS) include a familial excess of adenocarcinoma involving the colon and endometrium\(^{29}\) (and less frequently, the stomach, breast, and ovary\(^{30,31}\), occurring at much earlier ages (\(\bar{x} \sim 45\) years) than the same histologic varieties in the general population.\(^{32}\) Lesions involving the colon show a proximal colonic predilection (65 percent are so situated),\(^{33}\) in contrast to the 20 to 30 percent so located in the general population. Initially affected patients have an extraordinary risk of multiple primary cancer, typically involving the end organs cited above.\(^7\)

The tumor expression pattern is transmitted vertically, and segregation ratios are consistent with an autosomal dominant mode of inheritance.\(^2\) A number of investigators are actively searching for markers of the precancerous
state in the CFS,³⁴-³⁶ though none have been definitively identified to date. Consequently, diagnosis of the syndrome in a given family must still be predicated on the pedigree’s consistency with the above criteria. Management of the CFS patient with colonic cancer is much like that of FPC, namely subtotal colectomy, continued surveillance of the rectal stump, and a high index of suspicion for non-colonic cancer.³⁷-⁴¹ The proximal colonic excess precludes exclusive reliance on proctosigmoidoscopy as a screening measure. Other diagnostic and therapeutic approaches that differ from those utilized in FPC are described in Table 1.

Familial Breast Cancer

That familial breast cancer is a heterogeneous disease is evidenced by its association with other malignant neoplastic lesions in certain families (Table 1).³,⁴²,⁴³ With the exception of Cowden’s disease (multiple hamartoma syndrome) there are no reliable preclinical markers of high breast cancer risk (Table 1). Therefore, the familial risk for this disease can only be estimated in relation to the available family history. The occurrence of two or more first degree relatives with histologically verified breast cancer constitutes a reasonable basis for more intensive investigation of an extended family; studies of consecutive series of breast cancer probands have shown that approximately 15 to 20 percent will have another first degree relative similarly affected.⁴⁴ Pre-menopausal expression and bilaterality represent significant selection criteria in their own right.³,⁵,⁶,⁸,⁴²,⁴⁵

Fig. 1, a pedigree of an extended breast/ovarian cancer-prone family, illustrates four key issues in breast cancer genetics. Note the early ages at onset and associated cancer (ovarian). The pedigree includes an example of apparent transmission through an unaffected male (nuclear component D), a phenomenon observed in other families. The term “nuclear components” of the kindred emphasizes the somewhat limited nature of the information typically available to a given family physician. This is strengthened significantly when it can be incorporated into the larger unit of an extended kindred whose other branches may show similar expression and collectively enable the identification of a more complex hereditary cancer syndrome.

Prophylactic Surgery

Because of the great risk of cancer in the contralateral breast among patients from high risk families,⁶,⁸ patients in our institution are considered for contralateral mastectomy approximately one year following initial mastectomy. The procedure is deferred somewhat in patients having had high-risk initial lesions. All patients are carefully evaluated for metastatic disease and are considered for simultaneous reconstruction of the primary site. In all cases, the tissue removed at contralateral prophylactic mastectomy is carefully evaluated by both radiographic and histologic techniques, with appropriate treatment undertaken if cancer is found.

In highly selected unaffected patients at risk for familial breast cancer, prophylactic bilateral subcutaneous mastectomy with reconstruction is worthy of consideration and has been performed in a growing number of cases.⁴⁵,⁴⁶

Familial Atypical Multiple Mole-Melanoma Syndrome (FAMMM)

Familial clustering of malignant melanoma has been described frequently enough to suggest that in about three to 10 percent of occurrences, primary genetic factors may predispose to this disease.⁴⁷

As in the Cancer Family Syndrome and heredo-familial breast cancer, physical markers of the neoplastic state have been lacking. Recently, however, a hereditary, premelanotic cutaneous phenotype (characterized by multiple large moles, irregularly shaped, reddish-brown to pink in color, and with evidence of
Fig. 2. Pedigree of a family with variable expressivity of colon polyps, ranging from isolated adenomatous polyps of the colon to classical presentation of diffuse polyposis coli, in association with early onset colon cancer. (Reproduced by permission from: Lynch HT, et al: Familial Polyposis Coli: Heterogeneous polyp expression in two kindreds. J Med Gen 16:1-7, 1979.)
pigmentary leakage) has been identified by several investigators, working independently.48,49 This cutaneous precancer phenotype is transmitted in a manner consistent with an autosomal dominant mode of inheritance. To this syndrome we have ascribed the acronym FAMMM, for Familial Atypical Multiple Mole-Melanoma Syndrome.49

This phenotype is illustrated in a member of a family we have studied (Fig. 3), four of whose immediate relatives (two siblings, his mother and maternal aunt) have manifested malignant melanoma, secondary to multiple atypical moles in at least three cases. The significance of the cutaneous phenotype was not originally recognized in this family. Nevertheless, the striking melanoma cluster was maintained in our registry for a decade until it was observed in two other families, one of which was reported by Clark et al.48

The eventual demonstration of the phenotype in the family discussed above demonstrates the utility of longitudinal monitoring of such kindreds.

We urge that the following measures be adopted in the management of suspected FAMMM syndrome cases:

- Evaluate extended family for further evidence of the phenotype;
- Stress the same avoidance of excess sunlight that is recommended for any lightly pigmented individual;
- Examine the skin at least four times per year;
- Educate patients extensively regarding early signs of cutaneous malignant melanoma (our high-risk patients are shown color photographs of the progression of melanoma and are provided a walletsized card, laminated in plastic, listing early signs of melanoma);
- Promptly biopsy any suspicious lesions.

Multiple Endocrine Adenomatosis (MEA) Type I

MEA Type I, first described as a familial entity in 1954 by Wermer,50 is inherited as an autosomal dominant with gene penetrance of 60 to 80 percent.51 It consists of adenomatous changes in the anterior lobe of the pituitary gland, the parathyroid glands, and the pancreatic islet cells. Changes have also been noted in the adrenal cortex, thyroid, and ovary. Multiple glandular involvement is frequent in this entity.52 Attention must be focused on pancreatic neoplasms and the associated Zollinger-Ellison syndrome because of their high morbidity and mortality.53
Asymptomatic patients in MEA-I families should be screened via annual pentagastrin radioimmunoassay between ages 10 and 65. Emphasis should be placed on signs and symptoms of peptic ulcer disease, hypoglycemia, watery diarrhea, pituitary disorders, thyroid nodules, hyperparathyroidism, and Cushing's syndrome. A treatment protocol has been included in Table 1.\textsuperscript{50-53}

**MEA-II and MEA-III Syndromes**

MEA-II (also known as MEA-IIa or Sipple's Syndrome) is characterized by the association of medullary thyroid cancer, pheochromocytoma, and parathyroid neoplasm.\textsuperscript{51} The MEA-III (II-b, multiple mucosal neuroma syndrome) variant is, in addition, associated with marfanoid features and mucosal neuromas that may expedite its diagnosis. Central to the management of these syndromes is the early treatment of medullary thyroid cancer, since it is this component that most frequently leads to the affected patient's early demise.

Although sporadic occurrences of the disease are relatively more frequent, the autosomal dominant mode of inheritance has been well established for the hereditary variety. Familial medullary thyroid carcinoma bears a highly specific marker—calcitonin—that allows for the screening of high-risk relatives.\textsuperscript{54,55} Such screening should begin at age five and continue until age 60.\textsuperscript{56} In high-risk patients, hoarseness, dysphagia, watery diarrhea, or a neck mass should alert the physician to the possibility of a medullary thyroid carcinoma. Symptoms of hypertension, diaphoresis, or headache may suggest pheochromocytoma. Patients should undergo annual parathormone assay, serum calcium and phosphorous, to rule out the possibility of hyperparathyroidism.\textsuperscript{56}

Elevated calcitonin in these patients is diagnostic of medullary carcinoma of the thyroid.\textsuperscript{57-60} Early screening may allow for the detection of C-cell hyperplasia prior to the onset of malignant change.

In patients manifesting familial medullary thyroid cancer, it is imperative to rule out the associated pheochromocytoma prior to neck exploration. If a pheochromocytoma is diagnosed, patients should undergo bilateral adrenalectomy due to the high frequency of bilateral involvement in this population, even when there are no palpable abnormalities within the glands at exploration. A treatment protocol for MEA-II and III is included in Table 1.\textsuperscript{50, 54-61}

**Conclusion**

The historical perspective provided by familial multiple adenomatous polyposis of the colon (Table 2) provides an excellent example of the advances in cancer epidemiology and characterization of hereditary precancerous disease(s), through multidisciplinary study over a long period of time. Concomitant advances in surgical management and prophylaxis have been witnessed. However, it has also been seen that even in this most intensively studied disorder(s), a great deal remains unknown about the variability in clinical features.

Those disorders lacking the readily discriminable markers of the FPC, FAMMM and the MEA syndromes have been a particular concern in this discussion. Clinical research into these syndromes has been similar to the approach used in the study of FPC. This research has arrived at varying stages in the development of differential diagnostic and therapeutic protocols.

Due to the early ages of high-risk patients and their unfamiliarity with the role of genetic factors in cancer etiology, most would not otherwise be subject to screening for the diseases involved. A registry of such patients and their families could facilitate a greater recognition of their medical genetic significance. Our Registry-based program has clearly demonstrated the manner in which a carefully obtained family history can lead to the recognition of patients with exceedingly high cancer risk.
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THE LANGUAGE OF MEDICINE

Errors and misconceptions of former times are embalmed in terms like cholera, so called because the diarrhea and vomiting characteristic of the disease were believed to be a discharge of malignant bilious humor (chole-bile), and gonorrhea, which means literally a flow of semen. Hysteria is so named because in ancient times the uterus (hyster) was considered a seat of mental afflictions. There is another allusion to this notion in globus hystericus, which refers to the primitive belief that the “lump in the throat” of a distraught woman was the uterine fundus.

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