With a myriad of vexing abbreviations and obscure terminology, the genetics controlling the formation of colonic polyps and malignancies may be difficult to appreciate. A review of these colonic disorders will aid in an understanding of the underlying genetics.

SPORADIC, FAMILIAL AND INHERITED DISEASE

Eighty to ninety percent of cases of colon cancer occur sporadically.

Ten to fifteen percent of patients have familial colorectal cancer, meaning that there are two or more colorectal malignancies found in a given family and that a specific causative gene has not been identified.

Five percent of patients have an inherited or hereditary form of colon cancer and a genetic abnormality has been found to be associated with the malignancy. To further subdivide this group, the colonic malignancy may be associated with one of several polyposis syndromes in which there are a variable number of adenomatous or hamartomatous colonic polyps lining the mucosa, or with nonpolyposis syndromes in which there are few or no colonic polyps associated with the colon cancer.

POLYPOSIS SYNDROMES

Adenomatous Polyposis Syndromes

Perhaps the best-known disease in this group is Familial Adenomatous Polyposis (FAP). The mutation responsible for this syndrome is found in the adenomatosis polyposis coli (APC) gene. The gene is located on the long (q) arm of chromosome 5. The APC gene normally is responsible for the expression of a protein that prevents uncontrolled cellular growth and division. Six hundred mutations have been discovered in this gene and any of these mutations may give rise to an aberrant protein that is abnormally short, nonfunctional and unable to suppress the cellular overgrowth that leads to colonic polyp and cancer formation.

Inherited in an autosomal dominant manner, only one parent is required to have a copy of the defective gene and this gene must be transmitted to the child for the FAP phenotype to be expressed. At least fifty percent of offspring will receive this aberrant gene and develop FAP. Surgical treatment does not lessen this risk. As one third of newly diagnosed patients with FAP do not have an affected parent, the disease in these patients may represent a new mutation in the APC gene which may be passed down the family tree.

Alert to the genetics and findings in patients with hereditary colorectal cancer syndromes, physicians may be better able to diagnose and recommend treatment for the colonic manifestations of each disease.
In the teenage years, the number of colonic polyps observed in patients with FAP begins to increase. The average age of development of colon cancer is thirty nine years. Although associated with only one percent of colorectal cancers, without surgical treatment, there is an almost one hundred percent risk of developing of colon cancer.

In FAP, there is also a lifetime risk of developing desmoid tumors (15%), duodenal cancer (4%), thyroid cancer (2%), brain cancer (2%), ampullary cancer (1.7%), pancreatic cancer (1.7%), hepatoblastoma (1.6%) or gastric cancer (0.6%).

**Attenuated Familial Adenomatous Polyposis (AFAP)** is associated with fewer colonic adenomas, a tendency towards smaller and more proximal adenomas and a later age of onset of malignant transformation. The APC gene is also responsible for AFAP.

**MYH-associated polyposis (MAP)** is a form of polyposis caused by a mutation in the MUTYH gene, a base excision repair gene located on the short (p) arm of chromosome 1. MAP is inherited in an autosomal recessive fashion, meaning that each parent must have one copy of the gene and both copies of the gene must be present in the child for the phenotype to be expressed. MUTYH glycosylase, an enzyme expressed by the MUTYH gene, repairs nucleotide mismatches prior to DNA replication. A defective gene expresses faulty MUTYH glycosylase and thus allows for the uncontrolled cellular growth and division leading to the formation of colonic polyps with the possibility of subsequent malignant transformation. Polyps associated with a mutant MUTYH gene do not appear until adulthood and are less numerous than those found in patients with APC gene mutations.

Several other syndromes involving a defective gene have been described and now are thought to be variants of FAP. **Gardner’s Syndrome** describes the association of colorectal cancer with other malig-
dances. In women with Lynch II, there is a thirty to fifty percent lifetime risk of developing colon cancer.

**Juvenile Polyposis** is a rare disease in which those affected patients harboring greater than five polyps. Patients with single polyps have very little risk of developing colon cancer.

### NONPOLYPOSIS SYNDROMES

**Hereditary Nonpolyposis Colorectal Cancer** is also known as HNPCC or Lynch Syndrome. HNPCC is an autosomal dominant disease and is the most common hereditary colon cancer syndrome, accounting for two to four percent of all colon cancers. The syndrome occurs as a result of mutations in the mismatch repair genes MSH2 located on chromosome 2, MSH6, also located on chromosome 2, MLH1 located on chromosome 3, or PMS2, located on chromosome 7. These genes normally produce enzymes responsible for removing mispaired nucleotides which may have mispaired during faulty DNA replication. With these mutations, mismatch repair cannot be accomplished and cellular growth is altered or deranged leading to neoplastic growth. HNPCC is seen against the background of a normal colon, or in a colon with only a few small polyps. The disease is divided into Lynch I and Lynch II.

In Lynch I, colorectal cancer is the most common pathologic finding. The lifetime risk of developing a colorectal cancer in an individual with Lynch I syndrome is eighty percent. Most of the neoplasms are located proximal to the splenic flexure, produce mucin, and demonstrate signet ring cells and tumor-infiltrating lymphocytes on pathologic examination. Synchronous and metachronous lesions are not uncommon, signaling a mismatch repair defect. The average age of diagnosis is forty four years old, compared to age sixty four in the sporadic form of colon cancer.

**Lynch II** describes the association of colorectal cancer with other malignancies. In women with Lynch II, there is a thirty to fifty percent lifetime risk of developing endometrial cancer, with the average age of diagnosis being forty six. Gastric cancer, transitional cell carcinoma of the ureter and renal pelvis, small bowel cancers occurring most commonly in the duodenum and jejunum, and central nervous system tumors, most often glioblastomas, are part of the Lynch II syndrome.

**Familial Colorectal Cancer Type X** is a rare disease in which those involved meet the criteria of the nonpolyposis syndrome but have none of the positive genetic test results found in the nonpolyposis syndromes. More specifically, patients with familial colorectal cancer type X do not have a demonstrable mismatch repair defect. The risk of developing colorectal cancer is lower than in those patients with HNPCC, and the age of diagnosis of colon cancer is higher. Unlike patients with the Lynch II syndrome, these individuals do not seem to develop malignancies in other organ systems.

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