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INTERNAL MEDICINE GRAND ROUNDS

ADVANCES IN THE CAUSES AND TREATMENT OF COLONIC CARCINOMA

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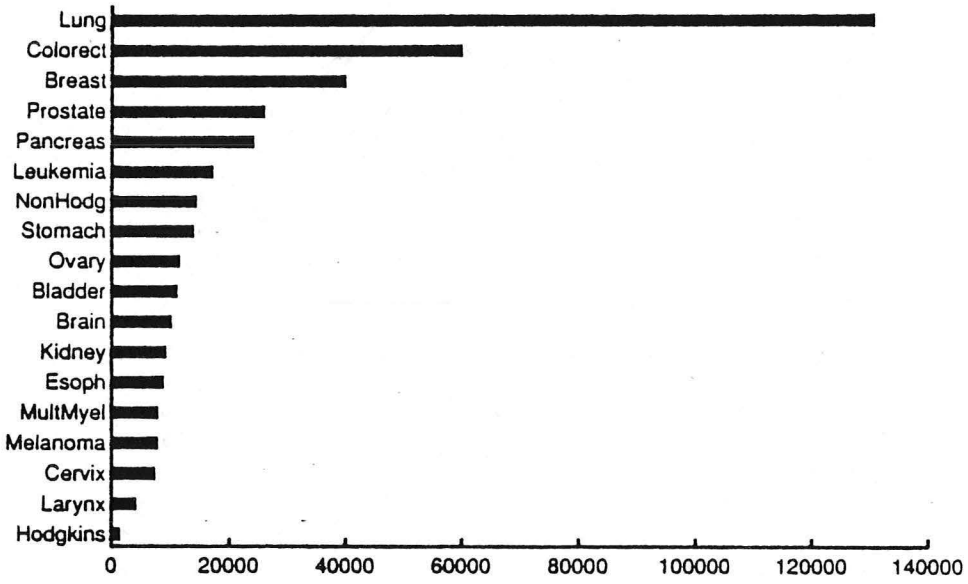
U.S. CANCER MORTALITY BY SITE



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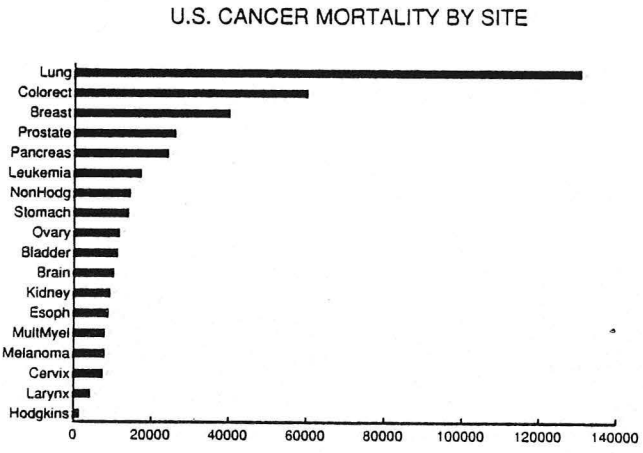
I. ADVANCES IN THE CAUSES AND TREATMENT OF COLONIC CARCINOMA

Carcinoma of the colon is one of the most common and important malignancies in the United States. Since most carcinomas of this type are thought to arise from, or in association with, colonic polyps, various surveillance programs can, in theory, lead to early detection and greater survivability with this tumor. In addition, there have been recent, remarkable advances in our understanding of the potential causes for this tumor which hold out the hope for more sophisticated and subtle tests for detecting susceptibility to carcinoma of the colon. This protocol briefly reviews these advances and, in addition, summarizes the major clinical findings in the inheritable and sporadic forms of colonic carcinoma.

A) Introduction

As illustrated in Fig. I-A carcinoma of the colon and rectum represents the second most important form of cancer in terms of mortality in the United States. Each year approximately 60,000 individuals die from this lesion. Presumably if smoking could be eliminated from the U. S. population, carcinoma of the colon and rectum would become the No. 1 cause of cancer deaths in this country. At this time approximately 5% of U. S. born males and 6% of females will develop colon cancer during their lifetime. The overall mortality rates continue to be in the area of 50-60%. However, with the detection of early lesions that do not have lymph node involvement, the mortality rate can be less than 20%. Thus, it is clear that early detection is critically important in reducing overall mortality from this lesion.

Figure I-A



It is of considerable importance that not all racial groups have similar incidences of this lesion. As illustrated in Fig. I-B the Dallas/Fort Worth area is similar to all other areas in the United States. After the age of 40, there is a striking increase in the incidence rate per 100,000 individuals. As is apparent in this figure beyond the age of 60 the incidence in both males and females increases abruptly from approximately 50 cases per 100,000 to approximately 300 cases per 100,000 at the age of 85.

Figure I-B

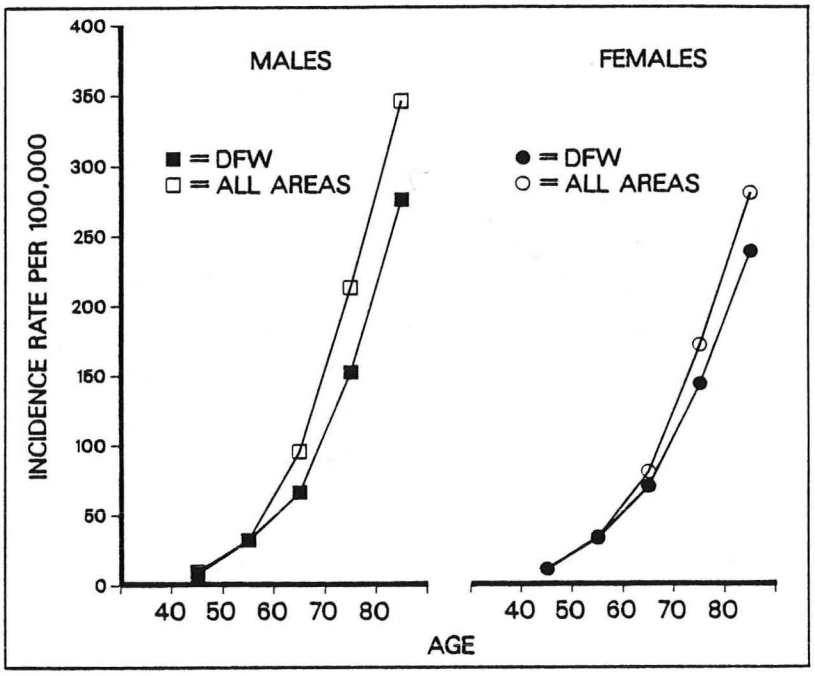
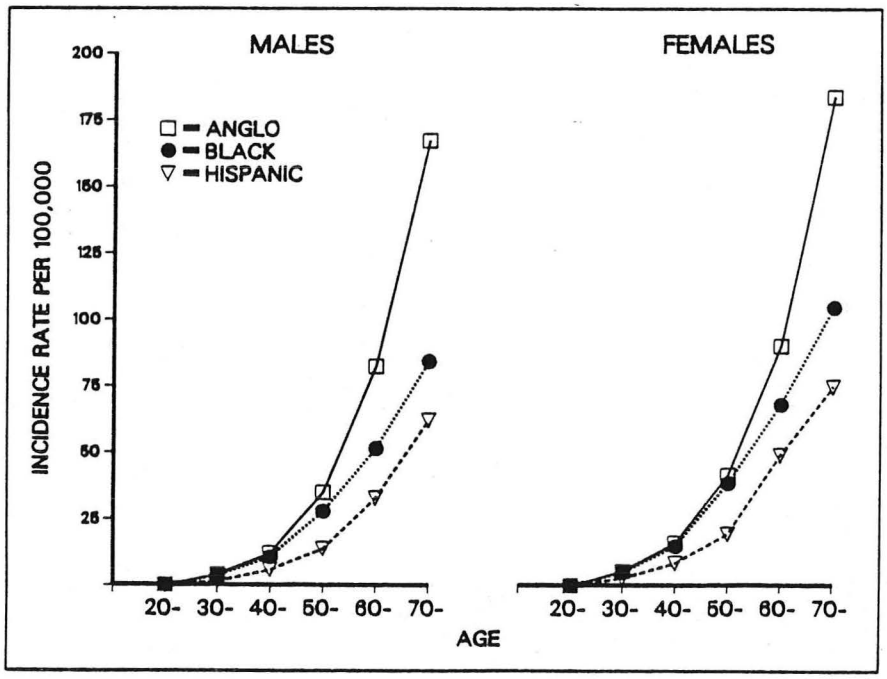
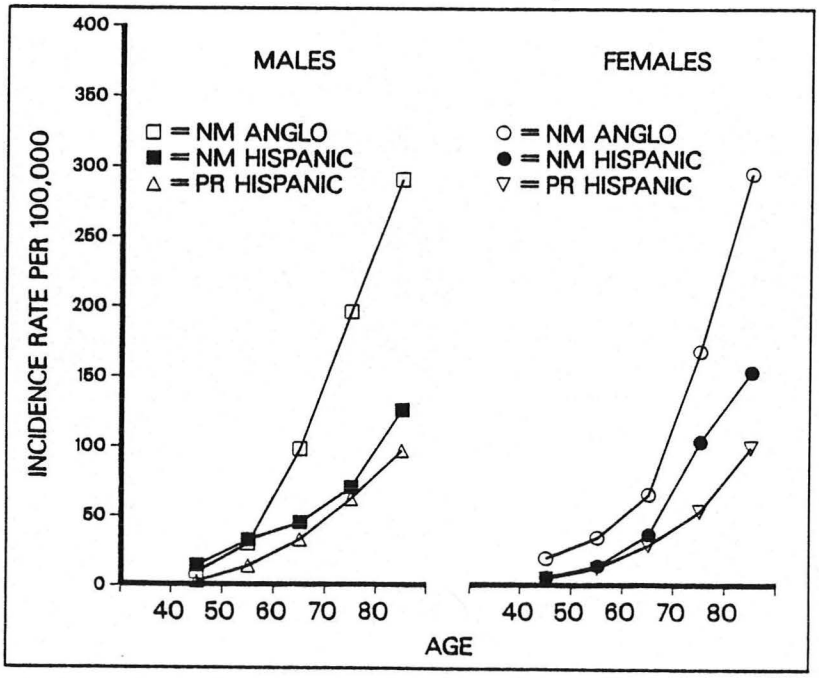


Figure I-C



However, there are rather striking differences in the incidence rates in different ethnic groups. As shown in Fig. I-C, for example, in any particular age group both male and female Hispanics have an incidence rate that is approximately half of that seen in Anglos. Blacks have an incidence rate that is intermediate between Hispanic and Anglos. The term "Hispanic" is meaningless with respect to genetic background since this term is applied to ethnic groups that, on the one hand, may be of European gene stock while other groups may be largely derived from archaic middle and North American aboriginal groups. That there are potentially important differences in the incidence of colonic carcinoma in different Hispanic subgroups is suggested by the data shown in Fig. I-D.

Figure I-D



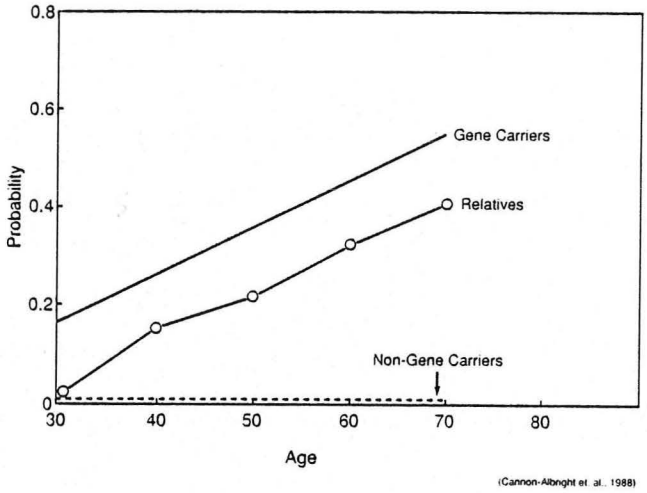
These incidence figures suggest that there is a significantly higher rate of adenocarcinoma in Hispanics from the New Mexico region (with a large admixture of American aboriginal genes) than in Hispanics from Puerto Rico. Clearly, these different ethnic groups have differences in environment, diet and other factors that may be etiologically important in the development of carcinoma; nevertheless, this type of data at least raises the possibility that differences in gene pools leads to significant differences in the incidence of adenocarcinoma of the colon.

Whatever the underlying genetic or biochemical defects that lead to carcinoma, there is a series of indirect observations that strongly suggests that there is a relationship between the development of "benign" neoplasms (adenomatous polyps) and malignant neoplasms. For example, it has been observed 1) that adenomas are frequently found in patients with colonic carcinoma; 2) that both severe dysplasia and frank malignant changes are seen in larger adenomatous polyps; 3) that in some cases there appears to be progression from severe dysplasia to frankly invasive malignancy; 4) that residual adenomatous tissue is occasionally found in a frank carcinoma; 5) that there is a similar anatomic distribution in the incidence of adenomas and carcinoma; 6) and that there is a high incidence of carcinoma in patient groups having a large number of adenomatous polyps. These observations suggest that the patients at risk for this disease have some underlying biochemical abnormality that leads, first, to the development of benign adenomas and, second, to the malignant degeneration of these adenomas. The progression from benign to malignant neoplasia provides an important technique from detecting and preventing this disease. Presumably, surveillance programs that detect the appearance of adenomatous polyps provide a means for identifying those individuals destined to develop carcinoma. In general, the greater the propensity to develop adenomas the greater the likelihood that an individual will eventually develop carcinoma. Furthermore, if a large percentage of carcinomas actually arise from benign adenomas, then, in theory, removal of adenomatous polyps could prevent the subsequent development of cancer.

II. THE CAUSES OF ADENOCARCINOMA OF THE COLON

Generally, adenocarcinoma of the colon has been divided into two groups: sporadic carcinoma occurring in individuals without any clear-cut familial incidence and hereditary adenocarcinoma occurring in syndromes where there is clearly an inherited tendency for the development of adenomas and cancer. Several lines of evidence have suggested that the familial forms of cancer account for only a few percent of the total number of adenocarcinomas that develop each year while the majority of adenocarcinomas are considered to be "sporadic." Such sporadic carcinoma has often been attributed to environmental or dietary factors. It is thought, for example, that carcinogens may be present in the diet and may relate to such things as the type and quantity of fiber ingested, the type and quantity of long chain fatty acids eaten in the meal or a variety of chemicals that are potentially carcinogens. This general concept has changed radically within the past year and there are now several lines of evidence which suggest that the great majority of cancers of the colon have a hereditary (genetic) basis.

Figure II-A



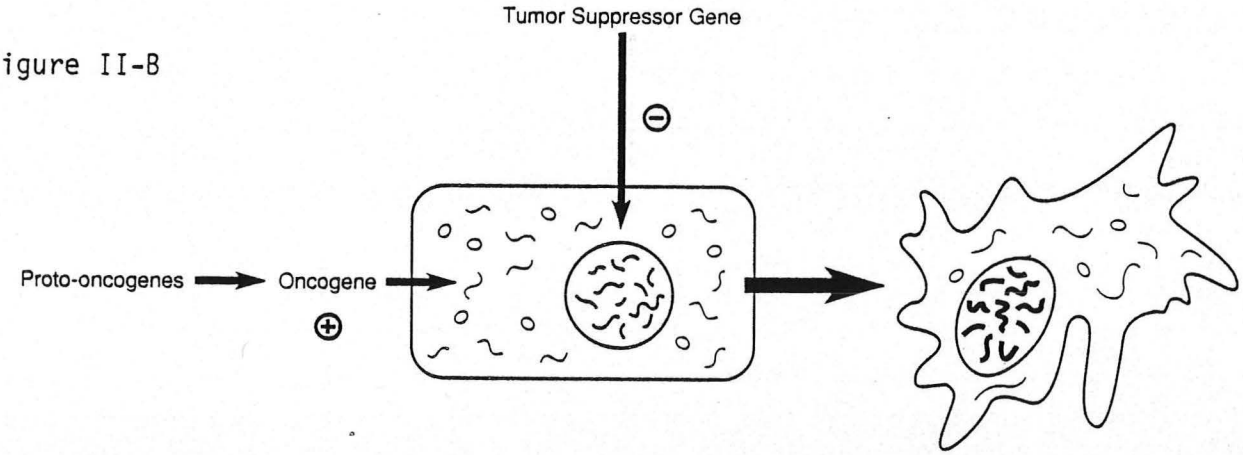
One such recent study examined a number of families for the presence of either adenomatous polyps or adenocarcinoma. It was found that the incidence of adenomas in the first degree relatives of the subjects found to have polypoid lesions was significantly higher than in the non-related spouses of these cases. From an analysis of these data it was concluded that these individuals carried a "susceptibility" gene that behaved as a dominant characteristic. The frequency of this susceptibility allele was estimated to be 19% (95% confidence interval, 14 to 28%) in the population. The probability of expressing this "susceptibility" gene varied according to the age of the patient, as shown in Fig. II-A. The probability of having an adenomatous polyp at age 30 was less than 20% but this probability increased with aging and reached 63% at age 80. While this study was done in a relatively small number of patients, it suggested that the majority of "sporadic" carcinomas of the colon occurred in a patient population that was genetically susceptible. The analysis of these data suggested that the incidence of this "susceptibility" gene was approximately 20% in the population and, equally important, approximately 80% of the population did not carry this

gene and therefore had a very low risk for developing adenocarcinoma. If these studies are correct, they imply that essentially all adenocarcinoma of the colon (both recognized familial and sporadic cases) have a genetic basis. These findings imply that if this genetic defect could be isolated and identified, it would be possible to identify the population at risk and this population could then be subjected to more intense surveillance.

These studies raise the important question of how genetic events could lead to the development of malignant transformation in a well differentiated cell such as the colonic epithelial cell.

Over the past few years it has become apparent that there are two general mechanisms, as shown in Fig. II-B, for bringing about malignant transformation. First, there are a group of genes that normally encode for products that are essential for normal growth and differentiation of the mature, specialized cell. Under certain circumstances these genes (known as proto-oncogenes) may become inappropriately active and cause the cell to grow excessively and, in some cases, to undergo malignant transformation. Thus, such oncogenes exert a positive influence on the cell and promote excessive growth. It is also clear that there are other types of genes that produce products which suppress and regulate cell growth. When such genes are lost or become mutated, normal restraints on cells are apparently lost and, once again, the cell may manifest unregulated growth and malignant transformation. In theory, at least, the worse situation would occur when oncogenes were activated and there was coincidental loss of the tumor suppressing genes. There has been recent and important new information in both of these areas.

Figure II-B



Oncogenes. Oncogenes were originally described as sequences present in the genes of retroviruses. As listed in Fig. II-C, a number of such oncogenes have been described. When mammalian cells become infected with these retroviruses, the cell commonly becomes transformed and exhibits the unregulated growth characteristic of a malignancy. It has become evident in recent years that these genes are, in fact, genes from normal mammalian cells that produce products that function to maintain and stimulate growth and differentiation. While the products of many of these genes have not yet been identified, a number of them such as colony-stimulating factor, platelet growth factor and epidermoid growth factor receptor, have to do with normal cell growth, differentiation and

RAPIDLY TRANSFORMING RETROVIRUSES

Figure II-C

Viral Oncogenes: ras
myc
erb
myb
src
fes
fms

intercellular communication. It is now felt that the oncogenes found in retroviruses were actually acquired in the distant past as these viruses passed through normal animal tissues. Thus, these genes play a normal role in regulating cell growth and differentiation. However, under certain circumstances these genes may be induced into an excessively active state. This may take place through point mutation of the gene, amplification of the gene or a transposition that brings the normal gene under the influence of a new regulator. Under all of these situations, the normal gene (a proto-oncogene) becomes activated to an oncogene.

As summarized in Fig. II-D, there are a variety of observations that suggest that in some circumstances such a transformation can lead to tumor production. For example, under proper circumstances some proto-oncogenes can produce tumors in vivo in experimental animals. Similarly, under in vitro conditions proto-oncogenes and the appropriate regulators can transform isolated cells into malignant cells. Viral infections that induce over activity of a particular proto-oncogene can lead to cancer. In some human tumors, there is direct evidence that proto-oncogenes are over expressed. Chromosomal translocations that bring a particular proto-oncogene under a new regulator can be shown to produce cancer. Finally, in some human tumors proto-oncogenes have been shown to be amplified many fold. Thus, taken together these data suggest that certain normal genes that produce products necessary for normal cell growth differentiation and communication (proto-oncogenes) may become activated and so produce either excessive amounts of the gene product or an abnormal product that causes the cell to manifest unregulated growth and malignant characteristics. However, it is also clear that such activated oncogenes do not always produce malignancy and, in fact, it may be necessary for the cell to lose certain "surveillance" activity before the oncogene can become manifest.

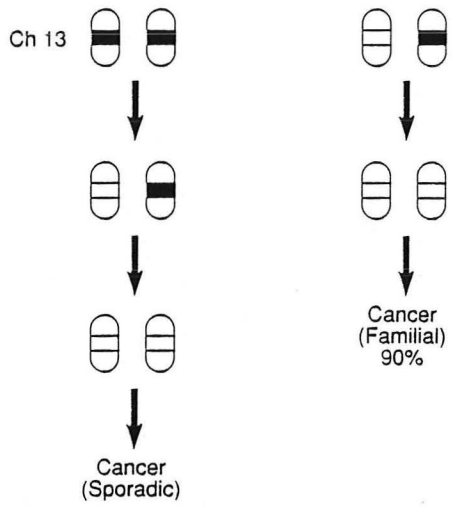
Tumor Suppressor Genes: There is now a second line of evidence which suggests that there is another series of genes whose function is to constantly monitor cell growth and differentiation and to produce products that suppress excessive growth and differentiation. The products of most of these genes have not been identified but the genes are referred to as "tumor suppressor genes."

PROTO-ONCOGENES ⟶ ONCOGENE

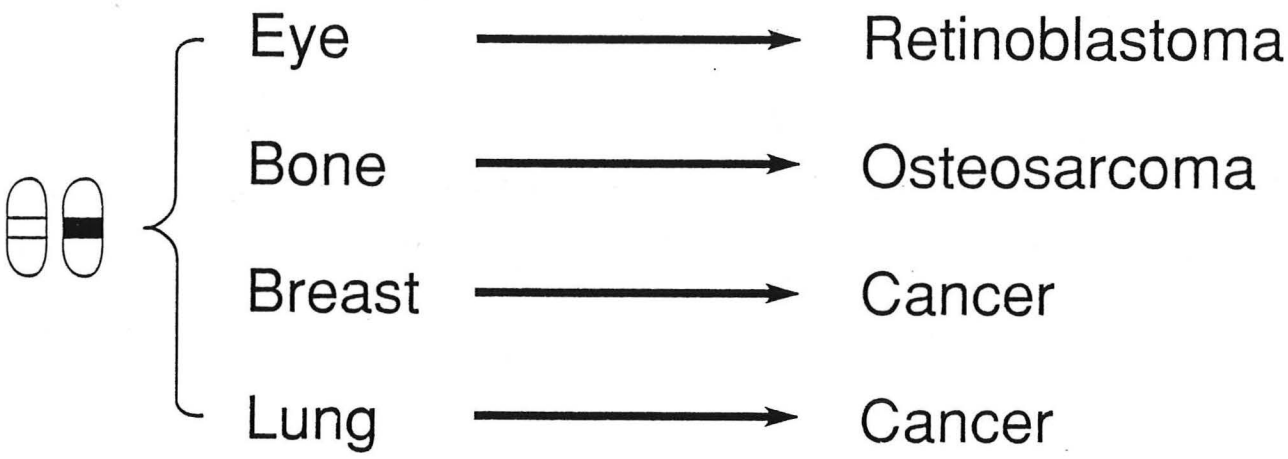
Figure II-D

1) Some proto-oncogenes produce tumors in animals
2) PO + Regulator can transform isolated cells
3) Viral induced PO leads to cancer
4) In human tumors some PO are overexpressed
5) Chromosomal translocations occur at PO sites
6) In some human tumors PO are amplified many fold

Figure II-E



One of the first examples of this type of gene was described by Knudson in young patients with retinoblastoma. This investigator postulated that there was a tumor suppressor gene that regulated the development of the malignancy and that this gene had to be lost from both alleles before retinoblastoma developed. Thus, as shown diagrammatically in Fig. II-E the tumor suppressor gene on chromosome 13 (the RB gene) has to be sequentially inactivated by two independent mutagenic events in normal individuals. Since such sequential mutagenic events are statistically unlikely to occur, the occurrence of sporadic retinoblastoma is relatively rare. On the other hand, some families are heterozygous with respect to the RB gene so that a single mutagenic event can inactivate the normal gene and lead to cancer formation. Thus, about 90% of individuals who are heterozygous with respect to this suppressor gene will develop retinoblastoma before the age of 3 years. More recent data has also shown defects in the RB gene in patients with osteosarcoma, cancer of the breast and cancer of the lung. While it is not clear what determines the specificity of the tissue in which the cancer develops, it has been postulated that carcinogens such as irradiation (osteosarcoma) or tobacco tars (cancer of the lung) leads to inactivation of the RB suppressor gene and, hence, cancer



production. Still other experimental evidence has shown that a number of human malignant tissues maintained in vitro have defective RB genes. Still other, very intriguing data suggest that a product of the RB gene may actually bind and inactivate other gene products that are capable of transforming tissue culture cells. Taken together these observations strongly suggest that the RB gene is one type of tumor suppressor gene that may produce a product which inactivates certain tumor inducing proteins (? oncogenes).

Similar observations have very recently been made in families that carry a inherited form of intestinal cancer. In patients with either familial colonic polyposis (FCP) or Gardner's syndrome, there appears to be a gene defect on chromosome 5 such that the affected family members are heterozygous with respect to this presumed tumor suppressor gene. Furthermore, it has been shown that the cells of the adenocarcinoma that these patients develop have often lost both alleles. Thus, as shown diagrammatically in Fig. II-F it is assumed that normal individuals are homozygous with respect to this suppressor gene on chromosome 5. One would therefore have to have two sequential mutagenic events that would result in an epithelial cell that had lost both suppressor genes and this cell, in turn, presumably would develop into adenocarcinoma. Such a sequence of events would be statistically unlikely in a given individual and would result in infrequent, sporadic cancer. However, if an individual inherited only one suppressor gene as in familial colonic polyposis, then independent mutagenic events would result in multicentric cancers. Essentially 90% or more of the individuals who have this heterozygous gene type would be expected to develop cancer during their lifetime.

While these various observations attest to the importance of such suppressor genes, other data now indicate that the process of cancer formation is far more complex. It now seems clear that a combination of events must occur, e.g., activation of one or more oncogenes and loss of one or more suppressor genes, before cancer formation takes place. The complexity of this situation is emphasized by very recent observations on the genetic defects found during the course of polyp and cancer formation in familial and sporadic colonic carcinoma.

Figure II-F

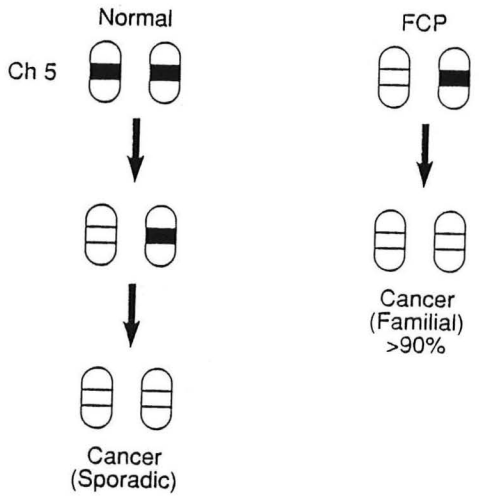


Figure II-G

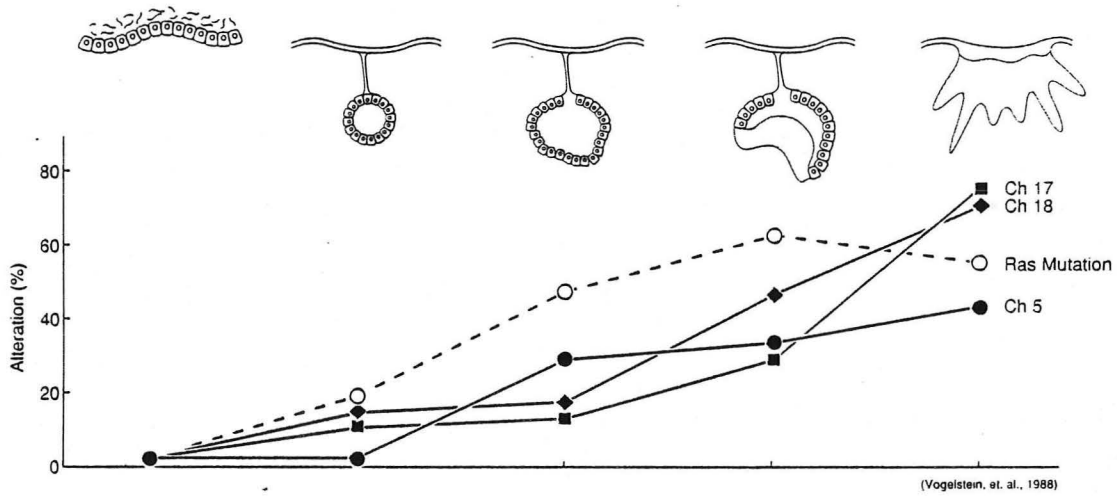


Fig. II-G illustrates the various genetic abnormalities that are found in normal, neoplastic and malignant tissues during the sequence of events that is seen in familial colonic polyposis. From the left of the diagram is shown normal colonic tissue, a well differentiated adenomatous polyp, an enlarged polyp showing progressive dysplastic changes, a large polyp with malignant changes and, finally, an adenocarcinoma. The lower part of the diagram shows the percentage of these respective histologic lesions that manifest abnormalities in chromosomes or oncogenes. In the adenomatous polyp there is no apparent loss of the suppressor gene in the fifth chromosome. Such loss occurs only in the dysplastic and malignant polyps. There is, however, a 20% incidence of activation of the RAS gene in these benign polyps. This percentage rises dramatically in the more malignant tissues. There are also significant deletions in chromosomes 17 and 18 as the tissues become progressively more malignant. These data suggest that in familial colonic polyposis, heterogeneity with respect to the suppressor gene on the fifth chromosome allows widespread tissue overgrowth in the colon with the formation of multiple benign adenomatous polyps. This massive hyperplasia, in turn, may lead to further deletions of

suppressor genes (? chromosomes 17 and 18) and activation of one or more oncogenes (the RAS proto-oncogene). It should be emphasized that if such a deletion or activation occurs in a single cell, that cell will have a marked growth advantage in the mucosa. Such marked hyperplasia may, in turn, lead to further genetic instability and further deletion of suppressor genes. Eventually a critical point is reached at which this monoclonal collection of cells assumes the characteristics of the malignancy and has the full potential for metastases through the lymphatic and vascular systems.

Thus, in this formulation in those familial syndromes associated with multiple colonic polyps, it is deletion of one of the suppressor genes (on chromosome 5) that results in hyperplasia of the intestinal mucosa and benign adenoma formation. A second event must then occur (? activation of an oncogene) and, possibly, further gene deletions to develop a full-blown cancer. In the non-familial syndromes, there is presumably a somatic mutation in the fifth chromosome that allows the occasional benign adenomatous polyp to develop. Unfortunately, this formulation fails to explain many of the features of the various familial colonic syndromes. For example, some of these syndromes develop extraintestinal tumors fairly commonly. This may prove to be akin to the situation recently described in familial retinoblastoma. This formulation also does not explain the long latent period commonly seen before familial colonic polyposis develops. Finally, it is also not clear why, in some patients, polyp formation occurs only in the colon whereas in other patients it takes place in the small intestine and stomach. Nevertheless, these studies hold the promise of not only being able to understand the pathophysiology of polyp and cancer formation in man but, equally important, of allowing the development of probes that will identify those particular individuals in the general population who are at risk with respect to the development of colonic adenocarcinoma.

III. SYNDROMES OF COLONIC CANCER

A) Histological Features of the Major Types of Colonic Polyps

Many of the clinical features of the syndromes associated with polyps of the gastrointestinal tract are determined, in part, by the anatomical location of the polyps and by their histologic characteristics. Any discussion, such as this, therefore, must begin with a definition of the histology of the various polypoid lesions.

One classification of benign tumors that occur in the gastrointestinal tract is shown in Table III-A:

TABLE III-A

CLASSIFICATION OF BENIGN TUMORS OF THE INTESTINE

	Single	Multiple (One Example)
Neoplasms	Adenoma Papillary adenoma Villous papilloma	Familial intestinal (colonic) polyposis
	Haemangioma Leiomyoma Lipoma Neurofibroma	Lipomatosis
Hamartomas	Juvenile polyp Peutz-Jeghers' Polyp	Juvenile polyposis Peutz-Jeghers' syndrome
Inflammatory	Pseudopolyp	Pseudopolyposis
Unclassified	Hyperplastic or metaplastic	

In this scheme, single polyps are divided into neoplastic, hamartomatous, inflammatory, and unclassified lesions. For the purposes of this review, however, only three specific histologic types of polyps require emphasis. These are the neoplastic lesion, the adenomatous polyp, which is the primary lesion seen in familial colonic polyposis, Gardner's syndrome and the Turcot-Després-St. Pierre syndrome; the juvenile polyp, which is found in the two syndromes associated with juvenile polyposis; and the Peutz-Jeghers' polyp, which is associated with the Peutz-Jeghers' syndrome.

These three types of polyps are of critical importance in understanding the occurrence of colonic adenocarcinoma and can be clearly differentiated on histological grounds as outlined in Table III-B.

TABLE III-B

HISTOLOGIC DIFFERENTIATION OF THREE MAJOR TYPES OF POLYPS

	Adenomatous Polyp (neoplasm)	Peutz-Jeghers' Polyp (hamartoma)	Juvenile or Retention Polyp (hamartoma)
Mucosa	Marked mucosal hyperplasia with loss of mucosal architecture; mild dysplasia; ↑ mitotic activity; loss of specialization, i.e., decreased mucus producing cells; nuclei crowded together, but normal polarity	Mucosal cells normal; normal distribution of cell types, i.e., absorptive cells, goblet cells, Paneth cells, etc.	Mucosal cells normal (including distribution) when present; but surface commonly denuded, many retention cysts filled with mucus or pus, much inflammatory infiltrate and sometimes hemorrhage
Submucosa	Muscularis mucosae intact and not involved	Muscularis mucosae intermixed in haphazard arrangement with mucosal elements	Muscularis mucosae intact and not involved
Malignant potential	+	0	0

Adenomatous Polyp: The adenomatous polyp is a true epithelial neoplasm. There is marked epithelial hyperplasia with loss of normal mucosal architecture. There may be hyperchromatic cell nuclei, but basal polarity is retained. There is a decreased number of goblet cells. The muscularis mucosae is smoothly continuous and usually is not involved in the structure of the polyp.

Peutz-Jeghers' Polyp: The Peutz-Jeghers' polyp is now considered to be a hamartomatous and not a neoplastic lesion. All of the normal tissue elements of the intestinal wall are present, including columnar cells, goblet cells, Paneth cells, etc., but the architecture is completely distorted. The muscularis mucosae commonly forms a prominent part of the core of the polyp is a tree-like structure. Peutz-Jeghers' polyps found in the stomach will show cell types characteristic of normal gastric mucosa, while those found in the small bowel and colon will contain cellular elements which are characteristic of these respective portions of the gastrointestinal tract.

Juvenile (Retention) Polyp: This polyp is also considered to be a hamartomatous and not a neoplastic polyp. The surface epithelium may appear normal with respect to cell architecture and the distribution of cell types. However, the surface epithelium commonly is denuded of any mucosal structure. The interior of the polyp consists of multiple dilated cystic spaces filled with mucus interspersed in a loose connective tissue stroma. Hemorrhage, secondary infection and autoamputation are all common in this tumor. It should be

emphasized that the term "juvenile" should not be construed to mean that these polyps are exclusively seen in childhood. This type of polyp is seen in all age groups; this is true both of the occasional single polyp and of the syndromes associated with juvenile polyposis.

B) Pathophysiologic Consequences of Intestinal Polyps

Before beginning a discussion of the individual syndromes of intestinal polyposis, a number of generalizations can be made regarding the clinical consequences of having one or more polyps within the gastrointestinal tract.

1. Malignant Degeneration: The most devastating consequence of intestinal polyposis is malignant degeneration associated with certain histologic types of polyps. It is of the utmost importance, therefore, that those syndromes associated with polyps that undergo malignant degeneration be separated from those syndromes where the polypoid lesions are not premalignant. Of the three major histologic types of polyps discussed above, only the adenoma is a true neoplasm and is associated with a higher incidence of intestinal malignancy. Whether or not the adenomatous polyps themselves are premalignant lesions that undergo malignant degeneration or whether benign adenomatous polyps and adenocarcinoma are both manifestations of an underlying defect in the intestinal mucosa has not been resolved. This controversy, however, is irrelevant to the clinical considerations of the familial polyposis syndromes; the critical observation is that any disorder associated with multiple adenomatous polyps is also associated with a very high incidence of gastrointestinal malignancy.

The early literature suggested that Peutz-Jeghers' polyps also underwent malignant degeneration. However, it has become apparent more recently that the diagnosis of malignant degeneration was based primarily on the disordered histology of these hamartomatous polyps. In point of fact, with only rare exceptions, there has never been a case reported of the development of carcinoma with metastases in a bona fide case of the Peutz-Jeghers' syndrome. Most authors, therefore, consider the Peutz-Jeghers' polyp to have no malignant potential (or, at the very most, a very low malignant potential).

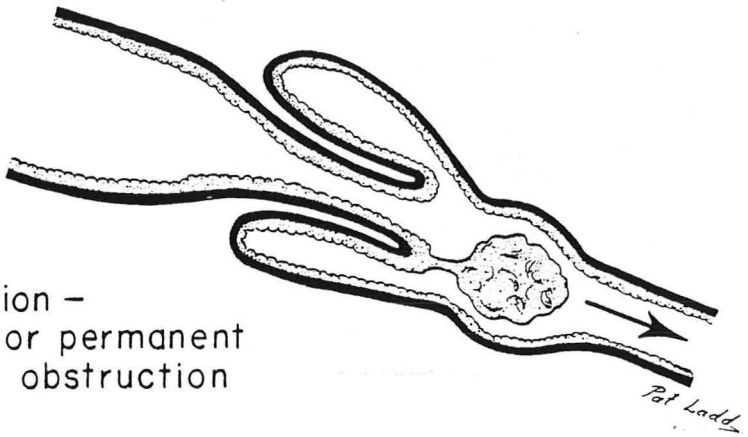
The juvenile polyp, like the Peutz-Jeghers' polyp, also does not appear to be a premalignant polyp. There is no reported instance in which either a single juvenile polyp or one of the juvenile polyposis syndromes has been associated with the development of gastrointestinal adenocarcinoma.

2. Change in Bowel Habits: Involvement of the colon with multiple intestinal polyps is almost invariably associated with a change in bowel habits, and in particular, diarrhea. The diarrhea commonly is associated with excessive mucus discharge, and blood loss, both occult and overt, if found almost invariably at some time during the clinical history. Melena and hematemesis are less common but are seen in those syndromes where the polyps are located higher in the gastrointestinal tract.

3. Passage of Tissue Per Rectum: Passage of tissue with bowel movements may occur and is the result of torsion of the pedicle and autoamputation of the polyp head. This appears to be particularly likely to occur in the case of the juvenile polyp, where passage of tissue is common.

SMALL BOWEL

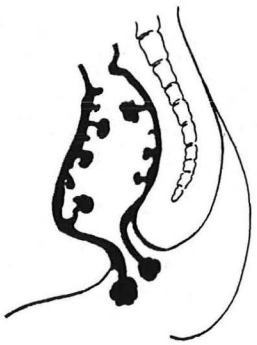
Figure III-A



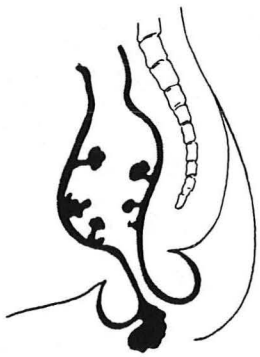
Intussusception –
intermittent or permanent
small bowel obstruction

Figure III-B

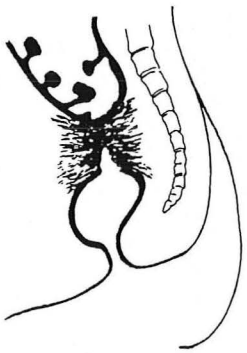
LARGE BOWEL



Prolapse of Polyps



Rectal Prolapse



Colonic Obstruction
from Adenocarcinoma

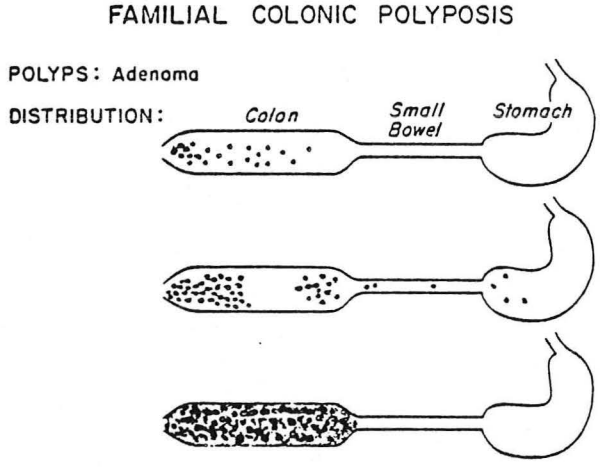
4. Intussusception: In those syndromes associated with polyps of the small intestine, intermittent intussusception is very common. This leads to clinical episodes characterized by cramping abdominal pain, nausea, vomiting, and a fleeting abdominal mass. These episodes commonly are self-limited and the intussusception may undergo spontaneous reduction; some patients find that manual reduction of the intussusception is possible by manipulation of the abdominal mass. A non-reducible intussusception, of course, may lead to complete small intestinal obstruction requiring surgery.

5. Local Manifestations of Polyposis of the large Bowel: Polyps involving the rectum may prolapse through the anus, or, alternatively, there may be rectal prolapse associated with rectal polyposis. Obstruction of the large bowel, however, is uncommon unless malignant degeneration and adenocarcinoma develop.

C) Specific Syndromes of Multiple Colonic Polyps

1. Familial Colonic Polyposis: As illustrated in Figure III-C, this disorder is associated with multiple adenomatous polyps involving primarily or exclusively the colon. Within affected families, some individuals are found who have thousands of sessile and pedunculated polyps involving the entire colon, so that no normal mucosa is visible, while other individuals will have fewer, more discrete, pedunculated adenomas. Occasionally, as few as 10 or 15 polyps may be seen in an affected member of a known family possessing this disorder. Rarely, an associated adenomatous polyp has been reported in the terminal ileum. No prognostication can be based upon the number of adenomatous polyps. Adenocarcinoma may develop early in an affected individual having relatively few polyps, or, alternatively, patients with thousands of polyps may live for a relatively long time without the development of malignancy.

Figure III-C



Estimates of the frequency of familial colonic polyposis have varied from 1/7,500 to 1/29,000 in the general population. Approximately 33% of propositi have no family history of affected members. In the 67% of cases with a family history, the sex ratio is males 54%:females 46%. Only those members of a family who are affected with the disease, male or female, have affected children. Chromosome morphology, insofar as it has been investigated, is normal. The familial form of this disease, therefore, appears to be transmitted as an autosomal dominant trait. Specific probes show a deletion in the fifth chromosome.

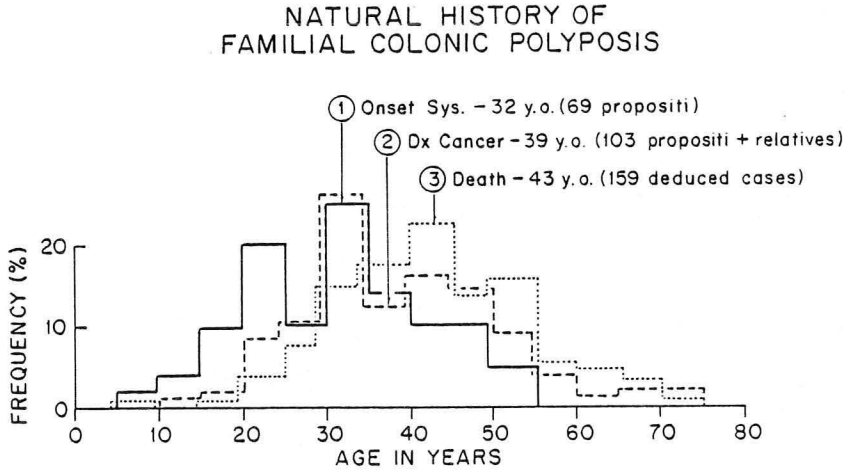
The adenomatous polyps seen in familial colonic polyposis are not congenital and are not present in affected members at the time of birth. The earliest reported case in which multiple colonic polyps were demonstrated is a 4-month-old infant; more commonly, however, the polyps develop during childhood or early adulthood. As shown by the solid line in Figure III-D, the average age of onset of symptoms (most commonly, bloody diarrhea) in index cases is 32 years. However, the great variability in the age of onset of symptoms should be emphasized; as is evident in this figure, initial symptoms were noted in children as young as 5 years of age and in older individuals up to the age of 55. Thus, it is apparent that there is tremendous variability in the age of onset of clinically apparent disease. Carcinoma of the colon develops in a very high percentage of these cases and, as also shown in Figure III-D, the average

age was 39 years at the time of diagnosis of malignancy. Death follows, on the average, 4 years later, and is almost invariably associated with metastatic carcinoma from the colon.

There is an important relationship, as illustrated in Figure III-E, between the incidence of carcinoma present at the time the diagnosis of intestinal colonic polyposis was first established and the age of the patient. If the diagnosis is made in individuals less than 20 years old, only approximately 15% will be found to already have adenocarcinoma of the colon. On the other hand, if the diagnosis is not made until after the age of 30, then approximately two-thirds of the patients will already have one or more colonic carcinomas.

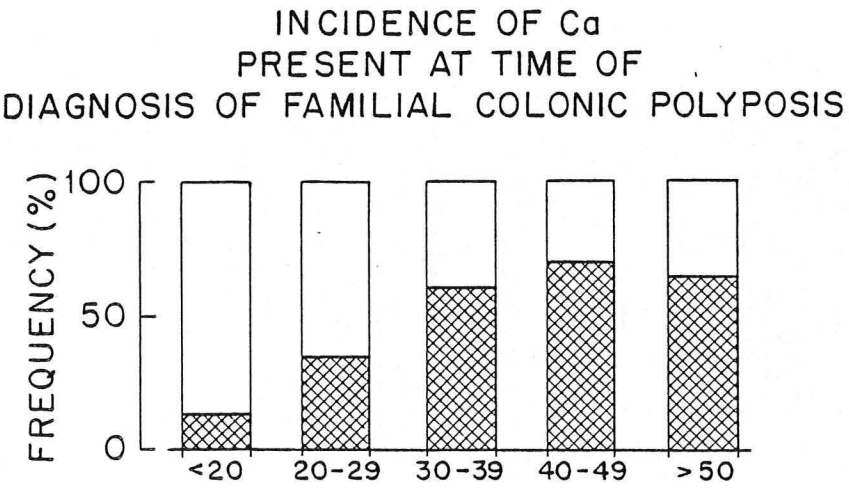
Once it has been established that an individual is affected with the syndrome of familial colonic polyposis then it is essential that the colon be immediately removed. In the past, some surgeons have attempted to treat this syndrome with a subtotal colonic resection and an anastomosis of the terminal

Figure III-D



(Veale, Intestinal Polyposis, 1965)

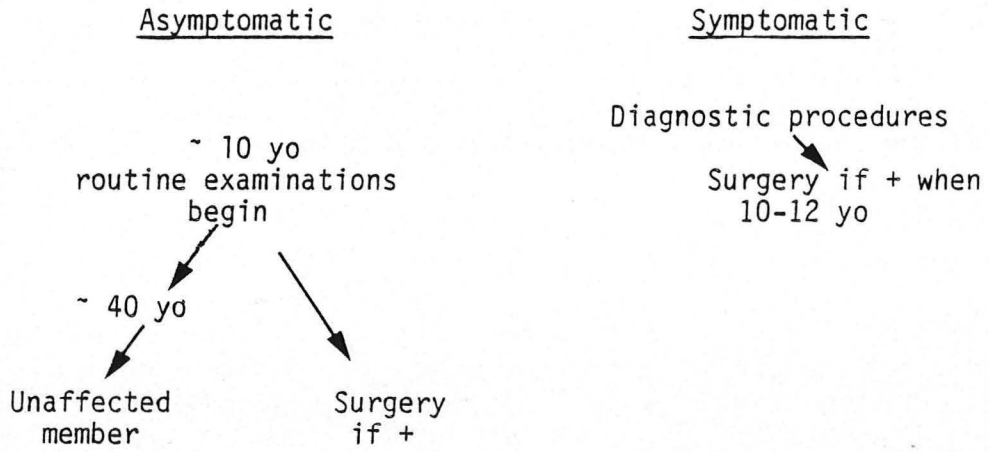
Figure III-E



ileum to the recto-sigmoid segment. This is a very dangerous procedure since the malignant potential is retained within the mucosa of the recto-sigmoid segment and the patient may well develop invasive adenocarcinoma in this area of retained colon even under very careful supervision. This procedure should never be undertaken unless the patient absolutely refuses total colectomy. The procedure of choice is clearly a total colectomy with either a permanent ileostomy or a rectal pull-through procedure.

Once it has been established that a family is affected with familial colonic polyposis, it is mandatory that all members be investigated and that very careful follow-up be undertaken. All individuals who are symptomatic (bowel dysfunction, bloody or mucoid diarrhea) should have immediate colonoscopic examination followed by an upper gastrointestinal series. If the diagnosis of multiple adenomatous polyposis of the colon is established, then colectomy should be performed immediately. If this diagnosis is established in a young child, however, most surgeons would prefer to wait until the age of approximately 10 to 12 years before performing colectomy. Asymptomatic individuals in the family should have periodic examinations by sigmoidoscopy beginning at the age of 10. Periodic examination must be repeated every 6 months to 1 year thereafter. If the individual reaches the age of 40 and has a negative colonoscopic examination, then one can be reasonably certain that he does not carry the genetic defect and that his offspring will not be affected with the disease.

MEMBER OF FAMILY KNOWN TO CARRY FAMILIAL COLONIC POLYPOSIS



2. Familial Colonic Polyposis--Variant: Multiple Adenomas of the Entire Gastrointestinal tract: As demonstrated by the data in Table III-C, a few cases have been reported in which adenomatous polyps are distributed throughout the entire length of the gastrointestinal tract. These polyps presumably also have the potential for malignant degeneration, but very little information is available concerning the natural history or genetics of this syndrome.

TABLE III-C

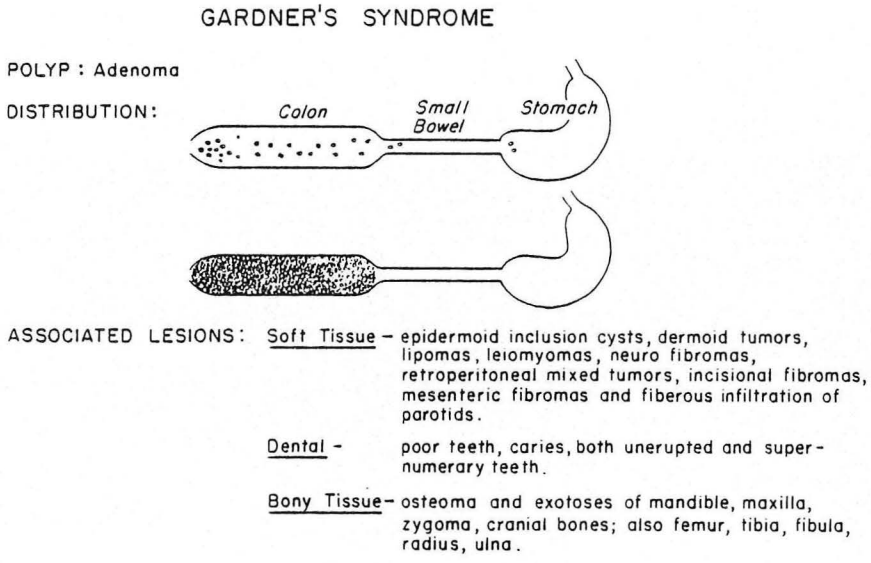
FAMILIAL COLONIC POLYPOSIS:
Variant-Polyposis of Entire GI Tract

1969	Yonemoto, et al.	9 yo F	Diarrhea and abdominal pain, passed mucus and blood. Father died of colonic Ca with classic colonic polyposis. X-rays: Polyps of stomach, small bowel and colon. Colectomy with local Rx of many polyps--living.
		10 yo M	Brother; pain; diffuse polyposis of stomach, small bowel and colon.
		11 yo M	Family history colonic polyposis. X-ray: Polyposis of stomach, small bowel and colon.

3. Gardner's Syndrome: As shown in Figure III-F, in Gardner's syndrome there are multiple adenomatous polyps localized primarily, if not exclusively, in the colon. The pattern of colonic involvement apparently is identical to that seen in familial colonic polyposis. In addition, there is the same high risk of malignant degeneration.

The frequency of Gardner's syndrome in the general population is unknown. The sex ratio of affected individuals is apparently equal and affected offspring come only from affected parents. Chromosome morphology is normal. This appears to be a familial syndrome inherited as an autosomal dominant trait. Specific probes show the same chromosomal deletion as in familial polyposis.

Figure III-F



Like familial colonic polyposis, the intestinal polyps are not present at birth in Gardner's syndrome. The clinical impression exists that colonic polyps in these families appear at a somewhat older age than in familial colonic polyposis but insufficient data are currently available to establish this point. The extracolonic lesions, i.e., the soft and bony tumors, usually appear at an early age, enlarge for several years and then remain relatively stable. Most of these lesions probably do not undergo malignant degeneration. In all reported cases thus far, the bony and soft tissue abnormalities appeared before the patients became symptomatic from their colonic polyposis. In general, the average age of onset of bloody diarrhea and the subsequent development of colonic adenocarcinoma probably occurs at a somewhat older age than seen in individuals affected with familial colonic polyposis. However, it should be emphasized that patients with Gardner's syndrome carry the same very high risk of malignant degeneration with the development of colonic adenocarcinoma as do patients with familial colonic polyposis. Also, there has been no dissociation of the skin and bone lesions from colonic polyposis, i.e., if a member of a family known to harbor Gardner's syndrome manifests the bony or soft tissue lesions, then he or she will develop colonic polyposis.

While there is the clinical impression that the colonic polyps develop at a somewhat older age in Gardner's syndrome than in familial colonic polyposis and, correspondingly, that malignant degeneration occurs somewhat later, these patients, nevertheless, should be handled in a manner identical to that discussed above for familial colonic polyposis. These individuals carry the same very high risk of developing colonic adenocarcinoma.

4. Turcot-Després-St. Pierre Syndrome: As demonstrated in Figure III-G, the Turcot-Després-St. Pierre Syndrome is the association of multiple adenomatous colonic polyps with central nervous system tumors. Only 6 cases of this syndrome have been reported to date. All died of or are under treatment for central nervous system tumors, commonly a glioblastoma. Since the polyps of the colon are adenomatous, these individuals presumably have the same high risk for development of colonic adenocarcinoma, and indeed two of the patients have had carcinomas. However, these patients usually succumb to their central nervous system lesions before the colonic polyposis becomes a major clinical problem.

TURCOT-DESPRÉS-
St. PIERRE SYNDROME

Figure III-G

POLYP: Adenoma

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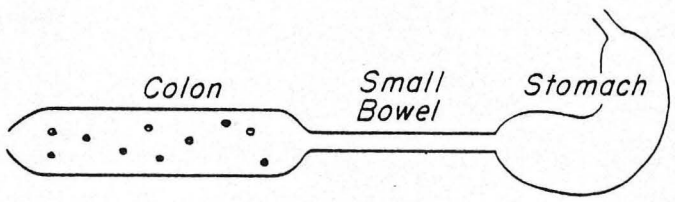


ASSOCIATED LESIONS: CNS tumors; nevi; ? café-au-lait spots

MODE OF TRANSMISSION: ? Recessive Trait

5. Peutz-Jeghers' Syndrome: As illustrated in Figure III-H, the polypoid lesion in the Peutz-Jeghers' syndrome is a hamartoma that never (or very rarely) undergoes malignant degeneration. These polyps are distributed throughout the gastrointestinal tract, including the stomach. Several points concerning the frequency distribution shown in Figure III-H require emphasis. Ninety-two percent of the 117 cases had polyps in the small intestine. Eight percent had polyps present only in the colon or in the colon and stomach.

The unique extracolonic manifestation of this syndrome is the characteristic pigmentation of cutaneous and mucous membranes. As shown in Figure III-I, the two most commonly pigmented areas are the perioral region and the buccal mucosa. The cutaneous lesions are typically flat, brown to black spots with hair. They are present at birth but tend to fade as puberty and early adulthood is reached. The pigment patches seen on the buccal mucosa, in contrast, do not fade and are almost invariably seen in affected individuals.

Figure III-H

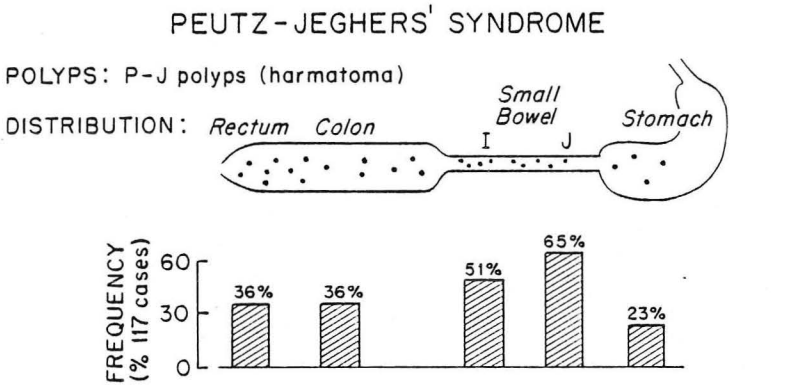
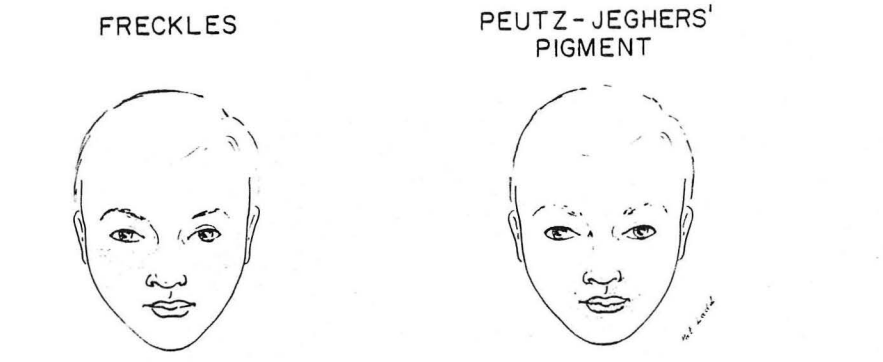


Figure III-I



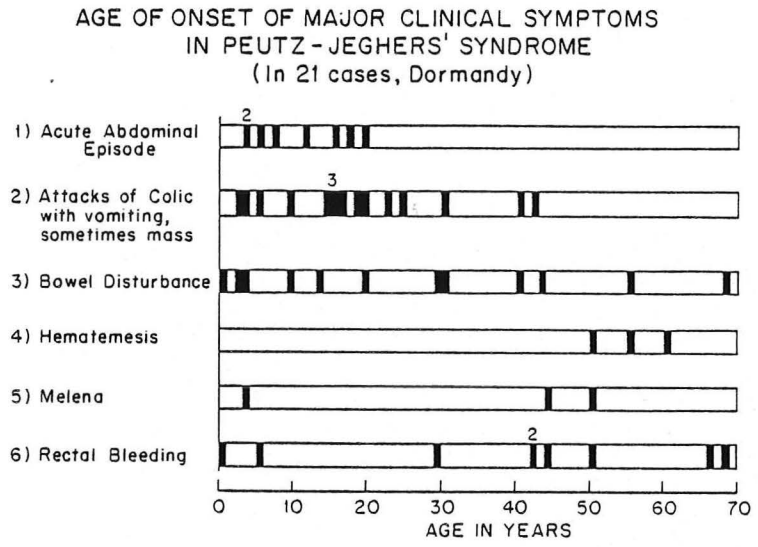
The frequency in the population at large is unknown. There are a large number of sporadic cases where the syndrome appears do novo without any evidence of familial involvement (approximately 43% in one series). In the familial cases, the sex ratio of affected individuals is approximately equal and affected individuals come only from affected parents. In the familial cases, this syndrome is assumed to be transmitted by an autosomal dominant.

The affected individual usually can be identified in infancy because of the associated mucocutaneous pigmentation. Since this syndrome involves polyposis of both the small and large intestine, one sees clinical syndromes of both intermittent small bowel obstruction secondary to intussusception and bowel disturbance with diarrhea and rectal bleeding. As shown in Figure III-J, these clinical symptoms commonly are seen first in childhood, but, in some individuals, may not appear for many years.

Because the polyp in this syndrome is a hamartoma without the risk of malignant degeneration, the surgical therapy of this syndrome is quite different from that used in the adenomatous polyposis disorders. In this syndrome, the surgical approach should be conservative and undertaken only when necessary to relieve intestinal obstruction, small bowel intussusception or bleeding from one of the polypoid lesions. At the time or surgery, minimal resection should be undertaken but as many polyps as possible should be removed; however, it must be recognized that this is a continuously evolving syndrome and even if all small bowel and colonic polyps can be removed at one exploration, it is to be expected that additional polyps will develop and become clinically manifest in the ensuing years.

Because of the familial nature of approximately half of these cases, the relatives of all index cases should be investigated. The identification of affected members is relatively easy on the basis of the mucocutaneous pigment lesions.

Figure III-J



6. Diffuse Gastrointestinal Juvenile Polyposis: In recent years, several series of patients have been reported that do not fit into any of the well-defined syndromes of intestinal polyposis. It has now become apparent, however, that a number of these cases probably can be grouped together as examples of multiple juvenile polyps involving various levels of the gastrointestinal tract. Three major subtypes have been described in the literature: juvenile polyposis coli, juvenile polyps with "cachexia", and the Cronkhite-Canada syndrome.

Juvenile Polyposis Coli: Veale recently has reviewed all of the pathologic material from the St. Mark's series of patients with colonic polyposis. On the basis of this review he concluded that 11 patients were misdiagnosed as familial colonic polyposis (adenomatous polyps) and, in reality, had a new syndrome characterized by multiple colonic polyps of the juvenile (retention) type. With two exceptions, these polyps appeared to be localized to the colon and it is noteworthy that many of these patients lived to an old age without the development of adenocarcinoma. The major clinical syndrome in this group of patients consisted of bloody diarrhea, prolapse of polyps and passage of tissue per rectum.

Juvenile Polyps with "Cachexia":

TABLE III-E

JUVENILE POLYPS WITH CACHEXIA

Ravitch 1948	10 mo M	Diarrhea, "foul" stools, undigested food; malnutrition. Pancreatic studies OK: prolapsed rectal polyps. Developed edema and clubbing; albumin 2.3 gm %	At autopsy, numerous polyps from stomach to rectum--sessile and pedunculated
Veale et al. 1966 (Case 3)	4 yo F	Passed blood and polyp per rectum prolapsed polyps	Died 2 yrs later of "inanition"
Ruymann 1969	9 mo M	Bloody diarrhea; anemia; serum albumin 2.3 to 1.7 gm %; edema, clubbing; GTT--normal; xylose absorption normal; ↑ K; terminally alopecia and ascites developed	Extensive GI polyposis with most severe involvement ileum > duodenum > jejunum--also colon and stomach

Three infants have been reported with a fatal disease characterized by foul diarrhea, probable malabsorption, marked hypoalbuminemia, edema, and, in one case, ascites. At autopsy these infants were found to have involvement of various parts of the gastrointestinal tract with multiple polyps probably of the juvenile type.

Cronkhite-Canada Syndrome: Between 1955 and 1966, six patients were reported, as summarized in Table III-D, all of whom manifest a devastating illness characterized by marked diarrhea, probable steatorrhea, hypoalbuminemia and edema, alopecia, atrophy of fingernails and diffuse skin pigmentation. These patients all manifest involvement of many areas of the gastrointestinal tract with multiple polypoid lesions. In several case reports, these were reported to be "adenomatous" polyps; however, in reviewing the photographs of these polyps and the rather sparse description of the histology, it is apparent that these very likely were not adenomatous polyps but, rather, typical juvenile or retention polyps. It is noteworthy in this regard that while these patients were all relatively old, none died from adenocarcinoma of the bowel.

TABLE III-D

CRONKHITE-CANADA SYNDROME

Case				
1	Cronkhite Canada 1955	42F	8 mo fatal illness with N, V and diarrhea; loss of hair and nails with pigmentation; GTT normal; achlorhydria	Extensive polypoid lesions of stomach small bowel and colon. "Simple adenomatous polyps"
2	Cronkhite Canada 1955	75F	Had pigmentation 9 years before P1; diarrhea 10 mo before P1 alopecia, loss of nails, fatal 17 mo.	Stomach, duodenum, colon, rectum
3	Kennedy Hirson 1961	69F	2-1/2 mo with recovery; achlorhydria; diarrhea, pigmentation loss of nails, GTT normal	Generalized polyposis
4	Martini Dölle 1961	71F	18 mo fatal illness; edema, diarrhea; albumin 1.6 mg %, + Ca Achlorhydria	Stomach, colon
5	Johnston et al. 1962	51F	Diarrhea, alopecia; fatal at 6 mo; histamine-fast achlorhydria normal GTT	Stomach, ileum, colon and rectum showed polyps
6	Jarnum Jensen 1966	58F	10 mo fatal illness. Xerostomia, anorexia, weight loss, marked diarrhea, + skin pigmentation alopecia, loss of fingernails and some toenails. + K, Ca, Mg, Hb, folate; albumin 1.5 gm %; stool fat 33 gm/24 hr; Schilling +; achlorhydria; Cr^{51} 5.5%/4 days; xylose 1.6 gm/5 hr; GTT "flat"	Extensive nodular and polypoid lesions of stomach, entire small bowel and colon

It is likely that these 19 cases can be grouped together as representing examples of a new syndrome characterized by multiple juvenile (retention) polyps of the gastrointestinal tract. It is equally apparent, however, that at least two distinctly different clinical syndromes are present. Ten of Veale's cases had polyposis predominantly or exclusively of the colon. These individuals all manifest bloody diarrhea, prolapsed polyps and passage of tissue per rectum, but, generally, did well with conservative therapy or colectomy.

In contrast, the three infants and six adults who had diffuse involvement of the entire gastrointestinal tract with juvenile polyposis presented with a devastating illness that almost invariably ended in a fatal outcome. On the basis of the limited laboratory data available, it is apparent that these individuals had severe diarrhea with water and electrolyte loss, severe steatorrhea, protein-losing enteropathy with hypoalbuminemia and edema, and finally, alopecia, marked atrophy of the nails and diffuse skin pigmentation. It is likely that these latter ectodermal changes can be explained as the secondary consequences of the massive depletion state that these patients had secondary to their malabsorption syndrome and protein-losing enteropathy. Whether or not this formulation of these 19 cases is correct must await further description of patients with this syndrome.

IV. RECOMMENDATIONS FOR DETECTION AND FOLLOW UP OF PATIENTS WITH ADENOCARCINOMA OF THE COLON

It is clear that within the near future it will be possible to detect by genetic testing those individuals who have deletions on the fifth chromosome and who are at risk for development of the various forms of familial adenocarcinoma. At present, however, it is still necessary to survey or follow such patients by looking for the end product of these presumed metabolic defects, i.e., the histologic lesion of dysplasia and the development of adenomatous polyps. Outlined below are the current recommendations of a joint committee of the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy for the follow up of specific patient groups.

For patients who have no history suggestive of unusual risks for development of colon cancer, the recommended screening techniques include 1) digital rectal examination beginning at the age of 40; 2) testing of stool for occult blood every year; 3) flexible sigmoidoscopic examination beginning at the age of 50 every 2-5 years. Such screening and flexible sigmoidoscopy can be safely and effectively performed by the trained primary physician and is expected to detect polyps in approximately 9% and cancer in approximately 0.3% of asymptomatic individuals over the age of 50.

For those patients who are at high risk for development of colonic carcinoma more careful surveillance is recommended. These recommendations are outlined in Table IV-A.

TABLE IV-A

SURVEILLANCE OF PATIENTS AT HIGH RISK FOR DEVELOPMENT OF COLONIC CARCINOMA

A. Markedly increased risk	
Familial adenomatous polyposis and associated syndromes	Flexible sigmoidoscopy every 6 months from teens to age 50: Colectomy if multiple polyps found.
Universal ulcerative colitis 8-10 yrs duration	Annual colonoscopy with multiple biopsies: colectomy if severe dysplasia is found and confirmed.
B. Moderately increased risk	
Previous colon cancer or adenomatous polyps	Colonoscopy 6-12 months after resection, then every 3 yrs. Annual tests for fecal occult blood
Familial cancer syndrome	Annual tests for fecal occult blood and colonoscopy every 3 yrs beginning at age 20

Left-sided ulcerative colitis 15-20 yrs	Colonoscopy every 1-2 yrs with multiple biopsies: colectomy if severe dysplasia found and confirmed
First degree relatives with history of colon cancer	Annual tests for fecal occult blood; flexible sigmoidoscopy every 3-5 yrs beginning at age 35-40; if 2 or more relatives are involved, colonoscopy every 3-5 yrs.
Women irradiated for gynecologic cancer	Annual tests for fecal occult blood and flexible sigmoidoscopy every 3 yrs after diagnostic and radiation therapy
C. Probable increased risk	
Previous gynecologic or breast cancer, ureterosigmoidoscopy	Institution of usual screening; tests and flexible sigmoidoscopy every 3-5 yrs after diagnosis of underlying associated disease.
Other gastrointestinal polyposis syndromes	Periodic examination of upper and lower gastrointestinal tract depending on cancer risk and specific syndrome

Finally, a specific follow-up protocol is recommended for patients who have been treated with colonic resection for adenocarcinoma. These recommendations are listed below in Table IV-B.

TABLE IV-B

FOLLOW UP PROTOCOL FOR COLORECTAL CANCER

Procedures	Frequency
History, physical, occult blood and liver chemistries	Every 3-6 months for 2 yrs; then every 6-12 months for 2 yrs; then yearly
Carcinoembryonic antigen (CEA)	Every 2 months for 2 yrs, then every 4 months for 2 yrs, then yearly
Flexible sigmoidoscopy	Every 6-12 months for rectal cancer
Colonoscopy	Preoperatively or during first year; repeat in 1 yr; then every 3 yrs
Chest roentgenography	Every 6-12 months for 2 yrs, then yearly

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IV. RECOMMENDATIONS

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