ADENOMATOUS POLYPOSIS COLI

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University of Texas Southwestern Medical Center at Dallas

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Gordon D. Luk, M.D.

H J R Bussey
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FAMILIAL POLYPOSIS COLI

Family studies, histopathology, differential diagnosis, and results of treatment

H. J. R. Bussey

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Definition

Adenomatous polyposis coli has been variously called familial polyposis, multiple polyposis, familial adenomatous polyposis and has also been occasionally used interchangeably with Gardner syndrome. For the purpose of this discussion, I prefer the term adenomatous polyposis coli (APC) to include all hereditary multiple adenomatous polyposis syndromes, including Gardner syndrome. This terminology is becoming generally acceptable, and is used, with some modification, in most recent published reports on the disease (1-4).

Using the above terminology that adenomatous polyposis coli (APC) is the all inclusive term for all hereditary polyposis syndromes, APC may be defined as an autosomal dominant hereditary syndrome with virtually 100% penetrance, manifested by more than 100 adenomatous polyps in the colon, which invariably lead to colorectal cancer if left untreated, and associated with variable extracolonic manifestations (2,3).

Most investigators and physicians recognize a distinct subgroup of APC, known as Gardner syndrome, which includes those patients and families that have a substantial number of extracolonic manifestations, including osteomas, epidermal cysts or fibromas, mandibular and jaw lesions, dental abnormalities, desmoids and mesenteric fibromatosis, congenital hypertrophy of the retinal pigment epithelium (CHRPE), and extracolonic cancers, including peri-ampullary cancers, papillary thyroid carcinomas, hepatoblastomas, intracranial tumors, biliary tumors, and adrenal tumors. It must also be emphasized that some families and patients with non-Gardner syndrome APC also exhibit a few of these extracolonic manifestations (2-7).

Some authors have pointed out that intestinal and colonic polyposis was first described in the 1860s and 1870s. The modern understanding of APC and Gardner syndrome came with the description by Dr. Eldon Gardner of the kindreds that he studied in Salt Lake City, Utah in the 1940s and 50s. Since then, this condition has always drawn the interest of geneticists and investigators with an interest in colorectal cancer or hereditary cancer. With the recent identification and cloning of the APC gene (8,9), we are poised to enter a new era of understanding into this syndrome, and potentially the pathophysiology of colorectal adenomatous polyps and colorectal cancers.

Clinical Manifestations

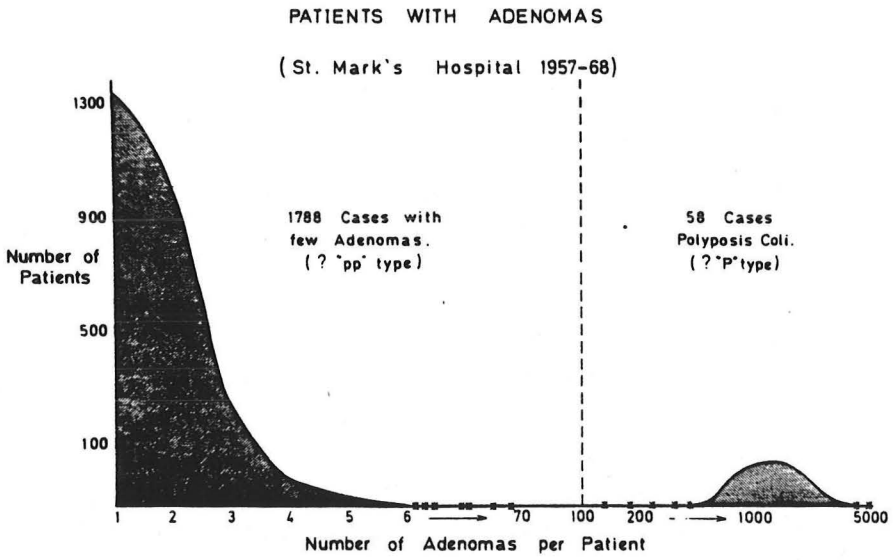
Most patients with APC (including Gardner syndrome) are totally asymptomatic until they have developed cancer or until their adenomatous polyps have become greatly enlarged. Therefore, clinical manifestations are a poor indication of the presence of the disease or of multiple adenomatous polyps. However, especially in the case of Gardner syndrome, extracolonic manifestations are present, often even before the appearance of adenomas (2,3,5-7).

The clinical importance of APC lies in the fact that there is an invariable progression to colorectal cancer if the disease is left untreated. Current treatment entails surgical resection of the entire colon (10). If left untreated, affected patients generally develop multiple adenomas by the age of 24 years with a range of 11-48 years and are dead by the age of 42, with a range of 22-56 years (1,11). Because much of these data are from pre-colonoscopy days, recent evidence suggests that adenomas may be detectable at a much earlier age. Even if adenomas

are not macroscopically visible, biopsies could show histological alterations of adenomatous changes or microadenomas (2,3).

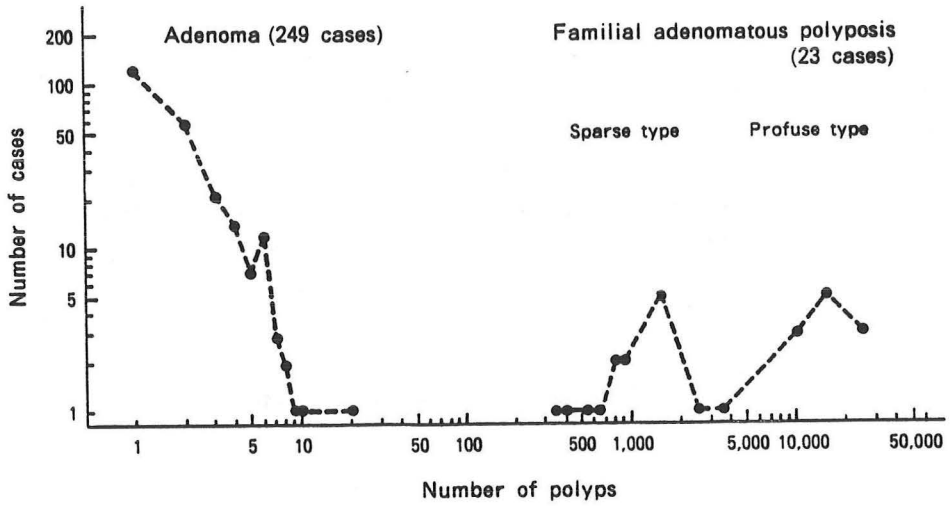
Most commonly, affected patients have a thousand or more adenomas. The number one-hundred was used in the definition because most studies show that virtually all patients with APC have more than a hundred adenomas (Figure 1). These adenomas are generally distributed evenly throughout the entire colon. The size of the polyps enlarge from small 1-2 mm pearl-like polyps when first diagnosed to 5-10 mm in the fully developed cases. However, even in the fully developed case, most adenomas are in the 5-10 mm size, with only occasional adenomas larger than 1 cm. Nevertheless, severe dysplasia and cancer have been found in adenomas as small as 5 mm (1,2).

Figure 1. Number of adenomas per patient, at St. Mark's Hospital, 1957-68 (1).



Recent studies suggest that there may be two distinct groups of patients in terms of number and distribution of adenomas. There appears to be a subgroup with literally thousands of adenomas carpeting the entire colon, known as the carpeting or profuse type. There appears to be a second group with a hundred to 1000 polyps. This distribution is known as the sparse or the discrete type, as the adenomas could be recognized as discrete polyps, with intervening flat mucosa (2) (Figure 2).

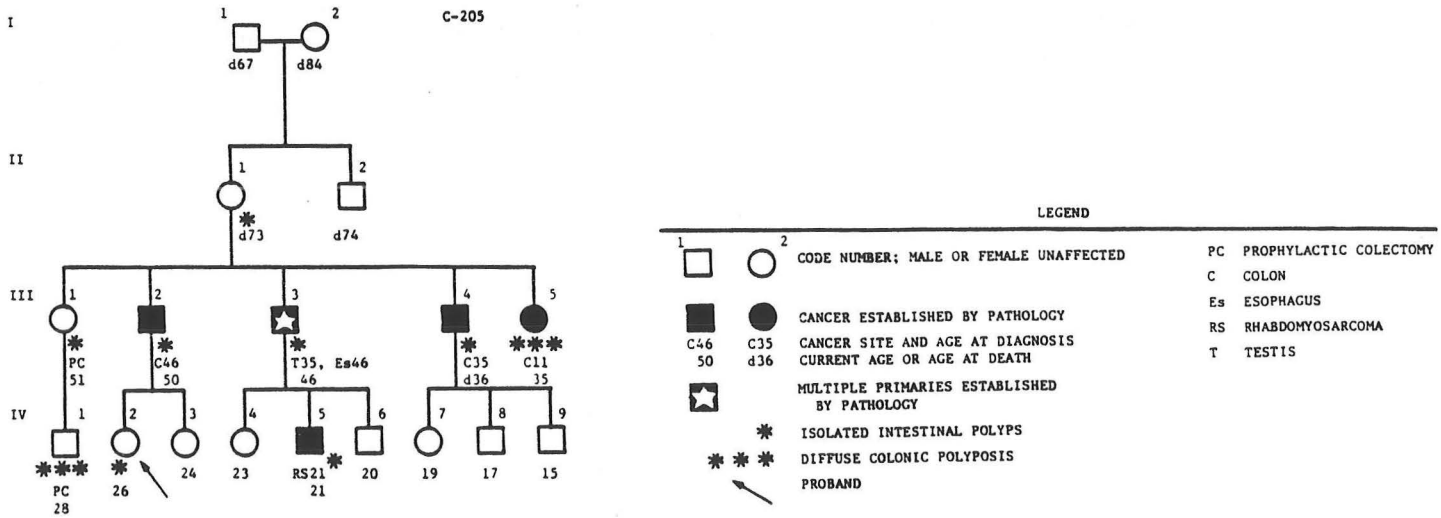
Figure 2. Number of adenomas per patient. Utsunomiya, Japan, 1990 (2).



Recent evidence suggests there may be a third group of patients, with patients having a small number of polyps, generally much less than one hundred. In some cases, there are patients and kindreds with confirmed diagnosis of APC, but who have single or less than 10 adenomas, and yet develop colorectal cancer before age 40 (12). Some of these patients have recently been confirmed to carry the mutated APC gene (White R., personal communication; unpublished observations).

This heterogeneity of expression in adenoma number also extends to the other extracolonic manifestations. Within one single kindred, the number of polyps and extracolonic manifestations can vary markedly (Figure 3). In fact, there are families where most affected members have extensive extracolonic manifestations, but with several family members having few or no extracolonic manifestations. The converse is also true. Although expression of the extracolonic manifestations can be variable, two in particular, CHRPE, and the radio-opaque jaw lesions, tend to be expressed rather consistently in certain families, and not to be expressed in others.

Figure 3. Variability of APC phenotype expression (2).



Natural History

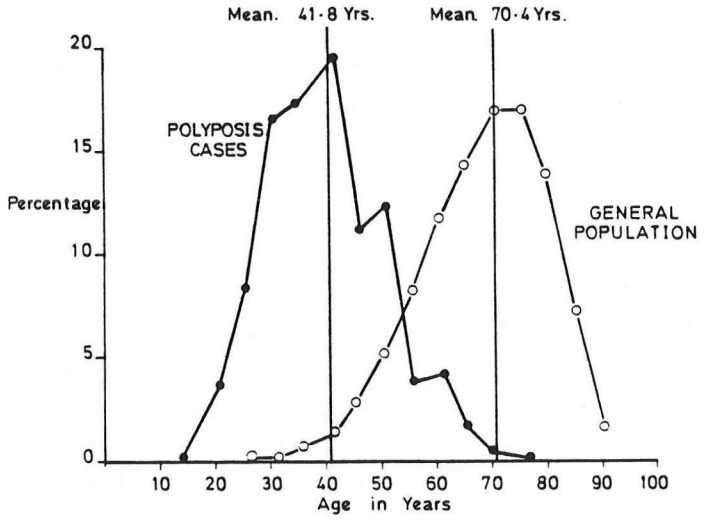
It is difficult to ascertain the exact natural course of adenomas and their progression to cancer. All patients diagnosed with APC are advised to have colectomy, thus removing the adenomas from further study. In older studies, before the advent of fiberoptic colonoscopes, autopsy and surgical studies gave us an idea of the natural course of APC if left untreated (Table 1). Some of the most extensive studies came from Drs. Bussey and Morson at St. Mark's Hospital in the UK, still the institution with the world's largest registry of APC families and patients (1,4).

Table 1. Natural history of APC (1)

Age of appearance of adenomas	24.5 years
Age of onset of symptoms	33.0 years
Age of diagnosis of adenomas	35.8 years
Age of diagnosis of cancer	39.2 years
Age at death from cancer	42.0 years

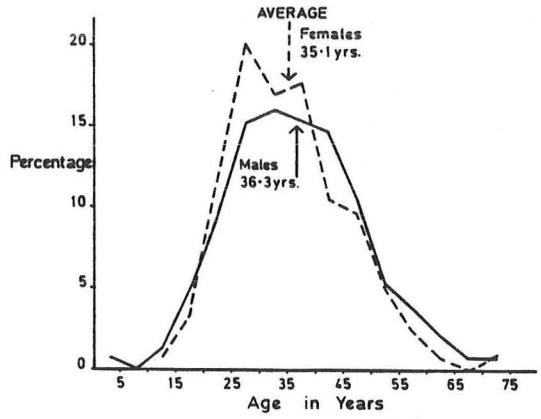
It is likely that the above results represent advanced stages of the disease, as patients did not undergo surgery until very late in their course. More recent data suggest that adenomas may first appear in the late teens or by age 20-22 (4). It is thus clear that patients with APC develop and die from colorectal cancer some 20-30 years before the general population (1-3) (Figure 4).

Figure 4. Age of death in APC patients and the general population (1).



There does not appear to be a difference in the natural history between males and females (1,2,4) (Figure 5).

Figure 5. Age at time of diagnosis of APC in males and females (1).



In addition, because of the early appearance of adenomas, more than half of the patients will have been diagnosed by age 35 (1). With the availability of colonoscopy and early institution of surveillance of at-risk family members, it is likely that most patients with APC will be diagnosed before age 35 and definitely by age 40-50 (2,13).

Presentation

Nowadays most patients are identified through family tracing, initiated once an affected family member is identified. However, it is important to remember that a substantial number (about a third) of newly diagnosed cases represents new mutations, without any evidence of APC in the parents or grandparents (14). APC occurs about once in every 8,000 live births, and Gardner syndrome appears to be a little less common, occurring about once every 14,000 live births (2,4).

For patients without a family history, the presentation most commonly is of bleeding, abdominal pain, abdominal cramps, and occasionally weight loss or other evidence of metastatic colorectal cancer (1,2).

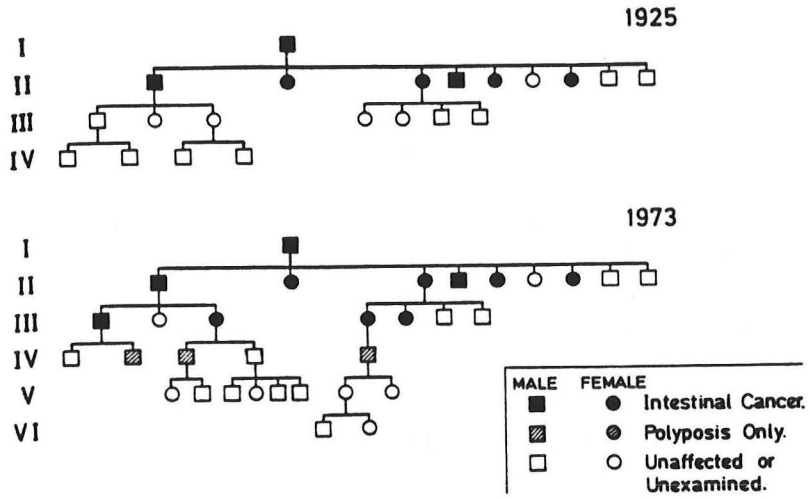
History

Because APC is generally asymptomatic until adenomas are far advanced, the clinical history is not really helpful. However, a complete family history is a must. With the current understanding of familial clustering of many cancers, in particular colorectal cancer, a complete family history must be obtained. This does not need to be a detailed formal pedigree analysis. One must take care to ask for history of cancer, polyps, tumors or deaths before age 50 unassociated with accidents in all first degree relatives, and as many second and third degree relatives that the patient is familiar with (3).

Because of the autosomal dominant inheritance, the clinical history of siblings, aunts and uncles, and cousins may also be informative. Once a family history is obtained, it is important to determine whether the patient or other members of the family or kindred are already registered in a tumor registry or APC registry. If not, the patient should be enlisted to assist

in tracing the clinical history of all potentially affected family members, obtaining at least a copy of the death certificate or the operative or surgical report (2,3).

Figure 6. Pedigree of an APC family at first contact and 48 years later (1).



Pedigree of a polyposis family at the time of first contact and again 48 years later. In the interval four individuals in Generation III developed polyposis and cancer. Three other family members in Generation IV were affected, but because they were known to be at risk, colectomies were carried out before carcinoma supervened.

As described later, intensive and exhaustive family tracing is especially important for individuals in the first three decades of life, as they are at risk and they still may be at a stage where advanced cancer has not intervened (Figure 6).

Physical Examination

The physical examination should be directed towards the search for extracolonic manifestations. Because of the presence of osteomas, jaw lesions, and desmoids, a complete physical examination should be performed, especially in the Gardner syndrome subgroup. All skin surfaces should be examined and palpated, paying special attention to the skull, jaw and long bones. The oral cavity should also be explored with a gloved finger with concurrent palpation of the exterior of the mandible. That way small jaw lesions or dental abnormalities may be palpated. Next comes examination of the trunk and the back, again with careful palpation for any epidermal cysts, fibromas, or desmoids. An abdominal exam should be performed to search for any masses. A rectal examination should also be performed. In patients with APC that have developed adenomas, invariably one or several adenomas are within reach of the examining finger. A fecal occult blood test should also be performed, as many of the patients, especially those with advanced disease, often have occult blood in their stool (2,3,5-7).

An ophthalmologic examination should be carefully performed to search for CHRPEs. These are darkly pigmented, often dark brown or black, circumscribed lesions found in the fundus. Although these are often detected only by indirect ophthalmoscopy by an

ophthalmologist, occasionally bilateral large or central lesions may be seen with a hand held ophthalmoscope (15).

A careful examination for lymph node enlargement, and palpation of the thyroid should also be done (16,17).

Laboratory Findings

In any at-risk individual over the age of 10, consideration should be given to performing a flexible sigmoidoscopy. Because the distribution of adenomas is rather even throughout the entire colon, sigmoidoscopy is more than adequate to confirm the presence of multiple adenomas in these patients. Biopsies should always be performed on any polypoid lesion, especially for multiple polyps, to provide histologic confirmation of diagnosis. Non-adenomatous polyposis syndromes appear virtually identical endoscopically (2,3).

Contract radiologic examinations can also be done. Because biopsy is not possible, an endoscopic procedure is generally recommended.

Extracolonic Manifestations

Osteomas

Osteomas are found most commonly on the skull, mandible, and long bones, but may be found on any bone in the body. A complete skeletal series is not usually indicated, as other manifestations generally can help confirm the presence of osteomas. The size of osteomas range from several millimeters to several centimeters in diameter, occasionally causing severe cosmetic problems for the patient (18-20).

Although some authors consider jaw and mandibular lesions and dental abnormalities as separate entities, I prefer to consider them all as radio-opaque (mostly bony) jaw lesions. If considered this way, these radio-opaque jaw lesions, easily monitored by use of dental films, may be a good predictor of the APC genotype.

These radio-opaque jaw lesions frequently occur before the onset of adenomas, and have been found to be rather reliable markers of patients that carry the genotype before the appearance of the multiple adenoma phenotype. In one of our early studies, it was found that, in families where jaw lesions were an extracolonic manifestation, their presence or absence in the first two decades correctly predicted subsequent development or lack of development of adenomatous polyps (18) (Table 2).

Table 2. Radio-opaque Jaw Lesions as Predictors for APC (18).

	APC	No APC
Jaw Lesions	7	0
No jaw lesions	0	5

Soft Tissue Tumors

These include epidermal cysts and fibromas. They may occur anywhere on the body, but occur most commonly on the trunk, legs, face, and scalp. Like osteomas, they range in size from several millimeters to several centimeters, and can occasionally pose cosmetic problems (2,7).

Soft tissue tumors occur also in the general population although they generally occur only after puberty. In APC, soft tissue lesions often occur before puberty and often precede the development of adenomas (7).

Desmoid Tumors

Desmoid tumors are benign fibrous tissue tumors that are locally invasive but do not metastasize. Multiple desmoids or fibrous tissue may also occur in the mesentery and are termed mesenteric fibromatosis. These may occur also in the general population, where they are usually small and occur singly or in small numbers in each individual (21).

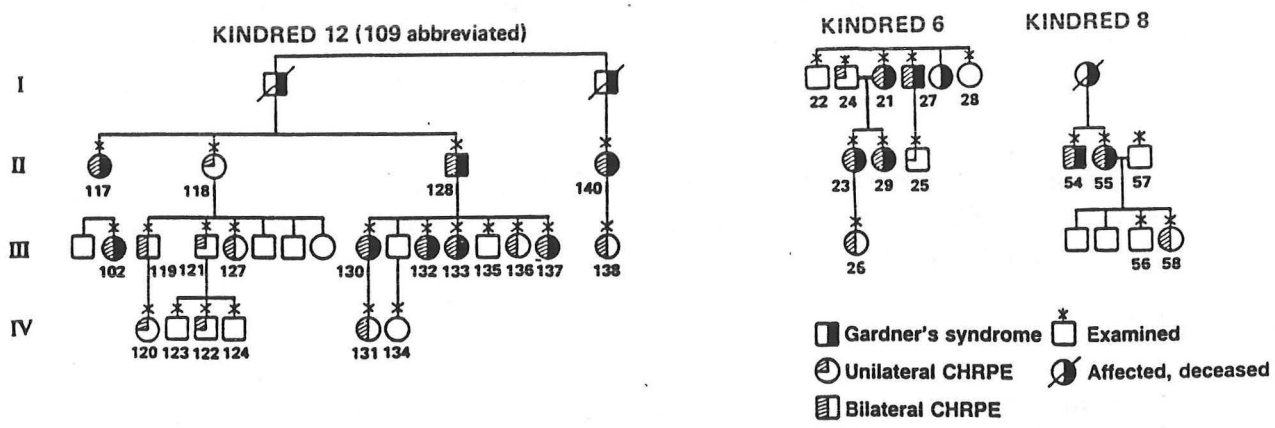
In APC, although the desmoids are not malignant, they are locally invasive and can infiltrate adjacent structures, eroding bone, blood vessels, nerves and can cause severe and even fatal complications. These desmoid tumors occur frequently near surgical scars, and can contribute to postoperative intraabdominal adhesions. Often large desmoids and mesenteric fibromatosis occur after colectomy for the APC (21).

Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE)

CHRPE are darkly pigmented, discrete, circumscribed lesions observed in the fundus. They range in size from 0.1 to 2 disk diameters. When found in the general population, they are usually single and unilateral. In APC they are multiple and bilateral. Usually indirect ophthalmoscopy for complete visualization of the entire fundus is required to detect CHRPE, but occasionally direct ophthalmoscopy with a hand-held ophthalmoscope may visualize larger lesions, especially if they are more centrally located (15,22).

Similar to radio-opaque jaw lesions, CHRPE are often found before the onset of adenomas and are a reliable marker of the presence of the genotype in families in which APC is associated with CHRPE (Figure 7). The lesion has been seen in children as young as 3 months old and hence the term congenital appears to be correct (23-27).

Figure 7. Association of APC with CHRPE in families (15).



Extracolonic Cancers

Several cancers, themselves also very rare, occur frequently enough with APC to be considered associated extracolonic cancers. These include most commonly duodenal and peri-ampullary cancer (28-30), but also papillary carcinoma of the thyroid (16,17), hepatoblastoma (31,32), intracranial cancer (33,34), biliary cancer, and adrenal cancer (2).

All these cancers are rare cancers that may also occur outside of the APC setting. Duodenal or peri-ampullary cancer is the most common, generally found in association with adenomas, and occurs in 4-12% of patients with APC (28,30). Hepatoblastoma occurs in children in APC families, who are subsequently found to carry the APC genotype if they survive the hepatoblastoma (31,32,35,36).

The association of APC with intracranial tumors has been termed Turcot syndrome. Only about 50 cases have been reported in the literature, and it still is not clear whether it is a variant of APC or an entirely separate syndrome. New investigations into the status of the APC gene in affected family members may help resolve this issue (33,34).

The intracranial tumors in Turcot syndrome are mostly gliomas, and have included glioblastomas, medulloblastomas, and astrocytomas. These patients develop multiple colonic adenomatous polyps, as well as the extracolonic manifestations found in Gardner syndrome (33,34).

Gastroduodenal Polyps

Gastroduodenal and small intestinal polyps are found in 50% or more of individuals with APC (Table 3). The gastroduodenal polyps are not strictly associated with Gardner syndrome or the extracolonic manifestations. Patients without other extracolonic manifestations may have gastroduodenal polyps, and patients with gastroduodenal polyps may have no other extracolonic manifestations (28-30,37-42).

Gastric polyps found in patients with APC are generally hyperplastic polyps, found mostly in the proximal stomach. They are also known as fundic gland polyps, and represent hyperplasia of the fundic glands with some cystic dilation. Endoscopically, they appear as polypoid lesions, 1-5 mm in diameter. Occasionally there are multiple fundic gland polyps that coalesce and form an irregular matted surface. These fundic gland polyps rarely cause symptoms, although occasionally they may result in GI blood loss. Adenomatous polyps may also occur, but they are much more uncommon, especially outside Japan. Adenomas account for probably 5% or less of all gastric polyps, and are more frequently found in the antrum than in the proximal stomach (28,29).

Table 3. **UPPER GI POLYPS IN APC**

	GASTRIC	DUODENAL
JAPAN	70%	90%
US	50%	50%

Duodenal polyps are found in about 50% of patients with APC, with some series, especially those from Japan, showing a much higher frequency. These are generally multiple, and range in size from several millimeters to 1 cm or larger. They have a predilection for the second portion of the duodenum, the peri-ampullary region, and the ampulla itself. The histology is frequently adenomatous, and often with villous architecture (Table 4). There is a 2-4% chance of duodenal cancer in patients with APC. They generally occur after the development of colonic polyps, with an average lag time of 5-7 years (2,30,41).

Table 4. **UPPER GI POLYPS IN APC**

GASTRIC	DUODENAL
FUNDUS + BODY	2ND PORTION
>100	5-10
2-3 MM	>5 MM
CONFLUENT	SESSILE
HYPERPLASTIC	ADENOMAS
LOW CA RISK	HIGH CA RISK

Jejunal and ileal adenomatous polyps have also been described in patients with APC, in some cases as high as 20% or more. In the small intestine, the adenomatous polyps appear to have a low malignancy rate, as the number of cases of small intestinal cancers is extremely small. Endoscopy with biopsy is necessary as prominent lymphoid hyperplasia or lymphoid polyps of the terminal ileum may occasionally be seen in younger patients (2,28,38,42).

Management

The primary mode of management of patients with APC is colonic resection, coupled with surveillance of any remaining anorectal mucosa and the gastroduodenal mucosa with resection of any lesions with high-grade dysplasia and/or cancer. This must be combined with a surveillance program for any at risk siblings or children. In some patients, the extracolonic manifestations, in particular desmoids and osteomas, may also require therapy. Management of patients and families with APC must also include genetic counseling, support groups and assistance with medical and health insurance, and attendant psychosocial difficulties (3,43).

Surgery

Colectomy is recommended promptly once multiple adenomas are found. In selected individuals, especially young children, in whom complete colonoscopic examinations show that all polyps are small (less than 5 mm), and no suspicious lesions or large polyps are found, and histopathologic examinations do not show high grade dysplasia or cancer, waiting for the patient to pass one of their milestones may be considered. It must be explained to the patient and family members that since colectomy is inevitable, earlier surgery improves the odds of removal of all neoplastic tissues before any potential metastatic spread. Few things in medicine are as tragic as having a patient wait too long to have a curative resection (43).

The choice of operation should be decided jointly by the patient and surgeon. The surgeon's experience and skills are to be taken into account, but the patient's preference should generally be considered overriding, if medically feasible. Since APC is still a rare disease, referral of patients to a surgeon skilled and experienced in the various colectomy techniques would be prudent (10).

The simplest surgical approach is total colectomy, leaving the rectum and with bowel continuity by an ileorectal anastomosis. But the patient is left with anorectal mucosa that is still at risk for developing cancer (44). More definitive operations include total colectomy and proctectomy, so that no anorectal mucosa is left, with the performance of an ileostomy (45). A third alternative is the performance of total colectomy, anorectal stripping, with an ileal mucosa pull-through and then anastomosis of ileal mucosa onto anorectal muscular layers - often termed colectomy with a pull-through operation (46). For patients with an ileostomy, they may either wear an appliance, or choose to have a continent ileostomy, made with one of the varieties of ileal pouches. Even with a continent ileostomy, patients still have multiple bowel movements daily, and the revision rate can be 30% or higher (10).

Although total colectomy with ileorectal anastomosis can preserve continence, the patient still has multiple bowel movements per day, and the remnant anorectal mucosa can be a ticking time bomb. Despite frequent surveillance of the remnant rectal mucosa, patients have succumbed to colorectal malignancy. Currently ileorectal anastomosis should only be considered as an interim option, allowing the patient to adjust to the reality of a surgical operation, with an eye towards conversion to a continent ileostomy, an ileostomy with an appliance or a pull-through operation. Many surgeons and patients prefer the first operation to be a pull-through operation, with the understanding that revision to a continent ileostomy or a simple ileostomy may be required later (10).

Treatment of gastroduodenal and peri-ampullary adenomas can be an extremely difficult proposition. Large pedunculated and even some sessile adenomatous polyps may be removed safely with snare cautery. For polyps that cannot be removed in toto or which leave residual adenomatous tissue, surgical excision must be considered. However, complete surgical excision often necessitates pancreaticoduodenectomy (Whipple's procedure), with all of its attendant morbidity and complications, and requirement for lifelong insulin and pancreatic enzyme supplementation, and cannot be recommended for all patients. Sometimes laser ablation may be tried, especially for a small number of small adenomas (<5 mm) that are not amenable to polypectomy. Despite our endoscopic advances, peri-ampullary adenomas and cancers remain the most difficult management challenge in APC. In fact, in most practices, including my own, the major (and often only) cause of mortality in APC patients is upper gastrointestinal neoplasia (2,30).

Surveillance

In first degree relatives of affected patients, such as younger siblings and offspring who have not yet developed multiple polyps, a surveillance program is mandatory. With the availability of genetic markers, surveillance strategies are being modified to take into account the results of genetic testing to determine the probability of an individual's having inherited the APC genotype. Where genetic testing is not available or uninformative, the following surveillance schedule might be recommended (2,43).

Patients should first be seen between the ages of 8 and 10 for a brief visit and physical examination, with the physician taking great care to establish rapport and to inflict no discomfort or pain. Beginning about age 10-12, yearly flexible sigmoidoscopy should be performed until age 35 and every 3 years thereafter. Biopsies of any suspicious lesions or polypoid lesions should of course be done.

Once the diagnosis of APC is made, surveillance of the upper GI tract should also be made. This should include gastroduodenoscopy at 1-3 year intervals. A side-viewing scope should be used so that the papilla can be examined carefully. The presence of duodenal or papillary adenomas or adenomatous changes should prompt annual endoscopy to detect high-grade dysplasia and/or early cancer. Small bowel radiographs may also be performed (28,29) (Table 5).

Table 5. **SURVEILLANCE FOR UPPER GI POLYPS**

GASTRODUODENOSCOPY AT TIME OF COLECTOMY
- NEGATIVE - SCOPE q 3-5 YRS
- ADENOMAS - SCOPE q 1 YR
- DYSPLASIA - LASER OR SURGERY
- CANCER - SURGERY

Counseling

Genetic counseling is key for patients and at risk individuals, especially those with young children, and needs to be coupled with education (Table 6). Counseling works best when the patient is not under the pressure of having to decide on colectomy and/or the type of surgical intervention. Thus it is desirable that genetic counseling be carried out as early as possible. In addition, patients generally desire that medical and genetic testing provide them with an assurance that they or their offspring do not have the disease, whereas the medical profession generally are searching for the presence of disease. With this understanding of the potentially conflicting perspectives, it appears that only rarely can our presently available tests offer 100% assurance that the patient is not a carrier of the genotype and thus be 100% satisfactory for the patient. Thus genetic testing should be carried out only in concert with surveillance and only after the age for surveillance has been reached, and then only in patients who understand the therapeutic options if disease is found (2,3) (Table 7).

Table 6. **GENETIC COUNSELING FOR APC**

EDUCATION
MUTUAL AGREEMENT FOR MANAGEMENT
PATIENT (CHILDREN'S) RIGHTS
BONDING WITH FAMILY (PARENTS)
PEER (FAMILY) REJECTION
SELF-IMAGE

Table 7. **GENETIC TESTING FOR APC**

PROS	CONS
CONFIRM DX	CONFUSION/FEAR
AVOID SURVEILLANCE	INSURABILITY
	EMPLOYABILITY
	STIGMATIZATION

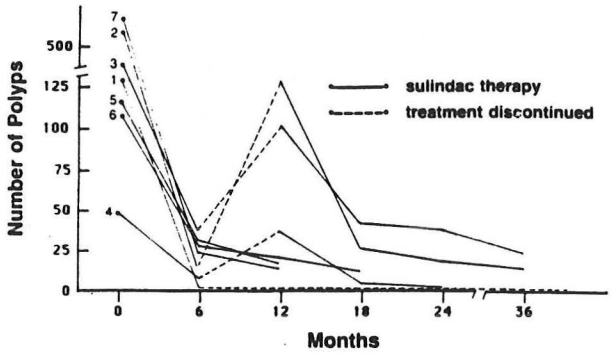
APPROACH
MAXIMIZE DIAGNOSTIC ADVANTAGE
MINIMIZE PSYCHOSOCIAL RISK
GENETIC TESTING AT SURVEILLANCE

Medical Treatment and Prevention

Recently several small non-randomized trials without strict controls suggest that sulindac, a nonsteroidal antiinflammatory drug (NSAID), may produce regression and/or disappearance of colorectal adenomatous polyps in patients with APC and other multiple polyposis syndromes (47-51) (Figure 8). Although the results are exciting, it must be emphasized that sulindac therapy remain experimental. It is most important that patients and physicians not be falsely

experimental. It is most important that patients and physicians not be falsely reassured that sulindac provides effective treatment. Many adenomas in APC have shown spontaneous regression, especially in the rectum after colectomy (52,53). Most patients that have been studied in the sulindac trials only have a short anorectal mucosal remnant. It is unclear whether sulindac will produce regression of adenomas throughout the entire colon. Until properly designed studies have proven conclusively that medical treatment will totally prevent or delay the progression of adenomatous polyps to cancer, the only defensible treatment is colectomy.

Figure 8. Regression of Polyps During Sulindac Treatment (51).



However, it is important that physicians and patients become familiar with the various clinical trials and protocols available to them locally or regionally. These trials can help improve patient education and understanding, and also enhance our knowledge of the disease and its prevention and treatment.

The APC Gene

The adenoma-carcinoma sequence seems established and generally accepted (54). In APC most investigators agree that the colorectal carcinoma is a result of progression of one or several of the adenomas present (2).

Other investigators have also found that colorectal mucosa of patients affected with APC show a higher cell proliferation status than the mucosa of control patients (3). This appears to be a general phenomenon, as patients with other types of premalignant disorders, such as sporadic adenomatous polyps, inflammatory bowel disease with dysplasia, all appear to have increased cell proliferation in their colorectal mucosa. Some mucosal proliferation markers have been explored as biomarkers of the inherited genotype (55,56).

Within the past several years, the APC gene was first localized to the long arm of chromosome 5 (57,58) and then subsequently identified and cloned (8,9). It is of interest that another gene, MCC (mutated in colon cancer), found in association with sporadic colon cancers, is localized in the same chromosomal region (59).

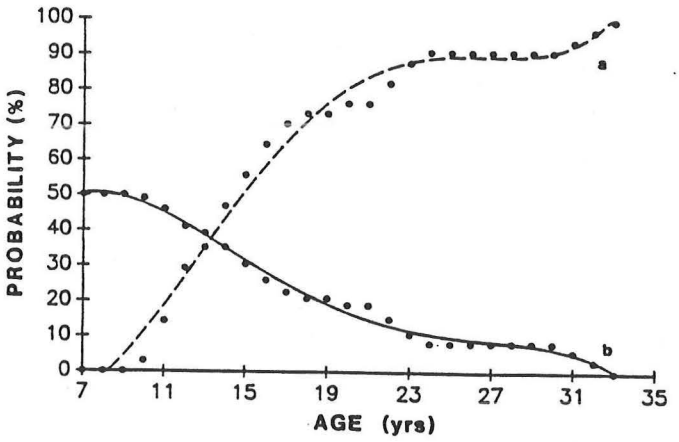
The APC gene (and the MCC gene) are currently hypothesized as tumor suppressor genes. Deletions of these genes have been found in colon cancer tissue, as well as germ cells

in patients affected with APC (60,61). In addition, complementation studies suggest that the reintroduction of an intact APC gene (or chromosome 5) may normalize the phenotype of cancer cells in experimental cell models (62,63). However, the APC gene appears to be a novel gene, in that there is no homology to other known gene families, and its function is still uncertain.

Genetic Markers

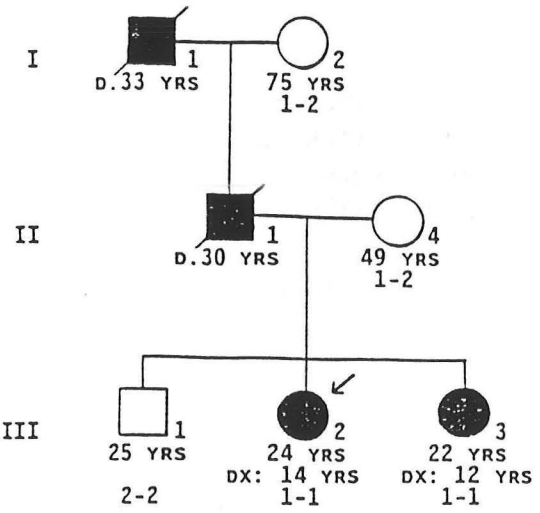
With the identification of the APC gene, genetic testing is facilitated. Even before the APC gene was pinpointed, genetic markers localized near the region of the APC gene were used for genetic testing. Using genetic markers together with phenotypic markers, several investigators have found that genetic testing was possible in 75% or more of APC families (13,64-66) (Figures 9 and 10). With the availability of the APC gene, the accuracy of genetic testing is being improved (67). It must be remembered that although APC gene deletions have been found in 100% of APC families thus far, it still falls short of that in individual patients, especially those with small families or with no or few living affected members.

Figure 9. Genetic Marker Linkage Testing in APC (13)



Curve a. **Probability of finding polyps during sigmoidoscopy in a relative at a given age if he or she has inherited the FAP gene.** *Curve b.* **Probability that an at-risk relative will be affected if a prior sigmoidoscopic result at a given age was negative.**

Figure 10. Probability of APC Genotype and After Genetic Testing and Sigmoidoscopy (13)



Family 2. With the linkage information, we could counsel the family that the risk of FAP in the brother (III-1) was <0.2%. In this family, allele 1 of the EF5.44 gene marker is segregating with the polyposis gene.

If genetic testing is done and the results are informative, they can help improve our surveillance strategies. Patients who appear to carry the genotype should have annual flexible sigmoidoscopies beginning at age 11 until age 35, and undergo prophylactic colectomy when adenomas appear. Patients in whom genetic testing is uninformative or negative should undergo flexible sigmoidoscopy at age 11 and 12 and then at intervals of every 3 years until age 35 (Table 8). With increasing understanding of the APC gene, it is likely that within the next decade, it will be possible to identify with great accuracy gene carriers and unaffected family members (2).

Table 8. Surveillance for APC (with Genetic Testing)

SURVEILLANCE FOR APC
(APC GENE LINKAGE)

FLEX SIG ANNUALLY BEGINNING AGE 11
PROPHYLACTIC COLECTOMY WHEN POLYPS APPEAR

SURVEILLANCE FOR APC
(NO APC GENE LINKAGE)

FLEX SIG AT AGE 11 AND 12
THEN q 3 YRS UNTIL AGE 35

Future Directions

The UT Southwestern gastroenterology research laboratory at the Dallas VA Medical Center is actively pursuing genetic studies and prevention trials of patients with APC and sporadic adenomatous polyps. We are happy to discuss potential services with any interested physician (Table 9). In addition, we will be delighted if patients with APC (including Gardner syndrome), sporadic adenomatous polyps, or colorectal cancer, are referred to us for study. We currently have an NIH-National Cancer Institute funded preventive trial using an amino acid analog of ornithine (DFMO) to prevent the increased cell proliferation seen in patients at high risk of adenomatous polyps or colon cancer. The investigators may be contacted at (214) 372-0467 or (214) 376-5451, ext. 5597.

Table 9. GENETIC TESTING FOR APC - UT SOUTHWESTERN

COUNSELING
MUTUAL AGREEMENT FOR MANAGEMENT
2 KNOWN AFFECTED RELATIVES
1 KNOWN UNAFFECTED RELATIVE
PERIPHERAL BLOOD

		Pager (640-7441)
Gordon D. Luk, M.D.	372-0467	17267
William V. Harford, M.D.	371-6441	14014
Loyce J. Cervantes, BSN	372-0467	19414
FAX 372-0467		
372-7948		
372-7986		

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