# Gardner's Syndrome
## Recent Developments in Research and Management

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*In recent years, a number of comprehensive reviews have been written on inherited intestinal polyposis syndromes (1-7), but none has dealt specifically with Gardner's syndrome and none has focused on basic research being carried out in an attempt to understand this syndrome and to improve the medical management of affected patients. A better understanding of this rare genetic disorder is essential for surgeons, gastroenterologists, cancer researchers, and geneticists alike. To the clinician, it poses difficult challenges in management; to the cancer researcher, it presents a rare opportunity to study very early premalignant transformations; and to the geneticist, it poses exciting questions at the cellular, chromosomal, and molecular levels.*

While there are several early case reports in the literature (8-10), the first description of the clinical and genetic aspects of the syndrome was made in the early 1950s by Gardner (11-15). As initially described, it consisted of multiple colorectal polyposis associated with various soft- and hard-tissue tumors including epidermoid cysts, fibromas, and osteomas. Additional manifestations have since been associated, including desmoid tumors (16, 17), mesenteric fibromatosis (18), dental abnormalities (19), gastric polyps (20), duodenal polyps (21), periampullary carcinoma (22), lymphoid hyperplasia of the terminal ileum (23), and ileal adenomas (24). Other manifestations have been reported but have not been established as part of the syndrome. These include osteochondromas (23, 25), papillary carcinomas of the thyroid (26-28), and adrenal adenomas (8, 29-31).

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## FORMAL GENETICS

Gardner was the first to interpret the pattern of inheritance of the colorectal and extracolonic tumors as being consistent with an autosomal dominant pattern of inheritance (11-15). He postulated that either a single pleiotropic gene controlling some fundamental process gave rise to all three manifestations or else three closely linked genes were responsible. In view of geographically separated and apparently unconnected families, Hughes and Hueston (32) felt that it was unlikely that three closely linked, but separate, genes were involved. They supported the idea that the mutant gene has only a single action, although many steps removed from any clinically obvious manifestations (pseudopleiotropism). Smith (27) supported this idea and suggested that the defective gene produces its effects either by causing some organ to produce a growth-stimulating molecular species which is abnormal in the amount produced or in its basic chemical properties, or by altering nuclear material, thus causing cells all over the body to respond vigorously to normal growth stimuli.

Pierce et al (33) determined that the syndrome affects the sexes equally. The gene frequency at birth was calculated to be 1 in 14,025, suggesting it is rarer than the gene for familial colorectal polyposis. Fitness was calculated to be 82.2%. This is in close



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agreement with the fitness of familial colorectal polyposis (34, 35). The mutation rate was calculated to be 13 mutations/million loci/generation. This is of the same order of magnitude as other mutation rates commonly quoted for man.

The Gardner's syndrome gene is considered to have a high degree of penetrance. An early study used two methods to estimate the penetrance at either 60.0% or 83.9% for their large kindred (33). These figures are similar to those reported for familial colorectal polyposis (35, 36), but it appears that these values were based on an incomplete evaluation of the kindred. Recently, a more complete estimation of penetrance has been published based on the original Utah kindred #109, plus 160 additional sibships from the literature (37). These data indicate the penetrance is essentially 100%, but that there is considerable variation in expressivity of the gene. The risk of a "skipped generation," with its impact on accurate genetic counseling, is at a minimum if the patients are fully evaluated clinically.

When studying families with familial colorectal polyposis, it is not always possible to make the clinical diagnosis in children under the age of 16 or in adults with delayed expressivity. This would, in turn, result in an underestimation of the penetrance of the familial colorectal polyposis gene. In Gardner's syndrome, however, the clinical diagnosis can almost always be made early in childhood, and frequently in infancy, based on the presence of multiple epidermoid cysts followed soon afterwards by osteomas, dental anomalies, or fibromas. Intestinal polyps have been observed as early as age 5, and generally occur by the late teens or early twenties. Variable expressivity of the gene, while it may affect one or two of the symptoms, will usually not result in failure to identify a family member with the affected gene. It is, therefore, possible to measure the penetrance of the Gardner's syndrome gene more accurately than that for familial colorectal polyposis.

The question of whether Gardner's syndrome is a distinct entity, however, remains to be fully answered. Smith (16) has submitted that it is merely the full-blown manifestation of a spectrum of pathological changes which can affect, in variable numbers and combinations, any patient with familial colorectal polyposis. Instead, it was suggested a variation in penetrance or expressivity might best explain the presence or absence of the extracolonic tumors. McKusick (5, 38), on the other hand, has submitted that the gene is distinct from that of familial colorectal polyposis. This was based on certain phenotypic differences plus the distribution of polyps. It was also suggested that the genes might be allelic.

Both of these hypotheses have support at the present time. Some authors support the hypothesis that the two disorders are at opposite ends of a disease spectrum produced by a simple pleiotropic gene (25, 39, 40), while others support the hypothesis that they are distinct entities (6, 41, 42). McKusick's classification, based on the distribution of polyps, has not been substantiated, but other observations, such as the demonstration of increased tetraploidy in skin cultures from syndrome patients but not from patients with simple familial colorectal polyposis (42), continue to support the hypothesis that they are distinct entities. Linkage studies would be helpful in answering this question, but early studies have not been helpful (35, 43). It has been our experience that the two syndromes tend to breed true. If members of different kindreds are fully evaluated, it will invariably be found that Gardner's patients give rise to offspring who will eventually develop the full-blown syndrome while patients with established simple familial colorectal polyposis will produce offspring devoid of extracolonic manifestations. The one exception to this appears to be the occurrence of desmoid tumors in both syndromes.

## CHROMOSOME STUDIES

Karyotyping of leukocytes from familial colorectal polyposis patients has shown numerically and structurally normal chromosomes (35, 39, 44). Direct chromosome analysis of cells from benign and malignant epithelial tumors of the gastrointestinal tract has been carried out (45). A normal karyotype was found in the earliest adenomas. In polyps undergoing malignant transformation, extensive alterations were found. These morphologic and numerical alterations were extremely irregular and not related to the site or degree of diffusion of neoplasia. Several studies (46–50) have demonstrated karyotypic changes in solitary polyps from different patients which were histologically noninvasive. In familial colorectal polyps and in sporadic types, the chromosomal changes preceded signs of invasiveness. In both types, preferential involvement of chromosomes 8 and 14 was found, suggesting a similar evolution in colonic adenomas regardless of whether they are hereditary or not. The rate of pro-

gression was faster in familial polyps, which may reflect the more malignant potential of these tumors.

## INCREASED TETRAPLOIDY IN CULTURED SKIN FIBROBLASTS

Somatic cell culture offers an opportunity to study isolated cells and to determine whether a cell carrying the gene responsible for Gardner's syndrome will express an abnormality which reliably and reproducibly reflects the gene's presence. If such a marker could be found, cell culture studies could be used for early diagnosis of family members who have inherited the gene. In an attempt to identify such a marker, Danes has reported increased endoreduplication with tetraploidy in skin fibroblast cultures from syndrome patients (51–56). In endoreduplication, chromosome replication occurs without an intervening mitosis resulting in a tetraploid nucleus. It occurs in cultured cells from normal individuals, but at a low incidence (57). In early studies, fibroblasts from 12 affected members of three families showed tetraploidy in 11–35% of all dividing cells while controls showed only 0–4%. Similar results were observed in 137 members of six families and in 49 members of the original Utah kindred #109. There was no correlation with age or clinical expression. Cultures from patients with familial colorectal polyposis, familial osteomatosis, and neurofibromatosis showed only 0–4% tetraploidy.

Increased tetraploidy was observed only in cultures derived from tissues at risk for undergoing malignant transformation *in vivo*. For familial colorectal polyposis, this was considered to be epithelial cells of colonic mucosa and for Gardner's syndrome it was epithelial cells of epidermis and colonic mucosa. Only when the biopsy contained epithelium or when epithelioid cells migrated from the biopsy and were part of the cell population from which the cell line was established was a culture derived from a syndrome patient distinguishable from normals. Since cultures obtained from skin biopsies are a mixed population consisting of epithelioid and fibroblast cells, it will be necessary to study clones of epithelioid cells before the true frequency of tetraploidy is known. These studies have also demonstrated that tetraploidy, as an expression of the gene, is cell specific. This is not unexpected considering that all human hereditary tumors so far recognized have shown tissue specificity (58).

Since biopsies were taken from areas of the skin free from sebaceous cysts or fibromas, the cells represent somatic cells prior to any abnormal growth activity. As tetraploidy was present at the first subculture and the percentage of dividing cells showing tetraploidy did not increase markedly in four culture months, it was unlikely that the tetraploidy was secondary to aging in culture or to viral infection.

As exciting as these observations are, it is important to note that they have all originated from a single laboratory. Before further speculation on their relationship to the inherited defect can be entertained, it will be necessary for them to be independently confirmed by other investigators.

## TRANSFORMATION OF CULTURED SKIN FIBROBLASTS

Assuming that phenotypic expressions which appear in cell culture closely reflect biologic abnormalities occurring *in vivo*, the study of skin fibroblasts from patients with familial polyposis phenotypes has provided a unique system for study of the oncogenic process and has resulted in development of a diagnostic index for identification of individuals at risk for the disorder (59–62).

Skin fibroblasts from familial polyposis phenotypes and from about half of their offspring were found to have lost serum- and density-sensitive growth control in culture. Lack of contact inhibition, elevated levels of plasminogen activator, and alterations in intracellular distribution of actin cables were also demonstrated. Cells did not grow in the absence of anchorage, nor did they form palpable tumors in congenitally athymic BALB/c *nu/nu* mice and they had normal cholesterol feedback regulation. Infection by Kirsten murine sarcoma virus yielded fully transformed cell lines, but polyposis fibroblasts were 100- to 1000-fold more susceptible. Thus the colorectal polyposis mutations partially decrease growth control of skin fibroblasts so that they resemble stable partial transformants of murine fibroblasts generated by simian virus 40. Kinetic analysis of contact- and serum-dependent growth regulation has also been carried out (63). Studies on saturation density indicate that fibroblasts from polyposis patients and from a fraction of clinically asymptomatic progeny became density saturated at an average cell number three times that observed with normal fibroblasts.

These growth abnormalities have been considered to represent steps in the changing phenotypic

expression of cells undergoing neoplastic transformation. Previously such changes had been attributed only to chemical or viral transformation of cells *in vitro*. It is significant that they can also occur in fibroblasts genetically predisposed to cancer. Results further suggest that these abnormalities are not in themselves sufficient to confer oncogenic potential. Rather, an RNA oncogenic virus was essential for malignant transformation to occur.

Appearance of growth abnormalities in fibroblasts from polyposis patients supports the notion that oncogenesis *in vivo* might indeed be an all-inclusive temporal multistage process, similar to that found *in vitro*. The preneoplastic phase could be defined as embracing those steps preceding the ability of cells grown in the absence of anchorage including growth in low serum, loss of contact inhibition, augmented levels of plasminogen activators, and deformed actin cables, but not defective regulation or sterol biosynthesis. The malignant phase would include the ability of cells to grow without anchorage and to form tumors *in vivo*.

It is important to note that these studies were carried out on cutaneous biopsies from hereditary colorectal polyposis phenotypes and not just on patients with Gardner's syndrome. The combining of these phenotypes persumably misses any real difference that might result from the different genotypes. The results do suggest a common systemic defect in the growth control of stromal cells in both syndromes which might prove useful for diagnosing individuals with latent colorectal polyposis.

## BOWEL TRANSIT TIME

As diarrhea is a common complaint, patients with Gardner's syndrome have been studied to determine their bowel transit time (64). Using barium sulfate-filled plastic pellets and periodic x-ray examinations (65), a threefold decrease in bowel transit time was noted. Average time to appearance of 80% of the pellets in normals was 55.8 hr while in 3 patients it was 17.4 hr.

The shorter transit time was not accompanied by watery stools or cramping, and the patients had two soft, formed bowel movements daily. The etiology of this decreased transit time is not fully understood, but it is interesting to note that bile salts can act as strong cathartics and that abnormal fecal flora can alter bile salt conjugation and even concentration.

## FECAL BILE ACIDS AND NEUTRAL STEROLS

Although familial colorectal polyposis is genetically determined, its malignant development may be due, at least in part, to environmental factors (66). High fat intake affects the fecal microflora, its metabolic activity, and ultimately levels of certain fecal bile acids and neutral sterols (67–70). It has been postulated that, in colorectal cancer not associated with polyposis, certain clostridia produce a carcinogen or cocarcinogen from bile acids and, retrospectively, that such patients had both high fecal bile acids and the relevant clostridia (71). In addition, absorption of aromatic carcinogens into cells of the glandular stomach is enhanced by natural bile or bile salts (72), cholesterol promotes tumor formation induced by 3,4-benzpyrene and 3-methylcholthanthrene (73, 74), and diverting bile from the proximal to the distal half of the small intestine doubles fecal bile salts and increases tumor production in azomethane-treated rats (75).

Since colorectal polyposis patients are at increased risk of developing carcinoma, their fecal bile acids and neutral sterols have been studied. Watne and Core (76) studied both patients with familial colorectal polyposis and Gardner's syndrome. Their first group consisted of patients with untreated polyposis, while their second was made up of patients who had undergone subtotal colectomy with ileorectostomy. Cholesterol, cholic acid, and chenodeoxycholic acid were higher in the untreated group, while ileorectostomy resulted in disappearance of coprostanol, a bacterial metabolite of cholesterol. Chenodeoxycholic and cholic acids were also higher in ileorectostomy patients. Lithocholic and deoxycholic acids were normal in the untreated group, but were lower in the ileorectostomy group.

Six groups of polyposis patients were studied prospectively at St. Mark's Hospital (77), including both diagnosed and undiagnosed children of affected parents, plus patients surgically treated for polyposis, ulcerative colitis, colon carcinoma, Peutz-Jegher's syndrome and juvenile polyposis coli. Investigation of colorectal polyposis patients and half of their undiagnosed children revealed that although they carried clostridia able to dehydrogenate the steroid nucleus, their average fecal bile and neutral sterol concentrations were low. In all cases, cholesterol was virtually undegraded while its metabolism was normal in Peutz-Jegher's

syndrome patients, indicating that these observations are not characteristic of all polyposis syndromes.

Dietary fat concentration was similar in all studies. Since the bacterial flora can metabolize cholesterol and since mass spectral studies confirmed the neutral sterol excreted is cholesterol, it was concluded that conditions in the intestine are unfavorable for its degradation. Further information has been gained from the study of urinary cyclic secondary amines which are synthesized by colonic bacteria from amino acids and excreted after absorption from the gut (77).

Preliminary studies have indicated that the proportion of aerobes is not abnormally high in polyposis patients (77). A slight decrease in fecal eubacteria and bacteroids and a slight increase in clostridia and bifidobacteria have also been reported (78). The total fecal anaerobic count was the same in polyposis patients and controls, but *in vitro* conversion of radioactive cholesterol to coprostanol by mixed cultures from feces was low in polyposis patients (79). About half of the prospective polyposis siblings behaved similar to those with confirmed polyposis; if these are the siblings who develop polyposis and if those with normal microbial activity remain unaffected, then this would be a simple diagnostic test for the disorder (77).

These studies, combined with the urinary phenol excretion studies presented in the next section, illustrate the complex interactions which are taking place between the genetic predisposition of the individual and his environment.

## URINARY PHENOL EXCRETION

Urinary phenols are the products of tyrosine metabolism by gut bacteria. Aerobes are responsible for phenol and anaerobes for *p*-cresol production (80). When urine from familial colorectal polyposis patients was analyzed, normal levels of phenol were found but there were greatly reduced levels of *p*-cresol. This suggests that, although anaerobic bacteria are inactive in these patients, the aerobic organisms have normal activity. In polyposis patients with ileorectal anastomosis, the mean level of phenol was increased, while *p*-cresol was largely unchanged. This operation results in colonization of the lower ileum and rapid transit of gut contents. There was no evidence, however, that the flora in these patients was less active than in nonpolyposis patients with a similar operation. It therefore appears that removal of the colon also removes the inhibition factor. This is in agreement with results on other substrates (77, 81) and adds support to the hypothesis that there is something secreted by the colon in these patients that inhibits bacterial activity.

## INTRACYTOPLASMIC COLLAGEN FIBERS IN DESMOID TUMORS

An attempt at understanding the pathophysiology of desmoid fibromatosis was made in 1966 by Welch (82). Using electron microscopy, unusual collagen fiber formations were found within the cytoplasm of fibroblasts from a desmoid fibroma. The fibers lay in narrow tubules or smooth endoplasmic reticulum and could be traced into clusters of Golgi tubules or smooth-surfaced dilatations. They were the same size as those in the extracellular environment, but occasionally appeared incompletely formed. Intracellular residual bodies were also found which contained coiled masses of collagen. These changes were not considered artifactual but rather to represent a pathologic process in collagen fiber formation.

Intracellular collagenosynthesis in a "desmoid fibroblastoma" has also been reported (83). This poorly vascularized tumor was composed of immature glycogen laden fibroblasts and presented ultrastructural evidence of simultaneous intracellular collagen production and extracellular lysis. Tumor fibroblasts differed from normal fibroblasts in the production of intracellular collagen and the accumulation of glycogen. The intracytoplasmic collagen production was similar to that reported by Welsh (82). It was concluded that normal fibroblasts possess an inhibitor which prevents premature cross-linking of the tropocollagen molecule in the Golgi system, while in desmoid fibroblasts this substance may fail to act, allowing collagen to complete its organization into intracytoplasmic fibers (84). If these observations prove to be correct, we may have the first direct evidence of a molecular defect which may be responsible for the uncontrolled fibroblastic proliferation in these unusual tumors. It would then be interesting to determine whether similar abnormal processes are present in simple fibromas or other tumors from patients with Gardner's syndrome.

## ELECTRON MICROSCOPIC STUDIES OF COLONIC EPITHELIUM

Polyposis patients, especially those with Gardner's syndrome, provide an ideal opportunity to study the histological evolution of colorectal carcinoma. Using light microscopy, various stages of polyp growth, from epithelial hyperplasia involving a single crypt to development of a recognizable adenomatous proliferation, have been observed (85). The histogenesis of the polyp-carcinoma sequence has also been described (86, 87). In an analysis of minute adenomatous polyps from familial colorectal polyposis patients, Maskens (88) suggested that adenomatous polyps result from an in-folding of surface epithelium between normal, preexisting glands. Ultrastructural studies have been rare and have focused primarily on mature polyps with little reference to intervening mucosa (89, 90). To study the earliest premalignant changes, however, it is necessary to look at this macroscopically normal mucosa.

Histochemical techniques have revealed that goblet cells in normal mucosa adjacent to an adenocarcinoma contain predominantly sialomucins, while those in mucosa remote from the tumor produce mainly sulfated material (91, 92). At the ultrastructural level adjacent mucosa also shows features distinct from those in more remote mucosa (93). Adjacent mucosa is characterized by an alteration in relative proportions of cell types along the crypt, with persistence of immature and intermediate cells at higher levels. This suggests a failure in normal cell differentiation along the crypt. Colectomy specimens from polyposis patients have also been studied (94). Normal mucosa between polyps was compared to biopsies from patients with no known gastrointestinal disease. All regions showed the same cell types, varying only in their ratio and height of epithelium. There were, however, ultrastructural features which distinguish normal mucosa in polyposis patients, including the presence of clear columnar cells. The ultrastructure of these cells suggests incomplete differentiation, the presence of which in the upper crypt and surface epithelium may represent an early stage of polyp and cancer formation.

This study has been extended and criteria established for the graduation of changes from normal mucosa to invasive adenocarcinoma (95). These criteria are based on vesiculation and increasing numbers of electron-dense bodies (secretory granules) and lysosomes in mature and undifferentiated cells, variation in goblet cells, appearance of atypical secretory cells, and nuclear changes.

If we are ever to discover the secrets of malignant transformation, it will be through an examination of normal cells which are in the very earliest stages of transformation. These ultrastructural studies are a first step in this direction. They are an attempt at attaining an insight into the cellular evolution that is taking place in these premalignant tissues.

## MANAGEMENT OF COLORECTAL POLYPOSIS

The first attempt at surgical management of colorectal polyposis was ileosigmoidostomy followed by colonic resection (96). Subsequently, preoperative fulguration of polyps was introduced (97). Since then, numerous variations have been reported, including total colectomy with removal of the rectum (98), total colectomy and proctectomy with establishment of permanent ileostomy (99), colectomy with side-to-side (100) or end-to-end ileorectal anastomosis (101), and total colectomy with anal ileostomy for preservation of sphincter function (102).

From 1950 to 1970, the procedure of choice was abdominal colectomy with ileorectosigmoidostomy followed by fulguration of rectal polyps and frequent proctologic surveillance. In 1970, this conservative approach was challenged (103). The occurrence rate of rectal carcinoma increased from 5% in patients followed for 5 years after subtotal colectomy to 59% in those followed for up to 23 years in spite of frequent sigmoidoscopic exams. It was concluded that the seemingly impregnable case for preservation of the rectum had been eroded by an element of doubt and that the polyp-to-carcinoma dogma had been seriously challenged. The evidence suggested that rectal carcinomas may arise without the necessary premalignant intervention of an adenoma.

While it is universally accepted that surgical removal of the colon is indicated, this study has resulted in a heated debate over the fate of the terminal bowel segment. Proponents of retaining the rectum argue that carcinoma originates in the polyps, and if they can be removed promptly, development of carcinoma can be prevented. The disfigurement, complications, and emotional trauma associated with permanent ileostomy can thus be avoided. Support for this position has come from studies

showing rectal carcinoma developing in only a small proportion of patients with retained rectums (85, 97, 104–113).

It has been suggested that ileorectal anastomosis is good management for patients who lack rectal polyps and for younger patients in whom good follow-up is assured if a low anastomosis is performed with no blind areas of rectal mucosa (112). On the other hand, proctocolectomy should be performed in patients in whom adequate follow-up is in doubt and in older patients with persistently recurring rectal polyps. Watne also favors colectomy with ileorectal anastomosis, but emphasizes anastomosis to the rectum rather than the sigmoid (111). To ensure this, a rectal tube is inserted to 12 cm and the anastomosis is performed at this level. Polyps are not fulgurated prior to surgery or for 1 year after, but the patients are proctoscoped at 3-month intervals. This has resulted in the observation that 15 of 17 patients had objective reduction in the size and number of retained polyps.

An alternative treatment involves total colectomy combined with endorectal pull-through. This removes all colonic mucosa and preserves rectal function. It has been available for some time (114, 115), but has been used only occasionally. Although most early cases had satisfactory results, complete continence was not always attained. The endorectal pull-through did not become popular until Soave (116) modified it for management of Hirschsprung's disease. Since then, 9 patients with familial colorectal polyposis or Gardner's syndrome have been successfully treated (117–121). A temporary loop ileostomy was considered advisable to prevent anastomotic complications (120) and to avoid excessive diarrhea and perianal excoriation. Because of physical and emotional advantages and the fact that possible precancerous lesions are avoided, it is preferable to methods generally in use today (119).

## EARLY DETECTION OF COLORECTAL POLYPOSIS

In Gardner's syndrome, development of colorectal polyps before age 10 has been considered a rare event (1–3, 30, 33, 35, 108, 121–128), and textbooks stress that polyps appear during the 2nd and 3rd decades of life (129, 130). The usual procedure has, therefore, been to begin periodic sigmoidoscopic, colonoscopic, or radiologic examinations after adolescence. Of the many patients described in the literature, only 7 have been reported with colonic symptoms prior to 10 years of age (41, 126, 131, 132). We have described four children between $1^1/_2$ and $8^1/_2$ years of age who were at risk for Gardner's syndrome but were clinically asymptomatic (121). Colonoscopy and mucosal biopsy revealed adenomatous polyps and hyperplasia in the oldest two. The youngest ones showed no evidence of polyps but biopsies of apparently normal mucosa revealed early adenomatous hyperplasia.

Examination of the colon in high-risk individuals should be routine from early childhood. Semiannual colonoscopy with mucosal biopsies should be performed on all patients with adenomatous hyperplasia, and colectomy should be performed when fully developed polyposis is noted. Since colonoscopy, combined with mucosal biopsies, is a more direct method of diagnosing early adenomatous hyperplasia than a barium enema, this should be the procedure of choice.

Of primary concern is the extent to which adenomatous hyperplasia had developed in the older children. Malignant changes have been reported as early as age 9, and the incidence of carcinoma in preadolescent polyposis patients has been reported to be 6.5% (133) and 5.3% (134). These studies indicate that by deferring examination, a patient is being unnecessarily placed at risk.

## MANAGEMENT OF GASTRIC POLYPOSIS

Multiple adenomatous polyps of the gastric antrum were described as early as 1895 in familial colorectal polyposis (135). Following this, a number of similar cases were reported (136–142), including two groups described as having Gardner's syndrome (140, 142). Most, however, lack adequate histologic descriptions. During this period, Yaffee (143) reported multiple adenomatous gastric polyps in a syndrome patient, but these turned out to be fundic grand polyps (144). Not until 1971 was the occurrence of adenomatous gastric polyps in colorectal polyposis syndromes established.

The frequency of gastric lesions has been estimated at 5% (145). Recently, however, reports of gastric polyps in 55–90% of colorectal polyposis patients have come out of Japan (144, 146–149). The reason gastric polyps have not been described with greater frequency may simply reflect a failure of investigation (150). Mayo (138) reported that radiographic examination of the stomach was performed in only 9 of 95 patients, 2 of which were found to have gastric polyps. In addition, traditional barium

radiography has not been a sensitive tool for investigating small lesions. The advent of air-contrast studies and fiberoptic endoscopy has increased our ability to detect these polyps.

It must be stressed that not all gastric polyps have been histologically described as adenomas. Simple regenerative or hyperplastic polyps have been reported (146, 147, 149, 150). The most extensive series was reported by Watanabe et al (144). Among their 15 patients, 6 had adenomas; 2 had adenomas, carcinomas, and microcarcinoids; 1 had adenomas and fundic gland polyps; 5 had fundic gland polyps; and 1 had carcinomas and microcarcinoids. This suggests the malignant potential of the gastric mucosa, particularly if adenomas are present. It also suggests that gastric polyps, both adenomatous and hyperplastic, should be considered an integral part of the syndrome.

Gastric adenomas associated with the syndrome seem to be identical to nonfamilial adenomas. They occur more often in younger patients, and generally occur in the pyloric glandular mucosa, a tendency not seen in nonfamilial cases (20, 144, 146, 147). The numerous polyps within the fundic mucosa are characterized by simple hyperplasia of the fundic glands with microcysts (144). Histologically, they are nonneoplastic and may be hamartomatous. Such fundic gland polyposis has not been described in any diseases other than familial colorectal polyposis or Gardner's syndrome.

The finding of gastric polyps in these patients raises questions about their long-term course and the appropriate treatment (150). Colectomy and partial gastrectomy have been recommended when both the colon and stomach are involved (139). Some patients have had antral sparing, which would allow for partial gastrectomy (147, 150). Termination of the procedure without resection has also been recommended when polyposis involves the jejunum or ileum (139). Conservative management is also supported by the observation that these lesions may regress, as evidenced by radiographic and endoscopic evaluation, following colectomy in two patients (147).

## MANAGEMENT OF DUODENAL POLYPS AND PERIAMPULLARY CARCINOMA

In recent years, there have been reports of adenomatous duodenal polyps (20–22, 29, 30, 130, 151, 156) and duodenal or periampullary adenocarcinomas (21, 22, 29, 30, 142, 153–159) occurring in Gardner's syndrome. This has significantly altered the assumption that the risk of adenocarcinoma is confined to the colon and rectum. Compared to gastric and other small intestinal polyps, their occurrence in the area of the ampulla of Vater presents more serious diagnostic and management problems. It has been suggested that in familial colorectal polyposis there is a greater frequency of gastric polyps, while in Gardner's syndrome there is a higher frequency of duodenal polyps and periampullary carcinoma (156).

It has been estimated that 5% of all colorectal polyposis patients have extracolonic polyps (145), but this is undocumented and the true incidence is unknown. A recent study demonstrated duodenal adenomas in 7 consecutive patients (160). These are generally multiple, relatively small, and are situated in the second portion of the duodenum. They are frequently overlooked because conventional techniques are not sufficient to detect such small, asymptomatic lesions. Techniques such as hypotonic duodenography, duodenofibroscopy, and endoscopic biopsy should be used, and careful study of this region should be an integral part of the surveillance of these patients. Once duodenal polyps have been discovered, they should be surgically or endoscopically removed as their presence is an ominous harbinger of development of periampullary carcinoma (22).

The incidence of periampullary carcinoma has been established at 12% in colorectal polyposis (161) and 0.04% in the general population (162). In a recent literature review, Jones and Nance (22) discovered 16 cases with associated periampullary carcinoma (9, 29, 30, 32, 142, 153–155, 157–159, 163–165). They also reported three cases of their own plus three unreported cases in the St. Mark's registry and two in Watne's kindreds (166). They summarized salient features and noted 14 of 19 cases had Gardner's syndrome. They concluded that periampullary malignancy could develop in the absence of extracolonic polyps, approximately 15 years after onset of colorectal polyps.

Radiographic detection of periampullary tumors is difficult. The upper gastrointestinal contrast roentgenogram is the best screening test for pancreatic or periampullary disease, while periampullary tumors are best detected by hypotonic duodenography (167). These techniques, however, do not differentiate ampullary carcinoma from other periampullary tumors (168). The flexible fiberoptic gastroscope, coupled with retrograde cannulation of

the ampulla of Vater, has made preoperative differentiation possible (169). Pancreaticoduodenectomy is the treatment of choice for the good-risk patient (170), provided no hepatic or distant metastases are present (171). Patients receiving this treatment have 10- and 15-year survival of 35 and 24%, respectively, if no lymph node metastases are present (172). If local lymph nodes are involved, the 5-year survival is 9.5%.

## MANAGEMENT OF JEJUNAL AND ILEAL POLYPS

While duodenal polyps pose potentially serious problems for Gardner's syndrome patients, the rare occurrence of jejunal and ileal polyps has been considered a less serious problem. While this may be true, the occurrence of polyps in this portion of the small bowel cannot be disregarded. A few patients have been reported with jejunal and ileal carcinomas (173–176), and several reviews have suggested polyps may occur anywhere in the small bowel (6, 38). For the most part, polyps are concentrated in the terminal ileum and consist of either hyperplastic lymphoid polyps or true adenomas.

Lymphoid hyperplasia of the terminal ileum has been reported in a number of patients (23, 165, 177–183). In these benign polyps, there is hyperplasia of the lymphoid follicles in the mucosa and submucosa with no atypia or invasive characteristics. It has been considered to represent a normal inflammatory response of lymphoid tissue to a variety of stimuli (184). In some cases, these lesions may regress spontaneously (185–188). Radiologically, they have been characterized by a fleck of barium at the center of the polyp which represents umbilication at the apex of the lymphoid nodule (180). Multiple biopsies, however, are the only reliable way of distinguishing adenomas from lymphoid polyps. Early investigators advocated treatment with radiotherapy and chemotherapy, with no appreciable results (187). Local excision has been curative for scattered or isolated polyps (189). Radical surgical intervention is only indicated when the diagnosis is in doubt or complications ensue (190). A genetic factor has been demonstrated in the etiology of this condition, and a definite link with Gardner's syndrome exists (183).

Adenomatous polyps of the ileal mucosa are a rare finding in Gardner's syndrome. Recently, however, nine patients were reported with ileal adenomas 2–26 years after colectomy (24). In seven they occurred proximal to an ileorectal anastomosis, while in two they occurred proximal to or in an ileostomy. This confirms that the ileal mucosa is susceptible to adenoma formation, expecially following colectomy. The adenomas present a variety of histologic appearances including epithelial proliferation on ileal villi, polypoid tubular adenomas, and villous adenomas. Evidence suggests that they develop after surgery and are pathologically related to the altered anatomy. Since adenomas can form in the distal ileum, this region should be examined periodically after colectomy. On the other hand, the adenomas were small and the risk of carcinoma of the small bowel distal to the duodenum appears to be minimal. As a result, resection of the ileum at colectomy or aggressive removal of all ileal lesions does not seem warranted.

## MANAGEMENT OF DESMOID TUMORS AND MESENTERIC FIBROMATOSIS

Desmoid tumors have been defined as nonmetastasizing, locally invasive, benign fibrous tissue tumors that arise in the musculoaponeurotic structures throughout the body. Grossly, they are characterized by an ill-defined margin, lack of encapsulation, and infiltration into surrounding muscle and fascia. Microscopically, they are composed of mature fibroblasts which are uniform in size and shape. At the periphery, fibrous tissue extends between muscle fasicles, eventually isolating and engulfing groups of muscle fibers which produce multinucleate giant cells.

In the general population, desmoid tumors are rare. Only 17 abdominal wall desmoids were found among 50,346 cases of neoplastic disease for a gross hospital incidence of 0.03% (191). In Sweden, the incidence was estimated to be 2 cases/year/million population (192). Smith (17), however, reported desmoids in 3.5% of his Gardner's syndrome patients. More recently, the incidence has been reported to range from 17 to 29% (124, 193, 194).

Classically, desmoids were considered to be tumors of the anterior abdominal wall which develop as a result of trauma, but it is now recognized that they can appear in musculoaponeurotic structures throughout the body (195, 196). Both abdominal and extraabdominal desmoids have been associated with Gardner's syndrome (16, 194). Mesenteric and retroperitoneal fibromatosis has also been reported

in syndrome patients (18, 193, 197), and this abdominal proliferation of fibrous tissue should be considered an impressive component of the syndrome. In most cases of fibromatosis, there is a history of intestinal surgery. The interval between original surgery and recognition of the mesenteric mass may vary from 3 months to 5 years (18).

Successful management of desmoids has been difficult because of their benign histologic appearance combined with the potential to attain large size, the tendency to aggressive infiltration of adjacent tissue, and the risk of recurrence. The recurrence rate has been estimated at 27–57% (189, 197–199) and has led to the use of radical excision as the treatment of choice (200). This may include removal of a margin of healthy tissue which may leave a large defect to be bridged. Recurrences are generally regarded as evidence of incomplete surgery, but it is best to preserve major blood vessels and nerves since these are normally not involved in the tumor, although they may be completely surrounded (198, 201). The same principle of wide excision, however, is very hard to apply to retroperitoneal and mesenteric tumors. Nevertheless, large ones have occasionally been resected (18).

Experience with radiation therapy is limited and its effectiveness has been controversial. Some reports have expressed a lack of conviction in its value (196, 200, 202) while others report successful control of inoperable desmoids (203, 204). Some have suggested that this was due to an indirect effect of radiation on ovarian function. Small local doses directly to the tumor in females did not check the growth, but larger doses to the whole abdomen had some effect. This, combined with the radioresistance of these tumors in males, tends to support this hypothesis (200). Gonatas (205) concluded that radiation therapy should be used in treatment of larger tumors and where surgical resection is incomplete, a view shared by others (206, 207). It has also been reported that radiation therapy is especially beneficial for children and young adults (208). If recurrences occur, aggressive radical surgery may still be used. The overall control rate of 81% is better than most surgical series.

Recent studies have also reported successful treatment of desmoids with drugs that affect the metabolism of cyclic AMP (209). The use of theophylline and chlorothiazide reportedly reduced the size of large pelvic and incisional desmoids and even reduced the size of some of the numerous sebaceous cysts.

## SUMMARY

Since Gardner first described the syndrome 30 years ago, considerable progress has been made in understanding and treating its various manifestations. The first clues have been found which may eventually lead to the discovery of the basic genetic and metabolic defect responsible for the various clinical manifestations. The eventual characterization of this defect will have a major impact on the basic understanding of malignant transformation. It is already apparent that a defect in normal cell growth regulation in a wide variety of cell types is involved. The demonstration of increased tetraploidy in cultured epithelioid cells, the greater sensitivity of skin fibroblasts to *in vitro* transformation, and the increased intracellular collagen production all support this hypothesis. The studies of bowel transit time, fecal bile acids and neutral sterols, and urinary phenol excretion all illustrate the genetic-environmental interaction that takes place in these patients, and the electron microscopic studies give an insight into the cellular evolution that is occurring in these premalignant tissues.

Considerable progress has been made in the management of the colorectal and extracolonic tumors in these patients. Early detection is now feasible by colonoscopy and mucosal biopsy of otherwise normal mucosa, and improved surgical techniques, including use of a Soave endorectal pull-through procedure, have been developed. In light of evidence for eventual malignant degeneration in the retained rectal mucosa, early detection and use of a Soave-type procedure is essential if ileostomy is to be avoided. The risk of upper gastrointestinal polyposis is considerable. Gastric, duodenal, jejunal, and ileal adenomas have been described in numerous patients, but the greatest risk lies in the malignant degeneration of periampullary adenomas. Hyperplastic gastric and ileal polyps have been described as well as unique fundic gland polyps in the stomach. These polyps, however, do not pose serious management problems. The development of post-surgical desmoid tumors or mesenteric fibromatosis, however, do pose serious problems and illustrate one of the many dilemmas which exist in the management of this unique genetic disorder.

## REFERENCES

1. Belleau R, Braasch JW: Genetics and polyposis. Med Clin North Am 50:379–392, 1966

2. Lockhart-Mummery HE: Intestinal polyposis: The present position. Proc R Soc Med 60:381-388, 1967
3. Bussey HJR: Gastrointestinal polyposis. Gut 11:970-978, 1970
4. Alm T, Licznerski G: The intestinal polyposes. Clin Gastroenterol 2:577-602, 1973
5. McKusick VA: Genetics and large bowel cancer. Am J Dig Dis 19:954-958, 1974
6. Erbe RW: Inherited gastrointestinal polyposis syndromes. N Engl J Med 294:1101-1104, 1976
7. Bussey HJR, Veale AMO, Morson BC: Genetics of gastrointestinal polyposis. Gastroenterology 74:1325-1330, 1978
8. Devic A, Bussey MM: Un cas de polypose adenomateuse: Generalisee a tout l'intest. Arch App Dig 6:278-289, 1912
9. Cabot RC: Case records of the Massachusetts General Hospital. Case 21061. N Engl J Med 212:263-267, 1935
10. Fitzgerald, GM: Multiple composite odontomes coincidental with other tumorous conditions: Report of a case. J Am Dent Assoc 30:1408-1417, 1943
11. Gardner EJ, Stevens F: Cancer of the lower digestive tract in one family group. Am J Hum Genet 2:41-48, 1950
12. Gardner EJ: A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. Am J Hum Genet 3:167-176, 1951
13. Gardner EJ, Plenk HP: Hereditary pattern for multiple osteomas in a family group. Am J Hum Genet 4:31-36, 1952
14. Gardner EJ, Richards RC: Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. Am J Hum Genet 5:139-147, 1953
15. Gardner EJ: Mendelian pattern of dominant inheritance for a syndrome including intestinal polyposis, osteomas, fibromas and sebaceous cysts in a human family group. Novant'anni delle Leggi Mendeliane Instituto G. Mendel. Rome, 1956, pp 231-329
16. Smith WG: Multiple polyposis, Gardner's syndrome and desmoid tumors. Dis Colon Rectum 1:323-332, 1958
17. Smith WG: Desmoid tumors in familial multiple polyposis. Mayo Clin Proc 34:31-38, 1959
18. Simpson RD, Harrison EG, Mayo CW: Mesenteric fibromatosis in familial polyposis: A variant of Gardner's syndrome. Cancer 17:526-534, 1964
19. Fader M, Kline SN, Spatz SS, Subrow HJ: Gardner's syndrome (intestinal polyposis, osteomas, sebaceous cysts) and a new dental discovery. Oral Surg 15:153-172, 1962
20. Hoffman DC, Goligher JC: Polyposis of the stomach and small intestine in association with familial polyposis coli. Br J Surg 58:126-128, 1971
21. Yao T, Iida M, Ohsato K, Watanabe H, Ornae T: Duodenal lesions in familial polyposis of the colon. Gastroenterology 73:1086-1092, 1977
22. Jones TR, Nance FC: Periampullary malignancy in Gardner's syndrome. Ann Surg 185:565-571, 1977
23. Thomford NR, Greenberger NJ: Lymphoid polyps of the ileum associated with Gardner's syndrome. Arch Surg 96:289-291, 1968
24. Hamilton SR, Bussey HJR, Mendelsohn G, Diamond MP, Pavlides G, Hutcheon D, Harbison M, Shermeta D, Morson BC, Yardley JH: Ileal adenomas after colectomy in nine patients with adenomatous polyposis coli/Gardner's syndrome. Gastroenterology 77:1252-1257, 1979
25. Haggitt RC, Booth JL: Bilateral fibromatosis of the breast in Gardner's syndrome. Cancer 25:161-166, 1970
26. Camiel MR, Mule JE, Alexander LL, Benninghoff DL: Association of thyroid carcinoma with Gardner's syndrome in siblings. N Engl J Med 278:1056-1058, 1968
27. Smith WG: Familial multiple polyposis: Research tool for investigating the etiology of carcinoma of the colon? Dis Colon Rectum 11:17-31, 1968
28. Keshgegian AA, Enterline HT: Gardner's syndrome with duodenal adenomas, gastric adenomyoma and thyroid papillary-follicular adenocarcinoma. Dis Colon Rectum 21:255-260, 1978
29. MacDonald JM, Davis WC, Crago HR, Berk A: Gardner's syndrome and periampullary malignancy. Am J Surg 113:425-430, 1967
30. Coli RD, Moore JP, LaMarche PH, DeLuca FG, Thayer WR: Gardner's syndrome: A revisit to a previously described family. Am J Dig Dis 15:551-568, 1970
31. Naylor EW, Gardner EJ: Adrenal adenomas in a patient with Gardner's syndrome (submitted for publication)
32. Hughes ESR, Hueston JT: Desmoid tumour in familial polyposis of the colon: Report of a case. Aust NZ J Surg 30:131-139, 1960
33. Pierce E, Weisbold T, McKusick VA: Gardner's syndrome: Formal genetics and statistical analysis of a large Canadian kindred. Clin Genet 1:65-80, 1970
34. Pierce ER: Some genetic aspects of familial multiple polyposis of the colon in a kindred of 1,422 members. Dis Colon Rectum 11:321-329
35. Veale AMO: Intestinal polyposis. Eugenics Laboratory Memoirs (Galton Laboratory), Vol 40. Cambridge University Press, 1965
36. Duhamel J, Berthon G, Dubarry JJ: Etude mathematique de l'heredite de la polypose rectocolique. J Genet Hum 9:65-1960
37. Naylor EW, Gardner EJ: Penetrance and expressivity of the gene responsible for the Gardner syndrome. Clin Genet 11:381-393, 1977
38. McKusick VA: Genetic factors in intestinal polyposis. J Am Med Assoc 182:271-277, 1962
39. Sachatello CR: Familial polyposis of the colon: I. Leukocytic chromosome determinations—report of a patient with familial polyposis of the colon and Klinefelter's syndrome. Dis Colon Rectum 13:368-371, 1970
40. Ushio K, Saragawa M, Doi H, Yamada T, Ichikawa H, Hojo K, Koyama Y, and Sano R: Lesions associated with familial polyposis coli. Studies of lesions of the stomach, duodenum, bones and teeth. Gastrointest Radiol 1:67-80, 1976
41. Johnson JG, Watne AL, Zimmerman B: Gardner's syndrome. GP 40:109-115, 1969
42. Danes BS, Krush AJ, Gardner EJ: Is Gardner syndrome a distinct genetic disorder? (letter). Lancet 2:925, 1977
43. Veale AMO: Possible autosomal linkage in man. Nature 182:409-410, 1958
44. McConnell TS, Parsons L Jr: Chromosome evaluation in familial polyposis of the colon. Rocky Mt Med J 65:51-53, 1968
45. Messinetti S, Zelli GP, Marcellino LR, Alcini E: Benign and malignant epithelial tumors of the gastorenteric tract—chromosome analysis in study and diagnosis. Cancer 21:1000-1010, 1968
46. Enterline HT, Arvan DA: Chromosome constitution of adenoma and adenocarcinoma of the colon. Cancer 20:1746-

1759, 1967
47. Lubs HA, Kotter S: The prognostic significance of chromosome abnormalities in colon tumors. Ann Intern Med 67:328-336, 1967
48. Baker MC, Atkins NB: Chromosome abnormalities in polyps and carcinomas of the large bowel. Proc R Soc Med (Suppl) 63:9-10, 1970
49. Mark J, Mitelman F, Dencker H, Norryd C, Tranberg KG: The specificity of the chromosomal abnormalities in human colonic polyps—a cytogenetic study of multiple polyps in a case of Gardner's syndrome. Acta Pathol Microbiol Scand 81A:85-90, 1973
50. Mitelman F, Mark J, Nilsson PG, Dencker H, Norryd C, Tranberg KG: Chromosome banding pattern in human colonic polyps. Hereditas 78:63-68, 1974
51. Danes BS: The Gardner syndrome—a study in cell cultures. Cancer 36:2327-2333, 1975
52. Danes BS: The Gardner syndrome: Increased tetraploidy in cultured skin fibroblasts. J Med Genet 13:52-56, 1976
53. Danes BS: Increased tetraploidy: Cell specific for the Gardner gene in the cultured cell. Cancer 38:1983-1988, 1976
54. Danes BS, Krush AJ: The Gardner syndrome: A family study in cell culture. J Natl Cancer Inst 58:771-775, 1977
55. Danes BS: Increased *in vitro* tetraploidy: Tissue specific within the heritible colorectal cancer syndromes with polyposis coli. Cancer 41:2330-2334, 1978
56. Danes BS, Gardner EJ: The Gardner syndrome: A cell culture study on kindred 109. J Med Genet 15:346-351, 1978
57. Turner JH, Wald N: Endoreduplication and disease. Lancet 1:915, 1965
58. Knudson AG Jr, Strong LC, Anderson DE: Heredity and cancer in man. *In* Progress in Medical Genetics, Vol 9, AG Steinberg, AG Bearn (eds). New York, Grune and Stratton, 1973, pp 113-118
59. Kopelovich L, Pfeffer L, Lipkin M: Recent studies on the identification of proliferative abnormalities and of oncogenic potential of cutaneous cells in individuals at increased risk of colon cancer. Semin Oncol 3:369-372, 1976
60. Kopelovich L: Phenotypic markers in human skin fibroblasts as possible diagnostic indices of hereditary adenomatosis of the colon and rectum. Cancer 40:2534-2541, 1977
61. Pfeffer LM, Kopelovich L: Differential genetic susceptibility of cultured human skin fibroblasts to transformation by Kirsten murine sarcoma virus. Cell 10:313-320, 1977
62. Kopelovich L, Conlon S, Pollack R: Defective organization of actin in cultured skin fibroblasts from patients with inherited adenocarcinoma. Proc Natl Acad Sci USA 74:3019-3022, 1977
63. Kopelovich L, Pfeffer LM, Bias N: Growth characteristics of human skin fibroblasts *in vitro*—a simple experimental approach for the identification of hereditary adenomatosis of the colon and rectum. Cancer 43:218-223, 1949
64. Watne AL, Johnson R: Bowel transit time in patients with Gardner's syndrome. Dis Colon Rectum 17:52-54, 1974
65. Hinton JM, Lennard-Jones JE, Young AC: A new method for studying gut transit times using radiopaque markers. Gut 10:842-847, 1969
66. Morson BC: Evolution of cancer of the colon and rectum. Cancer 34:845-849, 1974
67. Reddy BS, Mastromarino A, Wynder EL: Further leads on metabolic epidemiology of large bowel cancer. Cancer Res 35:3403-3406, 1975
68. Reddy BS, Weisburger JH, Wynder EL: Effect of high risk and low risk diets for colon carcinogenesis on fecal microflora and steroids in man. J Nutr 105:878-884, 1975
69. Reddy BS, Wynder EL: Large bowel carcinogenesis—fecal constituents of populations with diverse incidence rates of colon cancer. J Natl Cancer Inst 50:1437-1442, 1973
70. Wynder EL, Reddy BS: Metabolic epidemiology of colorectal cancer. Cancer 34:801-806, 1974
71. Hill MJ, Drasar BS, Williams REO, Meade TW, Cox A, Simpson JEP, Morson BC: Fecal bile acids and clostridia in patients with cancer of the large bowel. Lancet 1:535-539, 1975
72. Ermala P, Setala K, Ekwall P: Gastric absorption of 3,4-benzpyrene. I. The effect of physiological processes on absorption. Cancer Res 11:753-757, 1951
73. Weil-Malkerie H, Dickens F: Factors affecting carcinogenesis IV. The effect of tricoprylin solutions of cholesterol and phospholipins. Cancer Res 6:171-178, 1946
74. Altman RFA, Pugachiov O, Ballini-Kerr I: Phospholipids (PL) retard and cholesterol (Chol) promotes the formation of tumours induced by carcinogenic hydrocarbons. Z Naturforsch 23:1277-1279, 1968
75. Chomchai D, Bhadrachari N, Nigro ND: The effect of bile on the induction of experimental intestinal tumors in rats. Dis Colon Rectum 17:310-312, 1974
76. Watne AL, Core SK: Fecal steroids in polyposis coli and ileorectostomy patients. J Surg Res 19:157-161, 1975
77. Bone E, Drasar BS, Hill MJ: Gut bacteria and their metabolic activities in familial polyposis. Lancet 1:1117-1120, 1975
78. Watne AL, Lai HL, Mance T, Core S: Fecal Steroids and Bacterial Flora in Polyposis Coli Patients. Society for Surgery of the Alimentary Tract, San Antonio, Texas, 1975
79. Reddy BS, Mastromarino A, Gustafron C, Lipkin M, Wynder EL: Fecal bile acids and neural sterols in patients with familial polyposis. Cancer 38:1695-1998, 1976
80. Bone E, Tamm A, Hill M: The production of urinary phenols by gut bacteria and their possible role in the causation of large bowel cancer. Am J Clin Nutr 29:1448-1454, 1976
81. Drasar BS, Bone ES, Hill MJ, Marks CG: Colon cancer and bacterial metabolism in familial polyposis. Gut 15:824-825, 1975
82. Welsh RA: Intracytoplasmic collagen formations in desmoid fibromatosis. Am J Pathol 49:515-535, 1966
83. Allegra SR, Broderick PA: Desmoid fibroblastoma—intracytoplasmic collagenosynthesis in a peculiar fibroblastic tumor: Light and ultrastructural study of a case. Hum Pathol 4:419-429, 1973
84. Chvapil M, Hyrych J: Control of collagen biosynthesis. *In* International Review of Connective Tissue Research, DA Hall (ed). New York, Academic Press, 1968, pp 68-95.
85. Bussey HJR: Familial Polyposis Coli. Baltimore, Johns Hopkins University Press, 1975
86. Morson B: The polyp-cancer sequence of the large bowel. Proc R Soc Med 67:451-457, 1974
87. Muto T, Bussey HJ, Morson BC: The evolution of cancer of the colon and rectum. Cancer 36:2251-2269, 1975
88. Maskens AP: Histogenesis of adenomatous polyps in the human large intestine. Gastroenterology 77:1245-1251, 1979
89. Birbeck MSC, Dukes CG: Electron microscopy of rectal neoplasms. Proc R Soc Med 56:793-797, 1963
90. Lane N, Kaplan H, Pascal RR: Minute adenomatous and

hyperplastic polyps of the colon: Divergent patterns of epithelial growth with specific associated mesenchymal changes—contrasting roles in the pathogenesis of carcinoma. Gastroenterology 60:537-551, 1971
91. Filipe MI: Value of histochemical reactions for conditions of the colon and rectum. Gut 10:577-586, 1969
92. Filipe MI, Branfoot AC: Abnormal patterns of mucous secretion in apparently normal mucosa of large intestine with carcinoma. Cancer 34:282-290, 1974
93. Dawson PA, Filipe MI: An ultrastructural and histochemical study of the mucous membrane adjacent to and remote from carcinoma of the colon. Cancer 37:2388-2398, 1976
94. Dawson PA, Filipe MI, Bussey HJR: Ultrastructural features of the colonic epithelium in familial polyposis coli. Histopathology 1:105-113, 1977
95. Mughal S, Filipe MI: Ultrastructural study of the normal mucosa-adenoma-cancer sequence in the development of familial polyposis coli. J Natl Cancer Inst 60:753-768, 1978
96. Lilienthal H: Hyperplastic colitis: Extirpation of the entire colon, the upper portion of the sigmoid flexture and four inches of the ileum. Am Med 1:164, 1901.
97. Lockhart-Mummery JP: Proc R Soc Med. Sect 12, Surg, 43, 1918
98. Coffey RC: Colonic polyposis with engrafted malignancy; technic for removing the entire colon including the rectum. Ann Surg 83:364-380, 1926
99. Rankin FW, Mayo C: Carcinoma of the small bowel. Surg Gynecol Obstet 50:939-947, 1930
100. Gardner GMcG: Polyposis of the colon. Arch Surg 56:75-77, 1948
101. Wangensteen OH, Toon RW: Primary resection of the colon and rectum with particular reference to cancer and ulcerative colitis. Am J Surg 75:384-404, 1948
102. Ratvich MM: Anal ileostomy with sphincter preservation in patients requiring total colectomy for benign conditions. Surgery 24:170-187, 1948
103. Moertel CG, Hill JR, Adson MA: Surgical management of multiple polyposis—the problem of cancer in the retained bowel segment. Arch Surg 100:521-526, 1970
104. Everson TC, Allen MJ: Subtotal colectomy with ileosigmoidostomy and fulguration of polyps in retained colon. Arch Surg 69:806-817, 1954
105. Smith WG, Jackman RJ: Polyposis of the large intestine: Preservation of the terminal segment. Am J Surg 90:751-760, 1955
106. Flotte CT, O'Dell FD Jr, Coller FA: Polyposis of the colon. Ann Surg 144:165-169, 1956
107. Waugh JM, Harp RA, Spencer RJ: The surgical management of multiple polyposis. Ann Surg 59:149-154, 1964
108. Shepherd JA: Familial polyposis of the colon with special reference to regression of rectal polyposis after subtotal colectomy. Br J Surg 58:85-91, 1971
109. Schaupp EV, Volpe PA: Management of diffuse colonic polyposis. Am J Surg 124:128, 1972
110. DeCosse JJ, Adams MB, Condon RE: Familial polyposis. Cancer 39:267-273, 1977
111. Watne AL, Lai HY, Carrier J, Coppula W: The diagnosis and surgical treatment of patients with Gardner's syndrome. Surgery 82:327-333, 1977
112. Harvey JC, Quan SQ, Stearns MW: Management of familial polyposis with preservation of the rectum. Surgery 84:476-482, 1978
113. Gingold BS, Jagelman D, Turnbull RB: Surgical management of familial polyposis and Gardner's syndrome. Am J Surg 137:54-56, 1979
114. Ratvich MM, Sabiston DC: Anal ileostomy with preservation of the sphincter. Surg Gynecol Obstet 84:1095-1099, 1947
115. Ratvich MM, Handelsman JC: One stage resection of entire colon and rectum for ulcerative colitis and polypoid adenomatosis. Bull Johns Hopkins Hosp 88:59-82, 1951
116. Soave F: Hirschsprung's disease: a new surgical technique. Arch Dis Child 39:116-124, 1964
117. Katz J: An operation for multiple polyposis with preservation of rectal function. Int Surg 51:202-209, 1969
118. Sofaie-Shirazi S, Soper RT: Endorectal pullthrough procedure in the surgical treatment of familial polyposis coli. J Pediatr Surg 8:711-716, 1973
119. Wolfstein IH, Dreznik ZJ, Avigad IS: Total colectomy and anal ileostomy in multiple polyposis coli. Arch Surg 113:1101-1103, 1978
120. Heimann T, Beck AR, Greenstein AJ: Familial polyposis coli—management by total colectomy with preservation of continence. Arch Surg 113:1104-1106, 1978
121. Naylor EW, Lebenthal E: Early detection of adenomatous polyposis coli in the Gardner syndrome. Pediatrics 63:222-227, 1979
122. Jones EL, Cornell WP: Gardner's syndrome: Review of the literature and report on a family. Arch Surg 92:287-300, 1966
123. Gumpel RC, Carballo JD: A new concept of familial adenomatosis. Ann Intern Med 45:1045-1058, 1956
124. Kelly PB, McKinnon DA: Familial multiple polyposis of the colon: A review and initial description of a large kindred. McGill Med J 30:67-85, 1961
125. Cramer LM: Gardner's syndrome. Plast Reconstr Surg 29:402-407, 1962
126. Weary PE, Linthicum A, Cawley EP, Graham GF: Gardner's syndrome: A family group study and review. Arch Dermatol 90:20-30, 1964
127. Leppard B, Bussey HJR: Epidermoid cysts, polyposis coli and Gardner's syndrome. Br J Surg 62:387-393, 1975
128. Marshak RH, Lindner AE, Maklansky D: Familial polyposis. Am J Gastroenterol 67:177-189, 1977
129. Spiro HM: Clinical Gastroenterology. New York, Macmillan, 1970, p 853
130. Stauffer JQ: Heritable multiple polyposis syndromes of the gastrointestinal tract. *In* Gastrointestinal Diseases, MH Sleisenger, JS Fordtran (eds). Philadelphia, Saunders, 1973, p 1055
131. Alm T, Dencker H, Lunderquist A, Mark J, Mitelman F, Norryd C, Tranberg KG: Gardner's syndrome. Acta Chir Scand 139:660-665, 1973
132. Gorlin RJ, Chaudhry AP: Multiple osteomatosis, fibromas, lipomas and fibrosarcomas of the skin and mesentery; epidermoid inclusion cysts of the skin, leiomyomas, and multiple intestinal polyposis: A heritable disorder of the connective tissue. N Engl J Med 263:1151-1158, 1960
133. Reed TE, Neel JV: A genetic study of multiple polyposis of the colon (with an appendix deriving a method of estimating relative fitness). Am J Hum Genet 7:236-263, 1955
134. Abramson DJ: Multiple polyposis in children: A review and a report of a case in a 6-year-old child who had associated nephrosis and asthma. J Pediatr Surg 61:288-301, 1967

135. Hauser G: Uber Polyposis Intestinalis Adenomatosa und deren Beziehungen zur Krebsentwicklung. Arch Klin Med 55:429-448, 1895
136. Wechselmann L: Polyp un Carcinom in Magen-Darmkanal. Beitr Klin Chir 70:855-904, 1910
137. Halsted JA, Harris EJ, Bartlet MK: Involvement of the gastrointestinal tract. Report of a family. Gastroenterology 15:763-770, 1950
138. Mayo CW, DeWeerd JH, Jackman RJ: Diffuse familial polyposis of the colon. Surg Gynecol Obstet 93:87-96, 1951
139. Boley SJ, McKinnon WM, Marzulli VF: The management of familial gastrointestinal polyposis involving stomach and colon. Surgery 50:691-696, 1961
140. Martel AJ, Bonanno CA: Multiple polyposis of the gastrointestinal tract with osteoma and soft-tissue tumours. Am J Dig Dis 13:588-591, 1946
141. Yonemoto RH, Slayback JR, Byron RL Jr, Rosen RB: Familial polyposis of the entire gastrointestinal tract. Arch Surg 99:427-434, 1969
142. Parks, TG, Bussey HJR, Lockhart-Mummery HF: Familial polyposis coli associated with extracolonic abnormalities. Gut 11:323-328, 1970
143. Yaffee HS: Gastric polyposis and soft-tissue tumours. Arch Dermatol 89:806-808, 1969
144. Watanabe H, Enjoji M, Yao T, Ohsato K: Gastric lesions in familial adenomatosis coli—their incidence and histologic analysis. Hum Pathol 9:269-283, 1978
145. Estes WL Jr: Familial polyposis and carcinoma of the colon. Ann Surg 127:1035-1045, 1948
146. Utsunomiya J, Maki T, Hamaguchi E, Aoki N: Gastric lesion of familial polyposis of the large intestine. Cancer 34:745-754, 1974
147. Ushio K, Okazaki M, Takasugi T, Hagiwara K, Matsue H, Sasaguawa M, Doi I, Yamada T, Ichikawa H: Lesions associated with so-called familial polyposis of the colon. Stom Intest 9:1137-1148, 1974
148. Ohsata K, Itoh H, Ikesda S, Nishimura M, Yao T, Jida M, Watanabe H: Follow-up study on upper gastrointestinal lesions in familial polyposis of the colon. Jpn J Gastroenterol 72:141-148, 1974
149. Itai Y, Kogure T, Okuyama Y, Muto T: Radiographic features of gastric polyps in familial adenomatosis coli. Am J Roentgenol 128:73-76, 1977
150. Denzler TB, Harned RK, Pergam CJ: Gastric polyps in familial polyposis coli. Radiology 130:63-66, 1979
151. Kaplan BJ: Gardner's syndrome: Heredofamilial adenomatosis associated with 'soft and hard' fibrous tumors and epidermal cysts. Dis Colon Rectum 4:252-262, 1961
152. McCaughan JS Jr, Soder PD, Biddler LR: Gardner's syndrome: Report of two unrelated cases and discussion of management of the disease. Dis Colon Rectum 9:286-292, 1966
153. Duncan BR, Dohner VA, Priest JH: The Gardner syndrome: Need for early diagnosis. J Pediatr 72:497-505, 1968
154. Melmed RN, Bouchier IAD: Duodenal involvement in Gardner's syndrome. Gut 13:524-527, 1972
155. Schnur P, David E, Brown PW Jr, Beahrs OH, ReMine WH, Harrison EG Jr: Adenocarcinoma of the duodenum and the Gardner syndrome. J Am Med Assoc 223:1229-1232, 1973
156. Schulman A: Gastric and small bowel polyps in Gardner's syndrome and familial polyposis coli. J Can Assoc Radiol 27:206-209, 1976
157. Carter BN, Horsley GW, Horsley JS, Hughes RD: A new form of diffuse familial polyposis: A probable genetic explanation. Ann Surg 167:942-946, 1968
158. McFarland PH Jr, Scheetz WL, Kinsley RE: Gardner's syndrome: Report of two families. J Oral Surg 26:632-638, 1968
159. Mir-Madjlessi SH, Farmer RG, Hawk WA, Turnbull RB Jr: Adenocarcinoma of the ampulla of Vater associated with familial polyposis coli. Dis Colon Rectum 16:542-546, 1973
160. Ohsato K, Yao T, Watanabe H, Iida M, Itoh H: Small intestinal involvement in familial polyposis diagnosed by operative intestinal fiberscopy—report of four cases. Dis Colon Rectum 20:414-420, 1977
161. Bussey HJR: Extracolonic lesions associated with polyposis coli. Proc R Soc Med 65:294, 1972
162. Longmire WP Jr: Periampullary tumors. J R Coll Surg Edinburgh 18:131-136, 1972
163. Dorazio RA, Whelan TJ: Lymphoid hyperplasia of the terminal ileum associated with familial polyposis coli. Ann Surg 171:300-302, 1970
164. Capps WF Jr, Lewis MI, Gazzaniga DA: Carcinoma of the colon, ampulla of Vater and urinary bladder associated with familial multiple polyposis: A case report. Dis Colon Rectum 11:298-305, 1968
165. Dodds WJ, Lydon SB: Intestinal polyposis syndromes. CRC Crit Rev Clin Radiol Nucl Med 5:295-336, 1974
166. Watne AL, Core SK, Carrier JM: Gardner's syndrome. Surg Gynecol Obstet 141:53, 1975
167. Eaton SB, Fleischili DJ, Pollard JJ: The comparison of current radiologic approaches to the diagnosis of pancreatic diseases. N Engl J Med 279:389-396, 1968
168. Treadwell TA, Jiminez-Chapa JE, White RR III: Carcinoma of the ampulla of Vater. South Med J 71: 365-366, 1978
169. Gaisford WD: Proceedings: Endoscopic cannulation of the papilla of Vater. Arch Surg 108:519-525, 1974
170. Whipple AO, Parsons WB, Mullins CR: Treatment of carcinoma of ampulla of Vater. Ann Surg 102:763-779, 1935
171. Ingram IW, Davis LWC: Primary carcinoma of the jejunum. Am J Surg 87:747-753, 1954
172. Heffernon EW, Metcalfe O, Schwarz HJ: Polyposis of the small and large bowel with carcinoma in a villous polyp of the jejunum: Report of a case. Gastroenterology 42:60-62, 1962
173. Ross EJ, Mara JE: Small bowel polyps and carcinoma in multiple intestinal polyposis. Arch Surg 108:736-738, 1974
174. Case Records of the Massachusetts General Hospital (Case 47-1978). N Engl J Med 299:1237-1245, 1978
175. Thomas KE, Watne AL, Johnson JG, Roth E, Zimmerman B: Natural history of Gardner's syndrome. Am J Surg 115:218-226, 1968
176. VanHoutte JJ: Polypoid lymphoid hyperplasia of the terminal ileum in patients with familial polyposis coli and with Gardner's syndrome. Am J Roentgenol Radium Ther Nucl Med 110:340-342, 1970
177. Grunberg J, Mackman S: Multiple lymphoid polyps in familial polyposis. Ann Surg 175:552-554, 1972
178. Neitzschman HR, Genet E, Nice CM Jr: Two cases of familial polyposis simulating lymphoid hyperplasia. Am J Roentgenol Radium Ther Nucl Med 119:365-368, 1973
179. Tsuchiya M, Asakura H, Takagi K, Morita A, Morishita T, Hibi T, Baba S, Yagita A, Teramoto T, Mikata A: Polypo-

sis of the large intestine and stomach accompanied by multiple cancer of the large intestine and lymphoid polyposis of the terminal ileum. Jpn J Gastroenterol 71:1256–1263, 1974
180. Shull LN Jr, Fitts CT: Lymphoid polyposis associated with familial polyposis and Gardner's syndrome. Ann Surg 180:319–322, 1974
181. Venkitachalam PS, Hirsch E, Elguezabal A, Littman L: Multiple lymphoid polyposis and polyposis of the colon. Dis Colon Rectum 21:336–341, 1978
182. Heller EL, Lewis JR: Benign lymphoma of rectum. Am J Pathol 26:436–471, 1950
183. Cosens CG: Gastrointestinal pseudoleukemia: Case report. Ann Surg 148:129–133, 1958
184. Collins JO, Folk M, Guibone R: Benign lymphoid polyposis of colon: Case report. Pediatrics 38:897–899, 1966
185. Louw JH: Polypoid lesions of large bowel in children with particular reference to benign lymphoid polyposis. J Pediatr Surg 3:195–209, 1968
186. Fieber SS, Schaeffer HJ: Lymphoid hyperplasia of the terminal ileum—a clinical entity? Gastroenterology 50:83–98, 1966
187. Helwig EB, Hansen J: Lymphoid polyps (benign lymphoma) and malignant lymphoma of the rectum and anus. Surg Gynecol Obstet 92:233–243, 1951
188. Swartley RN, Stayman JW Jr: Lymphoid hyperplasia of intestinal tract requiring surgical intervention. Ann Surg 155:238–240, 1962
189. Pack GT, Ehrlich HE: Neoplasms of the anterior abdominal wall with special consideration of desmoid tumors: Experience with 391 cases and a collective review of the literature. Surg Gynecol Obstet (Int Abstracts Surg) 79:177–198, 1944
190. Dahn I, Jonsson N, Lundh G: Desmoid tumours: A series of 33 cases. Acta Chir Scand 126:305–314, 1963
191. Schiffman MA: Familial multiple polyposis associated with soft-tissue and hard-tissue tumors. J Am Med Assoc 179:514–522, 1962
192. Naylor EW, Gardner EJ, Richards RC: Desmoid tumors and mesenteric fibromatosis in Gardner's syndrome. Report of kindred 109. Arch Surg 114:1181–1185, 1979
193. Nichols RW: Desmoid tumors: A report of thirty-one cases. Arch Surg 7:227–236, 1923
194. Musgrove JE, MacDonald JR: Extra-abdominal desmoid tumors: Their differential diagnosis and treatment. Arch Pathol 45:513–540, 1948
195. Shepherd JA: Familial polyposis of the colon with associated connective tissue tumors. J R Coll Surg 4:31–38, 1958
196. Enzinger FM, Shiraki M: Musculo-aponeurotic fibromatosis of the shoulder girdle (extra-abdominal desmoid): Analysis of thirty cases followed-up for ten or more years. Cancer 20:1131–1140, 1967
197. Hunt RTN, Morgan HC, Ackerman LV: Principles in the management of extra-abdominal desmoids. Cancer 12:825–836, 1960
198. McAdam WAF, Goligher JC: The occurrence of desmoids in patients with familial polyposis coli. Br J Surg 57:618–631, 1970
199. Gerstman KE, Nimberg GA: Extra-abdominal desmoid tumor: A case report. Clin Orthop 64:250–254, 1969
200. Cole NM, Guiss LW: Extra-abdominal desmoid tumors. Arch Surg 98:530–533, 1969
201. Pack GT, Ariel IM: Tumors of the Soft Somatic Tissues: A Clinical Treatise. New York, Hoeber-Harper, 1961
202. Weinstein EC, Payne WS, Soule EH: Surgical treatment of desmoid tumor of the chest wall. J Thorac Cardiovasc Surg 46:242–251, 1963
203. Gonatas NK: Extra-abdominal desmoid tumors. Arch Pathol 71:214–221, 1961
204. Hill DR: Radiation therapy of desmoid tumors. Am J Roentgenol Radium Ther Nucl Med 117:84–89
205. Benninghoff D, Robbins R: The nature and treatment of desmoid tumors. Am J Roentgenol Radium Ther Nucl Med 91:132–137, 1964
206. Wara WM, Phillips TL, Hill DR, Bovill E Jr, Luk KH, Lichter AS, Leibel SA: Desmoid tumors: Treatment and progress. Radiology 124:225–226, 1977
207. Waddell WR: Treatment of intra-abdominal and abdominal wall desmoid tumors with drugs that affect the metabolism of cyclic 3′,5′-adenosine monophosphate. Ann Surg 181:299–302, 1975