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Reports concerning the natural history,  
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## Three Varieties of Hereditary Intestinal Polyposis\*

*file original under  
Peutz-Jeghers Syndrome*

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*CR - Polyposis of Colon  
CR<sub>2</sub> - Gardner's Syndrome -*

### INTRODUCTION

Intestinal polyposis occurs in both hereditary and non-hereditary forms. The Gardner syndrome, familial polyposis coli, and the Peutz-Jeghers syndrome are the three most frequent hereditary forms. Here we report an instructive case of each.

#### THE GARDNER SYNDROME WITH DEATH AT AGE 26 FROM EXTENSIVE ABDOMINAL FIBROMA

The Gardner syndrome (GS) (1) is characterized by adenomatous premalignant polyps in the colon and less often in the stomach and small intestine, osteomata of skull and jaws, subcutaneous and mesenteric fibromata (desmoids) and epidermoid cysts. The following report demonstrates the difficulties in managing a patient who had extensive abdominal fibromatosis as the main feature of GS.

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### Case Report

The patient was a white male dental student who died at the age of 26 years. Supernumerary teeth, the first manifestation of GS, were detected at age 13. At 18 years a mandibular osteoma was excised. At age 24 he developed dysphagia, regurgitation and a burning epigastric sensation. An upper gastrointestinal series showed a retroperitoneal mass, and a barium enema demonstrated multiple colonic polyps. Subtotal colectomy, with partial resection of a benign intra-abdominal fibroma, and a splenectomy were performed at another hospital. Post-operative complications included septicemia, a subphrenic abscess which required drainage, and an enterocutaneous fistula from the proximal jejunum. A few months later at laparotomy an extensive diffuse fibroma was found involving the mesenteric and celiac arteries, the small bowel, and the entire abdominal cavity. It could be only partially removed, and some observers considered it a well-differentiated fibrosarcoma. A few months later the patient, then aged 25 years, was seen for the first time in the Moore Clinic. None of his family was known to have intestinal polyposis, skin or other tumors, or dental abnormalities; however, his parents and two sisters repeatedly refused examination. His father and

nephrotic syndrome and erythrocytosis we have not been able to exclude a chance association between the two diseases. In addition, prolonged observation is needed to exclude the development of polycythemia vera. As evidenced by this patient's course of recurrent pulmonary emboli, erythrocytosis is not a benign condition and warrants careful follow-up with phlebotomy as needed. A review of the literature reveals that the association of renal disease with erythrocytosis is relatively common, and that the mechanism may involve hormonal stimulation of erythropoiesis by erythropoietin. Further elucidation of the kidney's role in erythropoietin synthesis and understanding of the relationship between erythrocytosis and the nephrotic syndrome await the development of a more sensitive assay for erythropoietin activity.

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Fig 1. A fibromatous mass of the abdomen in patient with the Gardner syndrome.

mother were aged 25 and 21 years, respectively, at the time of his birth.

The patient showed several soft tissue tumors on the nose, scalp, legs, feet, arms and shoulder. A drain was present on the left side of the abdomen. The surgical scar was infiltrated with fibromatous tissue, and a large, firm mass protruded from the anterior abdominal wall (Fig 1). On panoramic radiograph of the jaws, several osteosclerotic foci were found (Fig 2). Colonoscopy showed adenomatous polyps of the rectum and sigmoid.

Three months later he was admitted to The Johns Hopkins Hospital because of sepsis and purulent discharge from the abdominal catheter. An intra-abdominal abscess was found and drained. A fistulogram showed reopening of the jejunocutaneous fistula. The patient was managed conservatively, and at discharge he was afebrile with minimal drainage through the fistula.

He was readmitted two months later, again with sepsis. Laparotomy revealed an intra-abdominal abscess which was related to the enterocutaneous fistula and ex-

tended into the left upper quadrant subphrenic space. Following drainage of the abscess, a freely-draining jejunocutaneous fistula developed, necessitating intravenous hyperalimentation for several months. When the fistula failed to close, the patient again was operated on in an unsuccessful attempt to resect the fistulous tract. Because of the huge intra-abdominal fibroma, which occupied almost the entire peritoneal cavity, the fistula could not be dissected. Postoperatively the patient died of sepsis. Autopsy was not permitted.

### FAMILIAL POLYPOSIS OF THE COLON

In familial polyposis coli (FPC), multiple premalignant adenomatous polyps of the colon are not associated with extra-alimentary features.

#### Case Report

In the course of a family study, a white male, then 14 years old, was found by barium enema to have multiple polyps of the colon. Chronic diarrhea began as the first symptom at age 26. At age 28 after an episode of intestinal bleeding he underwent subtotal colectomy and ileoproctostomy with preservation of a 25 cm recto-sigmoid segment. At age 41 he was asymptomatic but sigmoidoscopy showed many rectal polyps. Total colectomy was advised but refused by the patient because he thought it would interfere with sexual function.

At age 42 when the patient was first seen in the Moore Clinic, many polyps were seen on sigmoidoscopy. Histology showed villous adenomatous polyps and adenomatous hyperplasia of the mucosa. Two months later at sigmoidoscopy numerous polyps were seen at distances of 10 to 25 cm from the anus. Colonic brushings showed mildly to moderately atypical columnar cells. Among the several biopsies of polyps and mucosa from the recto-sigmoid junction, one was found to have carcinoma *in situ*. One month later colonoscopy showed an

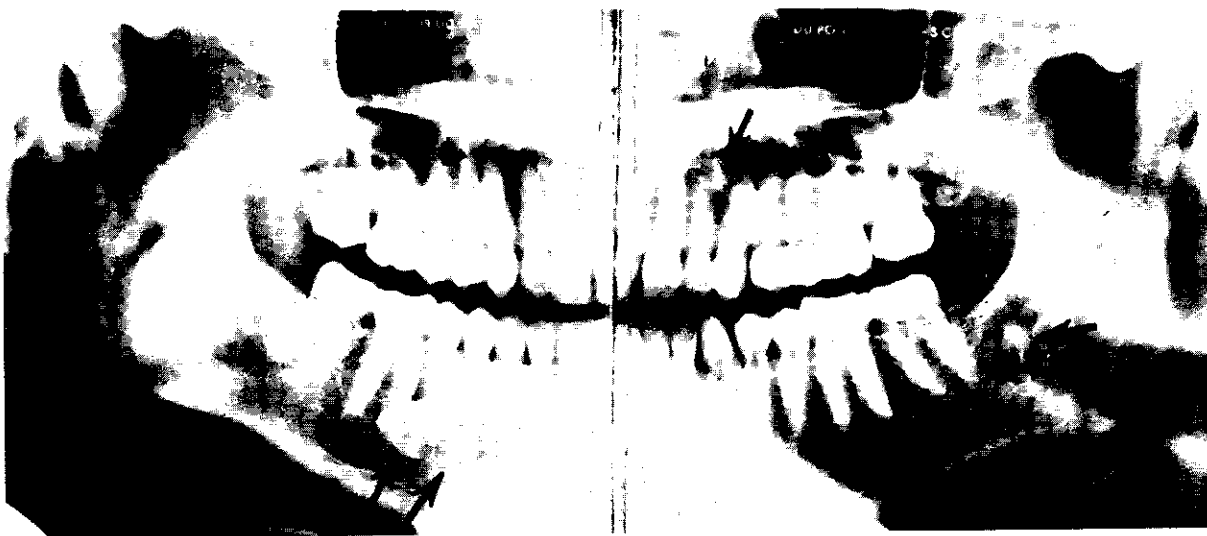


Fig 2. A panoramic radiograph of the jaws of the patient with the Gardner syndrome. Arrows indicate sclerotic jaw lesions. Radiopaque area in anterior portion of film is an artifact.

ulcerated polypoid lesion 15 to 18 cm from the anus, reported histologically as an infiltrating, poorly differentiated adenocarcinoma. Well-differentiated adenocarcinoma was reported from mucosal brushings. An abdominoperineal resection of the sigmoid and rectum was performed. A large tumor was present in the sigmoid colon, with involvement of multiple mesenteric nodes and three nodules palpable in the liver. The tumor proved to be a poorly differentiated adenocarcinoma of the colon invading the pericolonic fat, with metastases to one of three lymph nodes at level II (margin of the bowel) and one of two at level III (base of the mesentery).

The postoperative course was uneventful. He did not return for recommended chemotherapy and apparently received no treatment elsewhere. A few months later he was admitted to another hospital because of uncontrollable intestinal hemorrhage from which he succumbed. Autopsy was not performed.

### Genealogy

Thirteen of 19 members of the family over four generations had colonic polyps (Table I, Fig 3). The ages and symptoms at diagnosis, the method of diagnosis, the

type of operation, and the cause of death are shown in Table I. Seven members were discovered to be affected after the patient was seen in the Moore Clinic; five of them were among his eight offspring. The average age at diagnosis was 14.7 years among these seven members.

After the proband's death, his brother (Fig 3, III-2), who had previously undergone an ileoproctostomy, chose to have a complete resection of the colon and rectum, even though carcinoma had not been detected in the remaining sigmoid and rectum. On the other hand, the proband's 24-year-old daughter (Fig 3, III-I), who had adenomatous polyps throughout the colon, persistently refused operation.

Not all of the wives of the proband were previously aware of FPC in the family. All but one of them (accounting for 7 of the proband's 8 children) were located and alerted to the risk to each child.

### THE PEUTZ-JEGHERS SYNDROME

The Peutz-Jeghers syndrome (PJS) (2) comprises polyps of the intestine, which are usually hamartomatous and localized in the jejunum, and melanin spots of the lips, oral mucosa, and digits.

TABLE I

Affected Member	Age at Diagnosis	Method(s) of Diagnosis	Symptoms at Diagnosis	Operation		Cancer		Death	
				Age	Type	Age	Type	Age	Cause
I-1	39	operation	chronic diarrhea	39	abdominal operation	39	carcinoma colon	39	colon cancer
II-1	31	operation	—	37	colectomy	37	adenocarcinoma	65	recurrent adenocarcinoma
2	24	barium enema	—	27	colostomy	27	adenocarcinoma rectum	27	adenocarcinoma with metastasis
III-1	14	barium enema	—	38	subtotal colectomy ileoproctostomy	42	adenocarcinoma sigmoid & rectum	43	adenocarcinoma sigmoid and rectum
2	15	barium enema sigmoidoscopy	—	40	ileostomy		—		—
3	5	sigmoidoscopy	—	14	ileoproctostomy		—		—
IV-1	17	barium enema colonoscopy proctostomy	—		—		—		—
2	20	colonoscopy	—		—		—		—
3	15	proctoscopy barium enema	intestinal bleeding	16	ileostomy		—		—
5	15	colonoscopy	—	15	colectomy		—		—
7	11	colonoscopy	—		—		—		—
9	11	barium enema colonoscopy proctoscopy	—		—		—		—
12	14	sigmoidoscopy	—	14	ileoproctostomy		—		—

Note: All polyps histologically examined showed an adenomatous pattern.

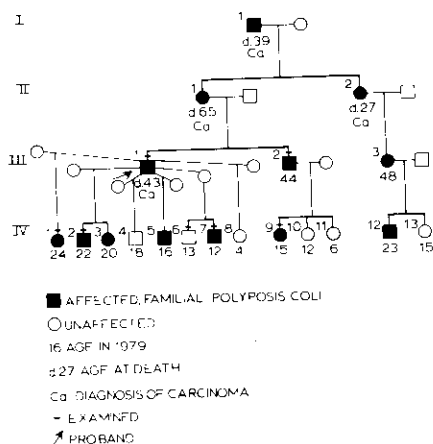


Fig 3. A partial pedigree of a family in which familial polyposis coli occurred.

Case Report

The proband (III-1, Fig 4), a white male, first developed acute abdominal pain at age 18; laparotomy showed a jejunal intussusception. About 110 cm of small bowel was resected containing multiple polyps, some of which were adenomatous. At age 24 he again developed acute abdominal pain and intestinal obstruction from intussusception, and he had a further intestinal resection. One polyp from the jejunum was adenomatous with well-differentiated adenocarcinoma. At age 28 he was first seen in the Moore Clinic. He had melanin spots on the lips and buccal mucosa (Fig 5). Neither air contrast barium enema nor colonoscopy showed polyps. At age 29 colonoscopy at the Moore Clinic showed a small adenomatous polyp in the colon. Colonoscopy in May 1979 showed several polyps in the colon and rectum; histology was most consistent with hamartoma.

Patient's Family

Six members of the family through two generations were affected with PJS (Fig 4). All six had polyps in

the small intestine, and the proband had the adenomatous type. Five of the six had had minor intussusception, three of them twice; all six had had a resection of small bowel and some had had colonic polypectomy. In one (II-7) a histologic diagnosis of adenocarcinoma ("grade I plus") in multiple jejunal polyps was made at age 20; he died at age 42 of autopsy-confirmed adenocarcinoma of the stomach. One (II-4) died of intestinal obstruction at age 16.

Six further members, without documented polyps, had mucocutaneous melanin spots. One of them (Fig 4, I-1) died at age 44 of radiologically documented gastric cancer; one (II-6) died at age 40 of metastatic carcinoma thought to be of pancreatic origin. Three of the six were progeny of a parent with the full syndrome and in one of the three (III-2), polyps were not found.

One member of the family (II-3) without spots or polyps died of breast cancer at age 55.

DISCUSSION

These three kindreds are part of an ongoing study of hereditary intestinal polyposis being conducted by the Moore Clinic in a six-state area (3). The objectives of the study include search for the basic gene-determined mechanisms, optimal methods for early detection in persons at genetic risk and approaches to the practice of preventive medicine at the level of the family. The study indicates that the Gardner syndrome is the most frequent of the three varieties; 72 families with the Gardner syndrome, 43 with familial polyposis coli and 16 with Peutz-Jeghers syndrome have been ascertained.

All three forms are inherited as autosomal dominants. The mutation in each case is presumed to be at a separate and distinct locus; no information is yet available as to the chromosomal localization of any of them. The Gardner syndrome in the first patient resulted presumably from new mutation; paternal age was not advanced, however.

Autosomal dominant disorders show a notoriously wide variability in expression, both within families and among families (4). It is to be expected that some pa-

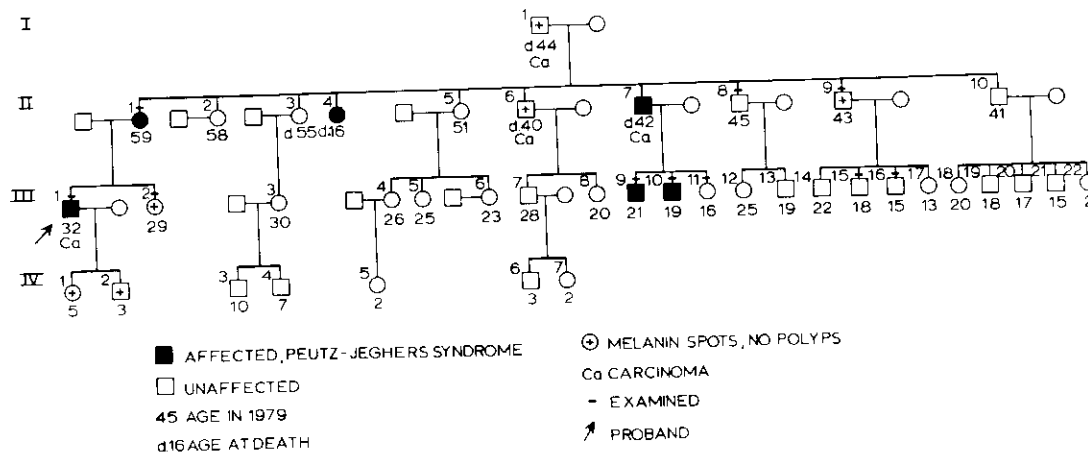


Fig 4. A partial pedigree of a family with the Peutz-Jeghers syndrome.



Fig 5. Melanin spots on lips of the proband with the Peutz-Jeghers syndrome.

tients with the Peutz-Jeghers syndrome may have only melanin spots and some have only polyps. Cases with only polyps are reported by Jeghers et al. (5). The intestinal polyposis is age-dependent in all three disorders, and the age of onset can vary widely.

Malignant degeneration of intestinal polyps is an inevitable development in all cases of familial polyposis coli and the Gardner syndrome, although carcinoma may not develop until the seventh decade in rare instances. Malignancy is, in general, uncommon in the polyps of the Peutz-Jeghers syndrome, which as a rule are hamartomatous, not adenomatous. However, the kindred reported here and others previously reported (6-10) illustrate that this syndrome also is not immune from malignancy. Polyps in the stomach, duodenum and colon in the Peutz-Jeghers syndrome are particularly suspect. (Polyps in PJS may occur even in the ureter [11].)

In familial polyposis coli and the Gardner syndrome, polyps also occur sometimes in the stomach and may give rise to gastric cancer (12, 13). The patient with the Gardner syndrome is also vulnerable to periampullary carcinoma of the duodenum (14-16), which may not originate in a premalignant polyp at that site. This observation has prompted consideration of an abnormal constituency of bile in the Gardner syndrome.

The patient with the Gardner syndrome shows a tendency to a variety of extra-alimentary neoplastic processes: the desmoid abdominal fibromatosis, mandibular osteomas and epidermoid cysts demonstrated by the patient reported here are the most frequent, but adrenal carcinoma (17), thyroid carcinoma (18) and fibromatosis of the breasts (19) have also been reported. The "malignant" nature of the abdominal fibromatosis is strikingly evidenced in the first patient and others reported (20). Although the fibromata are locally infiltrative and grow to a great size, metastasis occurs rarely if at all. On the other hand, sarcomatous change in the bone tumors of the Gardner syndrome has been observed (21, 22).

A distinctive form of ovarian tumor (8, 23) has been observed rather often in the Peutz-Jeghers syndrome.

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