THE SYNDROMES ASSOCIATED WITH MULTIPLE POLYPS OF THE GASTROINTESTINAL TRACT

1) Familial Colonic Polyposis
2) Polyposis of the Entire GI Tract
3) Gardner's Syndrome
4) Turcot-Després-St. Pierre Syndrome
5) Peutz-Jeghers Syndrome
6) Juvenile Colonic Polyposis
7) Diffuse Gastrointestinal Juvenile Polyposis

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SUMMARY OF THE MAJOR PATHOLOGICAL AND CLINICAL ASPECTS
OF THE INTESTINAL POLYPOSIS SYNDROMES

Syndrome	Type Polyp	Major Symptoms	Malignant Potential	Inheritance	Associated Lesions
Familial colonic polyposis	Adenoma	Bloody diarrhea	+	Autosomal dominant	None
Polyposis of the entire GI tract	Adenoma	Bloody diarrhea	+	?	None
Gardner's syndrome	Adenoma	Bloody diarrhea	+	Autosomal dominant	1) Bony tumors 2) Soft tissue tumors
Turcot-Després-St. Pierre syndrome	Adenoma	Bloody diarrhea CNS symptoms	probably +	? Recessive	CNS malignant tumors
Peutz-Jeghers syndrome	P-J polyp	Recurrent SB obstruction	0	Autosomal dominant	Mucocutaneous pigmentation
Juvenile colonic polyposis	Juvenile	Bloody diarrhea	0	?	None
Diffuse gastrointestinal juvenile polyposis	Juvenile	Diarrhea Edema	0	?	Alopecia Onchotropia Pigmentation

A. HISTOLOGIC FEATURES OF THE MAJOR TYPES OF POLYPS

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

One classification of the benign tumors that occur in the gastrointestinal tract is shown in Table 1, and is based on the data of Morson (1962).

TABLE 1

CLASSIFICATION OF BENIGN TUMORS OF THE INTESTINE

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

(Based on Morson, JAMA 179:316, 1962)

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

TABLE 2

HISTOLOGIC DIFFERENTIATION OF THREE MAJOR TYPES OF POLYPS

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

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

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

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

in childhood. As shown in Figure 1, this type of polyp is seen in all age groups; this is true both of the occasional single polyp and of the syndromes associated with juvenile polyposis.

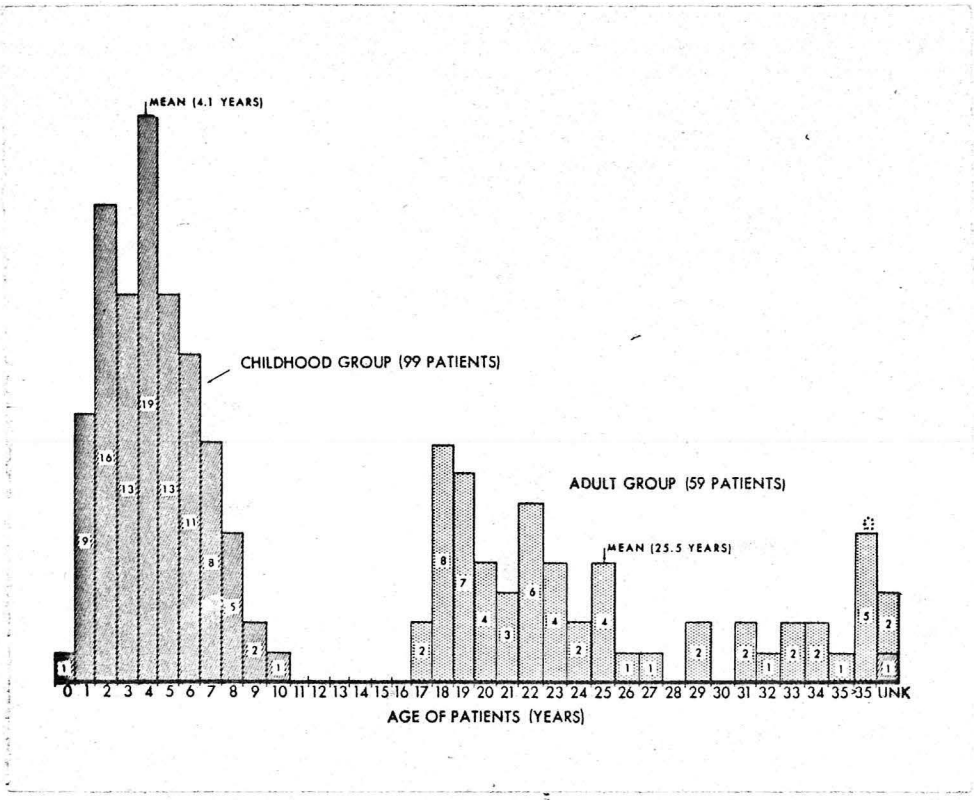

FIGURE 1. Age Distribution of Patients With Juvenile Polyps

B. PATHOPHYSIOLOGIC CONSEQUENCES OF INTESTINAL POLYPOSIS

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

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

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

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

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

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

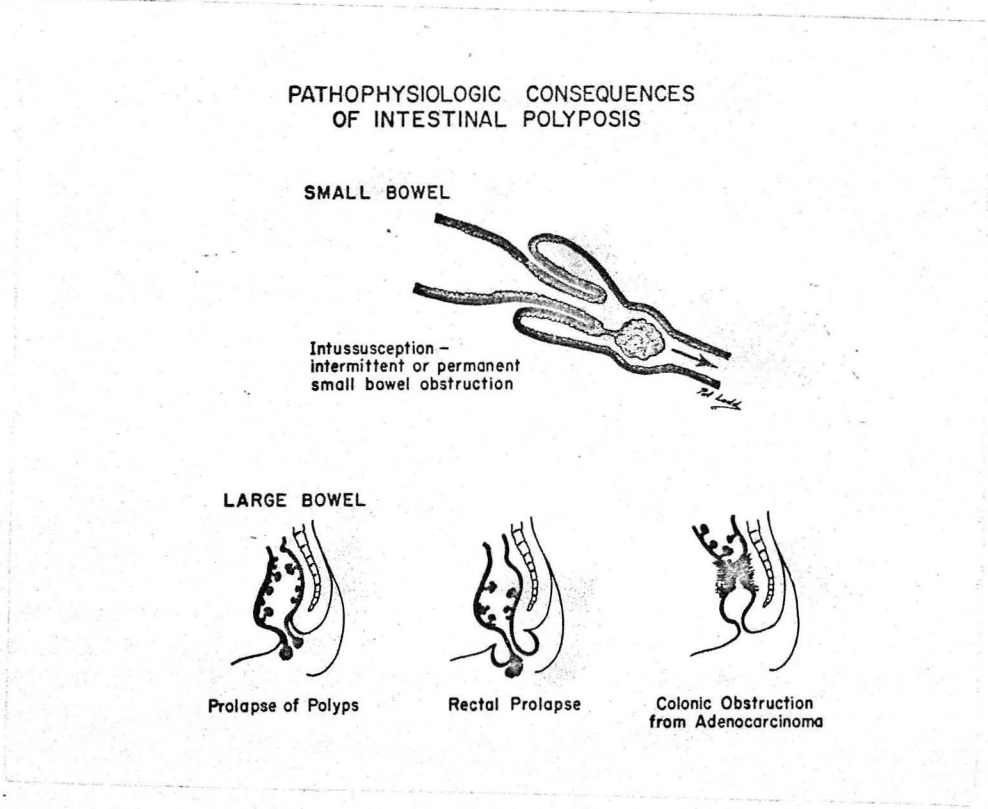

FIGURE 2. The Clinical Consequences of Polyps in the Small and Large Bowel

4. Intussusception: In those syndromes associated with polyps of the small intestine, intermittent intussusception is very common (Fig. 2). This leads to clinical episodes characterized by cramping abdominal pain, nausea, vomiting, and a fleeting abdominal mass. These episodes commonly are self-limited and the intussusception may undergo spontaneous reduction; some patients find that manual reduction of the intussusception is possible by manipulation of the abdominal mass. A non-reducible intussusception, of course, may lead to complete small intestinal obstruction requiring surgery.

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

C. FAMILIAL COLONIC POLYPOSIS

As illustrated in Figure 3, this disorder is associated with multiple adenomatous polyps involving primarily or exclusively the colon. Within affected families, some individuals are found who have thousands of sessile and pedunculated polyps involving the entire colon, so that no normal mucosa is visible, while other individuals will have fewer, more discrete, pedunculated adenomas. Occasionally, as few as 10 or 15 polyps may be seen in an affected member of a known family possessing this disorder. Rarely, an associated adenomatous polyp has been reported in the terminal ileum. No prognostication can be based upon the number of adenomatous polyps. Adenocarcinoma may develop early in an affected individual having relatively few polyps, or, alternatively, patients with thousands of polyps may live for a relatively long time without the development of malignancy.

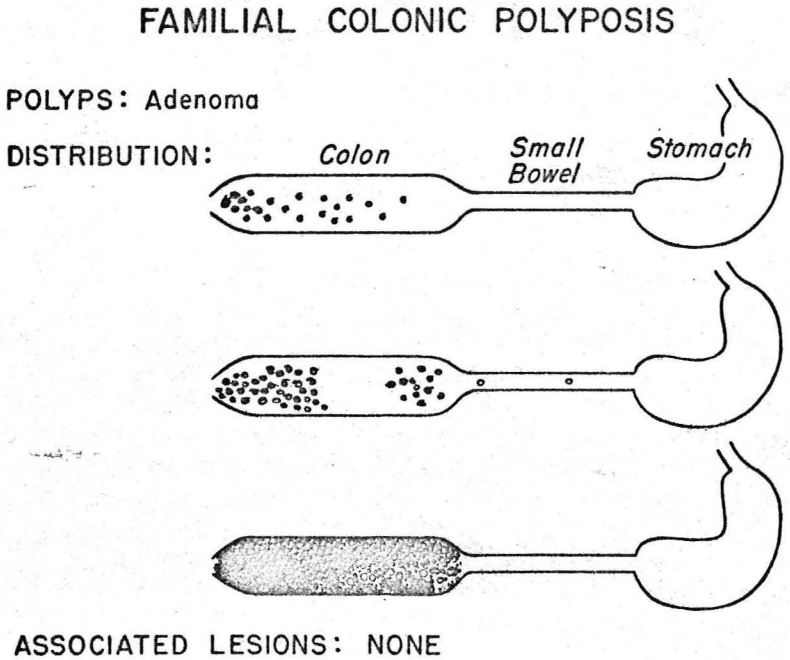

FIGURE 3. Distribution of Polyps in Familial Colonic Polyposis

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

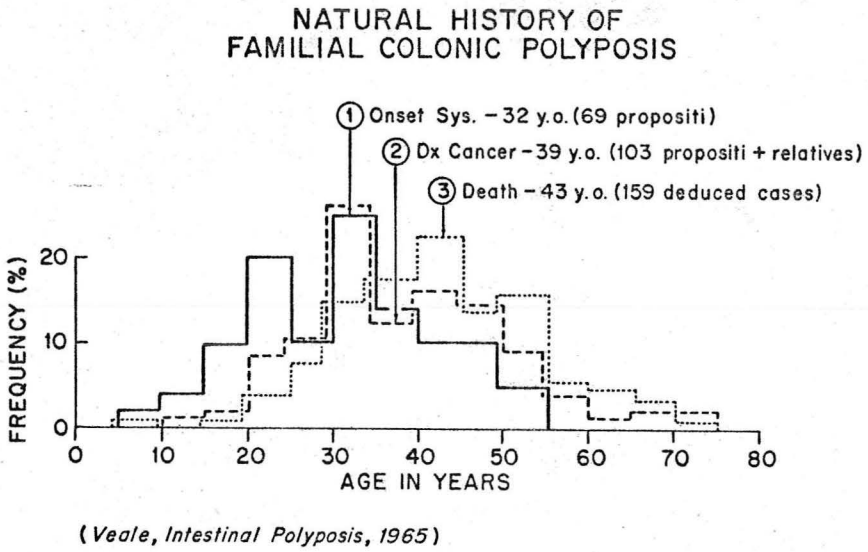

FIGURE 4. Natural History of Familial Colonic Polyposis

Natural History: The adenomatous polyps seen in familial colonic polyposis are not congenital and are not present in affected members at the time of birth. The earliest reported case in which multiple colonic polyps were demonstrated is a 4-year-old infant; more commonly, however, the polyps develop during childhood or early adulthood. As shown by the solid line in Figure 4, the average age of onset of symptoms (most commonly, bloody diarrhea) in index cases is 32 years. However, the great variability in the age of onset of symptoms should be emphasized; as is evident in this figure, initial symptoms were noted in children as young as 5 years of age and in older individuals up to the age of 55. Thus, it is apparent that there is tremendous variability in the age of onset of clinically apparent disease. Carcinoma of the colon develops in a very high percentage of these cases and, as also shown in Figure 4, the average age was 39 years at the time of diagnosis of malignancy. Death follows, on the average, 4 years later, and is almost invariably associated with metastatic carcinoma from the colon.

There is an important relationship, as illustrated in Figure 5, between the incidence of carcinoma present at the time the diagnosis of intestinal colonic polyposis was first established and the age of the patient. If the diagnosis is made in individuals less than 20 years old, only approximately 15% will be found to already have adenocarcinoma of the colon. On the other hand, if the diagnosis is not made until after the age of 30, then approximately two-thirds of the patients will already have one or more colonic carcinomas.

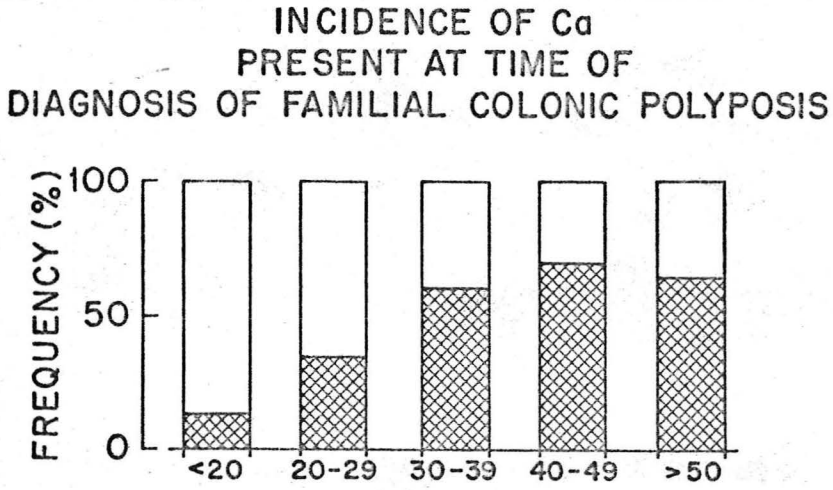

FIGURE 5. Relationship of the Presence of Colonic Ca to the Age at Which the Diagnosis of Familial Colonic Polyposis Was First Established

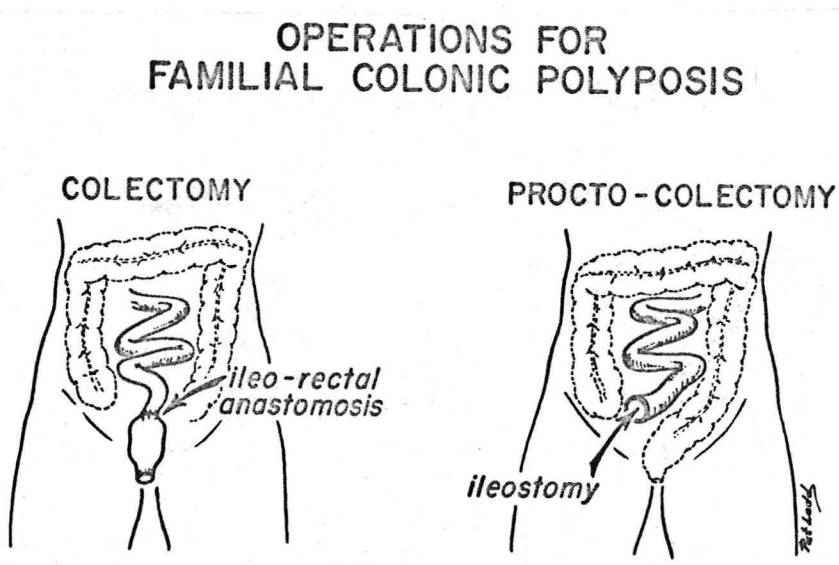

FIGURE 6. The Two Major Operations for Familial Colonic Polyposis

Therapy: Once it has been established that an individual has multiple adenomatous polyps of the colon, then surgery is mandatory because of the almost inevitable development of multiple adenocarcinomas of the bowel. As demonstrated in Figure 6, one of two operations usually is employed: the subtotal colectomy with ileorectal anastomosis or total proctocolectomy with a permanent ileostomy. The subtotal colectomy with ileorectal anastomosis can be utilized only where 1) the rectal segment contains only relatively few pedunculated polyps that can be

removed through the sigmoidoscope and 2) the physician is assured that the patient is reliable enough to return for repetitive follow-up sigmoidoscopic examinations. The proctocolectomy must be utilized in those patients who have continuous "carpeting" of the entire colon including the rectum with thousands of sessile polyps.

If the subtotal colectomy has been performed, then extremely careful and prolonged follow-up care is required. In a few cases, as illustrated by the case reports in Table 3, apparently there is spontaneous regression of the adenomatous polyps present in the rectum after subtotal colonic resection. Those polyps which do not spontaneously subside must be removed through the sigmoidoscope. In the majority of patients, however, all remaining rectal polyps must be removed through the sigmoidoscope 3 to 4 weeks after the subtotal colectomy has been performed. These individuals must be sigmoidoscoped repeatedly and all new rectal polyps removed as they develop over the subsequent years. These patients will carry the constant risk of spontaneous development of rectal adenocarcinoma. As shown by the data in Table 4, the incidence of malignancy in the retained rectum varies from 4 to 20%. It should also be emphasized that in the cases presented by Everson and Allen, 4 patients out of 6 had metastatic disease at the time the diagnosis of rectal carcinoma was made, even though these 6 patients were being periodically examined.

TABLE 3

REGRESSION OF RECTAL POLYPS FOLLOWING COLECTOMY IN FAMILIAL COLONIC POLYPOSIS

(1) 1957, Hubbard	9 yo WM	-6 months, marked decrease in number of polyps -9 months, only 6 polyps -1 year, 0 polyps
(2) 1959, Cole and Holden	17 yo BM	-6 weeks, decreased size -8 months, 0 polyps -2 years, no new polyps
	32 yo WM	-6 weeks decreased size -21 weeks, 0 polyps but "cobblestone" appearance
(3) 1959, Cole et al	17 yo WM	-Complete regression for 1 year
	30 yo WM	-Decreased size
	39 yo BF	-Marked reduction in size and number
	34 yo BF	-Marked reduction in size and number
(4) 1959, Dunphy et al	26 yo M	-Disappearance of polyps by 1 year

TABLE 4

CARCINOMA OF RECTUM AFTER COLECTOMY

(1) Everson and Allen	-122 cases ⟶ 12 carcinoma of rectum (1-17 years post-operative) [4 of 6 of these patients who were closely followed had metastasis when diagnosed]
(2) Hubbard	-incidence of malignancy in retained rectum of 4-16%
(3) Osler	-despite periodic examination malignant degeneration may occur in 20% of cases

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

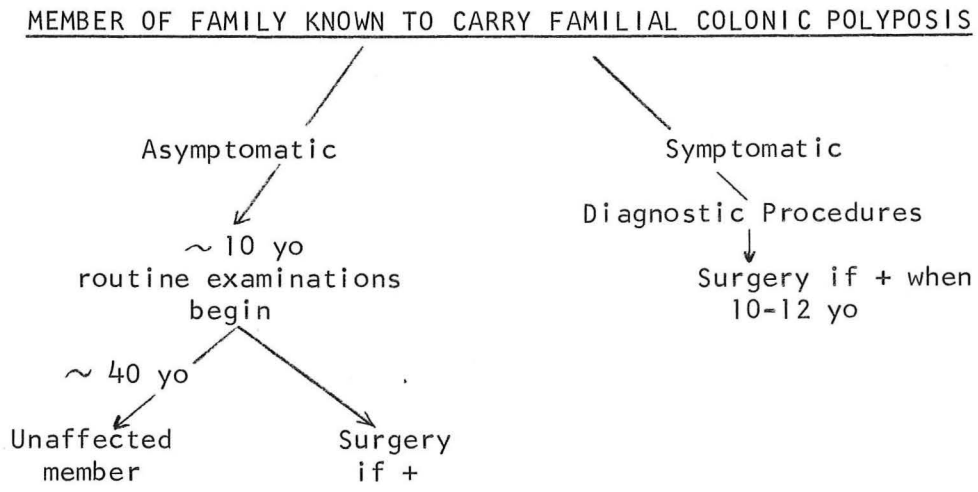

FIGURE 7. Flow Sheet for Following Family Members in Familial Colonic Polyposis

D. FAMILIAL COLONIC POLYPOSIS--VARIANT: MULTIPLE ADENOMAS OF THE ENTIRE GASTROINTESTINAL TRACT

As demonstrated by the data in Table 5, a few cases have been reported in which adenomatous polyps are distributed throughout the entire length of the gastrointestinal tract. These polyps presumably also have the potential for malignant degeneration, but very little information is available concerning the natural history or genetics of this syndrome.

TABLE 5

FAMILIAL COLONIC POLYPOSIS:
Variant-Polyposis of Entire GI Tract

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

E. GARDNER'S SYNDROME

As shown in Figure 8, in Gardner's syndrome there are multiple adenomatous polyps localized primarily, if not exclusively, in the colon. The pattern of colonic involvement apparently is identical to that seen in familial colonic polyposis. In addition, there is the same high risk of malignant degeneration.

GARDNER'S SYNDROME

POLYP : Adenoma

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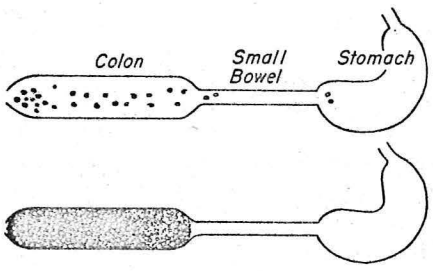

ASSOCIATED LESIONS:

Soft Tissue – epidermoid inclusion cysts, dermoid tumors, lipomas, leiomyomas, neuro fibromas, retroperitoneal mixed tumors, incisional fibromas mesenteric fibromas and fiberous infiltration of parotids.

Dental – poor teeth, caries, both unerupted and supernumerary teeth.

Bony Tissue – osteoma and exotoses of mandible, maxilla, zygoma, cranial bones; also femur, tibia, fibula, radius, ulna.

FIGURE 8. Distribution of Polyps in the Gardner's Syndrome

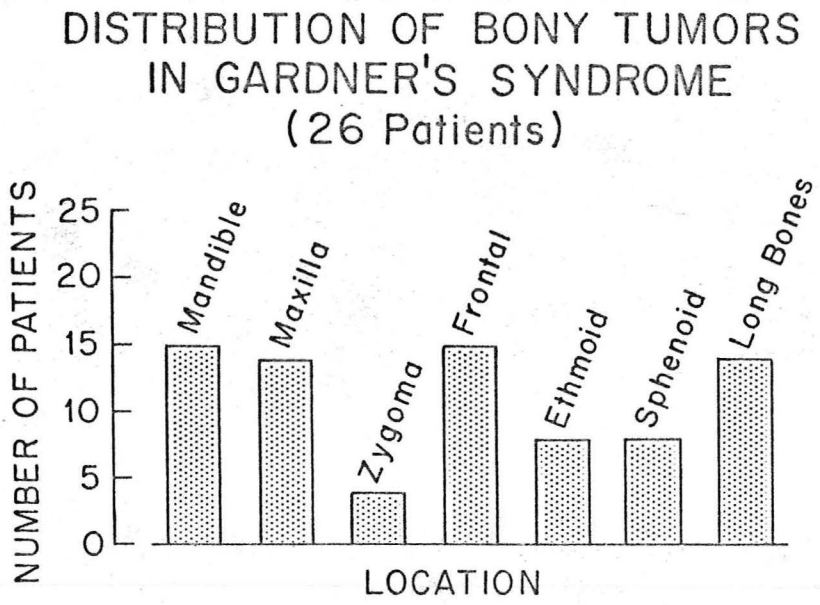

FIGURE 9. Distribution of Bony Tumors in Gardner's Syndrome

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

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

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

F. TURCOT-DESPRÉS-ST. PIERRE SYNDROME

TURCOT-DESPRÉS-
St. PIERRE SYNDROME

POLYP: Adenoma

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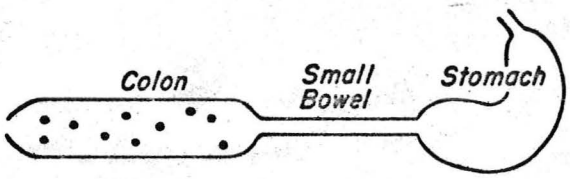


FIGURE 10. Distribution of Colonic Polyps in the Turcot-Després-St. Pierre Syndrome

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

MODE OF TRANSMISSION: ? Recessive Trait

TABLE 6

TURCOT -DESPRÉS-ST. PIERRE SYNDROME

1955	Turcot Després St. Pierre	15 yo M	Bloody diarrhea for 4 years; no family history of GI disorder; had colonic polyposis with two Ca at surgery; had recurrent rectal polyps. 3 years after surgery died following acute transverse myelitis--found to have medulloblastoma invading spinal cord.
		13 yo F	Sister of above patient; bloody diarrhea; colonic polyposis; subtotal colectomy; recurrent rectal polyps; 8 years after surgery complained of headaches--died of glioblastoma of left frontal lobe.
1969	Baughman List Williams Muldoon Segarra Volkel	12 yo F	Hospitalized after seizure; also had diarrhea; father (47), mother (41) and sisters (18, 6, 5) in "good health"; however, 2 brothers had brain tumors (below). Died--3 rectal polyps and glioblastoma multiforme (? multicentric).
		25 yo M	At 20 yo, had Ca of colon; admitted with hemiparesis; died--"2 dozen" polyps in colon and rectum and glioblastoma multiforme.
		12 yo M	Convulsions, headaches; died--glioblastoma multiforme; bowel not examined.
		21 yo F	Seizures--operated for glioblastoma multiforme; 1 year later 2 small rectal polyps found.

As demonstrated in Figure 10, the Turcot-Després-St. Pierre syndrome is the association of multiple adenomatous colonic polyps with central nervous system tumors. As shown in Table 6, only 6 cases of this syndrome have been reported to date. All died of or are under treatment for central nervous system tumors, commonly a glioblastoma. Since the polyps of the colon are adenomatous, these individuals presumably have the same high risk for development of colonic adenocarcinoma, and indeed two of the patients have had carcinomas. However, these patients usually succumb to their central nervous system lesions before the colonic polyposis becomes a major clinical problem.

G. PEUTZ-JEGHERS SYNDROME

As illustrated in Figure 11, the polypoid lesion in the Peutz-Jeghers syndrome is a hamartoma that never (or very rarely) undergoes malignant degeneration. These polyps are distributed throughout the gastrointestinal tract, including the stomach. Several points concerning the frequency distribution shown in Figure 11 require emphasis. Ninety-two per cent of the 117 cases had polyps in the small intestine. Eight per cent had polyps present only in the colon or in the colon and stomach.

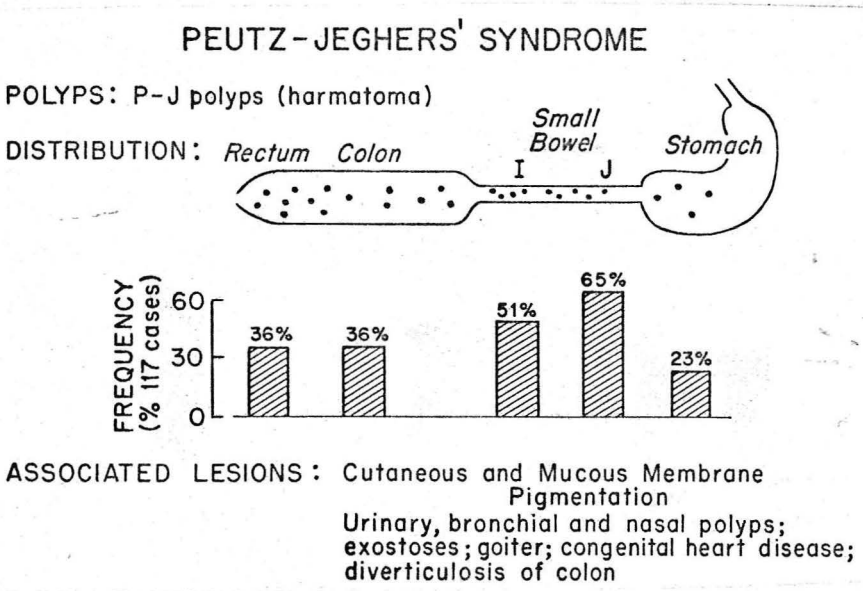


FIGURE 11. Distribution of Polyps in the Peutz-Jeghers Syndrome

The unique extracolonic manifestation of this syndrome is the characteristic pigmentation of cutaneous and mucous membranes. As shown in Figure 12, the two most commonly pigmented areas are the perioral region and the buccal mucosa. The cutaneous lesions are typically flat, brown to black spots without hair. They are present at birth but tend to fade as puberty and early adulthood is reached. The pigment patches seen on the buccal mucosa, in contrast, do not fade and are almost invariably seen in affected individuals.

Genetic Data: The frequency in the population at large is unknown. There are a large number of sporadic cases where the syndrome appears de novo without

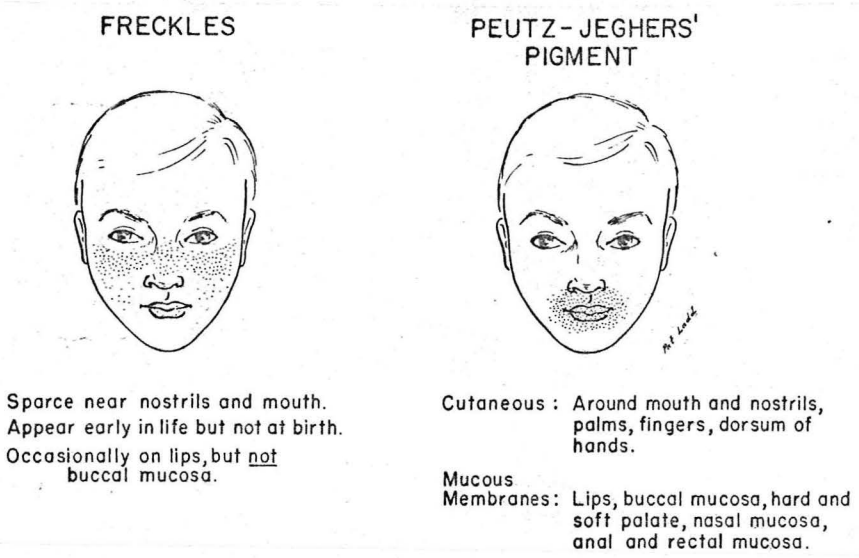


FIGURE 12. Distribution of the Mucocutaneous Lesions in the Peutz-Jeghers Syndrome

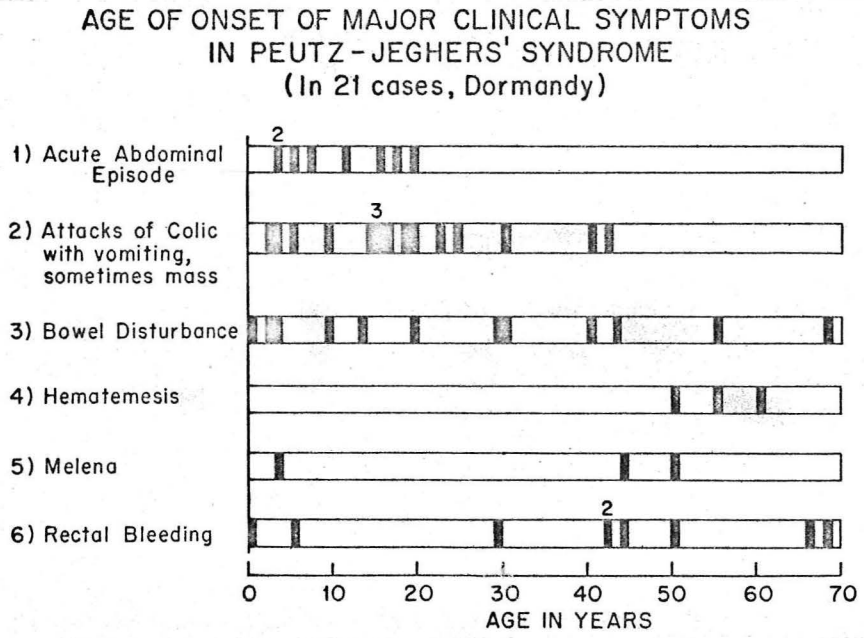


FIGURE 13. Age of Onset of Major Clinical Symptoms in the Peutz-Jeghers Syndrome

any evidence of familial involvement (approximately 43% in one series). In the familial cases, the sex ratio of affected individuals is approximately equal and affected individuals come only from affected parents. In the familial cases, this syndrome is assumed to be transmitted by an autosomal dominant.

Clinical History: The affected individual usually can be identified in infancy because of the associated mucocutaneous pigmentation. Since this syndrome involves polyposis of both the small and large intestine, one sees clinical

syndromes of both intermittent small bowel obstruction secondary to intussusception and bowel disturbance with diarrhea and rectal bleeding. As shown in Figure 13, these clinical symptoms commonly are seen first in childhood, but, in some individuals, may not appear for many years.

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

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

H. DIFFUSE GASTROINTESTINAL JUVENILE POLYPOSIS

TABLE 7

JUVENILE POLYPOSIS COLI (Veale et al, 1966)

Case	Age	Symptoms	Polyps		Outcome
			Colon	Ileum	
1	18 mo F	Bloody diarrhea and prolapsed polyps	+	+	Well after polypectomy
2	13 yo F	Bloody diarrhea and prolapsed polyps (↓ K, ↓ serum proteins)	+++	?	?
3	4 yo F	Blood per rectum + tissue; prolapse	+++	?	Died from "inanition"
4	2 yo M	Rectal bleeding	++	+	Well after colectomy
5	13 yo F	Prolapsed polyps	++	?	Well to age 52
6	8 yo F	Mucoid, bloody diarrhea; prolapsed polyps	++	?	Well to age 50
7	40 yo F	Asymptomatic	++	?	Well
8	20 yo F	Mucoid diarrhea, prolapsed polyps	+++	?	Well after colectomy
9	12 yo M	Prolapsed polyps	++	?	Died at 63
10	10 yo F	Rectal bleeding	++	?	Well after colectomy
11	8 yo M	Rectal bleeding; prolapsed polyps	+++	?	Died at age 17 of intestinal obstruction

In recent years, several series of patients have been reported that do not fit into any of the well-defined syndromes of intestinal polyposis. It has now become apparent, however, that a number of these cases probably can be grouped

together as examples of multiple juvenile polyps involving various levels of the gastrointestinal tract. Three major subtypes have been described in the literature: juvenile polyposis coli, the Cronkhite-Canada syndrome, and juvenile polyps with "cachexia".

Juvenile Polyposis Coli: Veale recently has reviewed all of the pathologic material from the St. Mark's series of patients with colonic polyposis. On the basis of this review he concluded that 11 patients, as shown in Table 7, were misdiagnosed as familial colonic polyposis (adenomatous polyps) and, in reality, had a new syndrome characterized by multiple colonic polyps of the juvenile (retention) type. With two exceptions, these polyps appeared to be localized to the colon and it is noteworthy that many of these patients lived to an old age without the development of adenocarcinoma. The major clinical syndrome in this group of patients consisted of bloody diarrhea, prolapse of polyps and passage of tissue per rectum.

Cronkhite-Canada Syndrome:

TABLE 8

CRONKHITE-CANADA SYNDROME

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

Between 1955 and 1966, six patients have been reported, as summarized in Table 8, all of whom manifest a devastating illness characterized by marked diarrhea, probable steatorrhea, hypoalbuminemia and edema, alopecia, atrophy of fingernails and diffuse skin pigmentation. These patients all manifest involvement of many areas of the gastrointestinal tract with multiple polypoid lesions. In several case reports, these were reported to be "adenomatous" polyps; however, in reviewing the photographs of these polyps and the rather sparse description of the histology, it is apparent that these very likely are not adenomatous polyps but, rather, typical juvenile or retention polyps. It is noteworthy in this regard that while these patients were all relatively old, none died from adenocarcinoma of the bowel.

Juvenile Polyps With "Cachexia":

TABLE 9

JUVENILE POLYPS WITH CACHEXIA

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

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

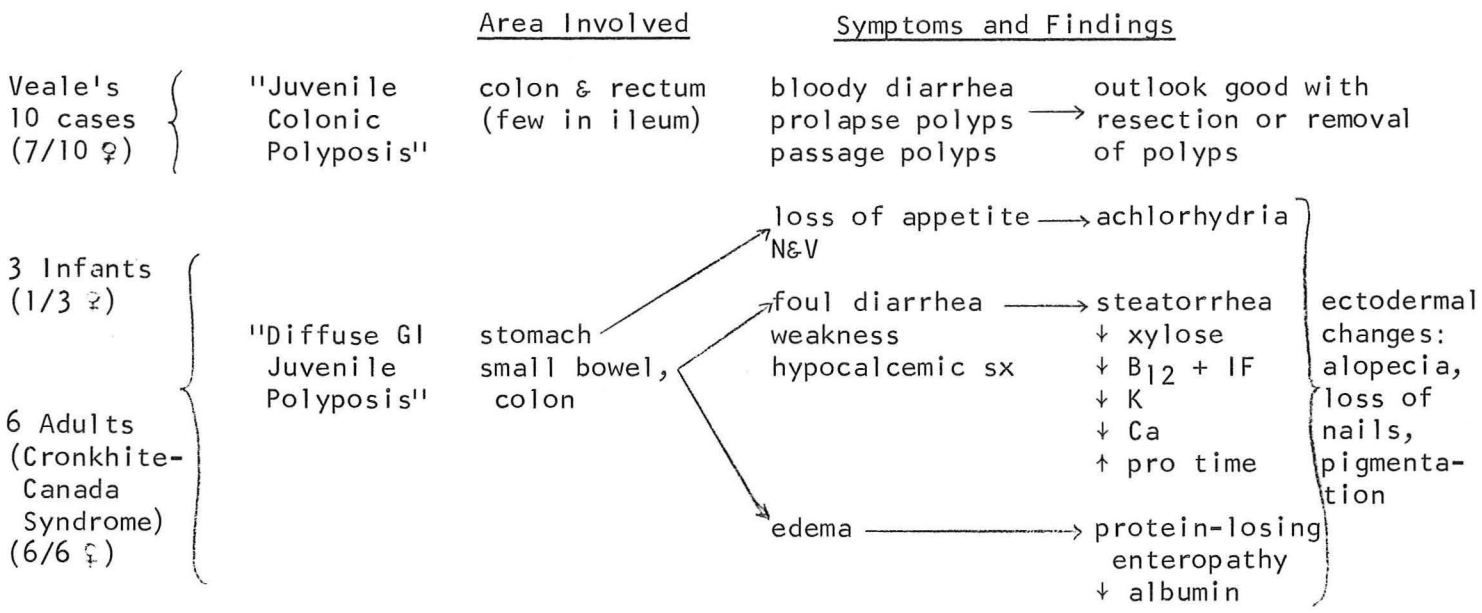
It is likely that these 19 cases can be grouped together as representing examples of a new syndrome characterized by multiple juvenile (retention) polyps of the gastrointestinal tract. It is equally apparent, however, that at least two distinctly different clinical syndromes are present, as shown in Table 10. Ten of Veale's cases had polyposis predominantly or exclusively of the colon. These individuals all manifest bloody diarrhea, prolapsed polyps and passage of tissue per rectum, but, generally, did well with conservative therapy or colectomy.

In contrast, the three infants and six adults who had diffuse involvement of the entire gastrointestinal tract with juvenile polyposis presented with a devastating illness that almost invariably ended in a fatal outcome. On the basis of the limited laboratory data available, it is apparent that these individuals had severe diarrhea with water and electrolyte loss, severe steatorrhea, protein-losing enteropathy with hypoalbuminemia and edema, and, finally, alopecia, marked atrophy

of the nails and diffuse skin pigmentation. It is likely that these latter ectodermal changes can be explained as the secondary consequences of the massive depletion state that these patients had secondary to their malabsorption syndrome and protein-losing enteropathy. Whether or not this formulation of these 19 cases is correct must await further description of patients with this syndrome.

TABLE 10

SYNDROMES OF JUVENILE POLYPOSIS



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