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Inflammatory Bowel Disease in Children

—Clinical, endoscopic, radiologic and histopathologic investigation—

Jeong Kee Seo, M.D., Kyung Mo Yeon, M.D.* and Je Geun Chi, M.D.**

Department of Pediatrics, Radiology and Pathology***
Seoul National University College of Medicine, Seoul, Korea

This paper reviews our five years' clinical experience (1987 to 1991) of 22 patients with inflammatory bowel disease (IBD). There were 12 patients with Crohn's disease and 10 patients with ulcerative colitis. The mean age at diagnosis was 8.7 years (2 to 14 years). Clinical impressions before referral were chronic diarrhea in 11, irritable bowel syndrome in 5, colon polyp in 4, lymphoma in 3, intestinal tuberculosis in 2, amoebic colitis in 2, ulcerative colitis in 2 children and other diseases. The mean interval from the onset of symptoms to the diagnosis of IBD was 18 months. Diagnosis of Crohn's disease was delayed for more than 13 months in 8 (67%), whereas that of ulcerative colitis was delayed for more than 13 months in 4 (40%).

Diarrhea (50%), abdominal pain (36%) and rectal bleeding (36%) were the three most frequent presenting complaints of IBD. Moderately severe abdominal pain was a more common chief complaint in Crohn's disease (58%) than in ulcerative colitis (10%). Hematochezia (90% vs 17%) and moderately severe diarrhea (90% vs 75%) were more common gastrointestinal manifestations in ulcerative colitis than in Crohn's disease. The associated extraintestinal manifestations were oral ulcer in 7, arthralgia in 11 and arthritis in 4, skin lesions in 2, eye lesions in 2 and growth failure in 9 patients.

Of 12 children with Crohn's disease, granuloma was found in 5, aphthous ulcerations in 8, cobble stone appearance in 8, skip area or asymmetric lesions in 6, transmural involvement in 7, and perianal fistula in 3. Among 10 children with ulcerative Colitis, there were crypt abscess in 8, granularity or friability in 10 and rectosigmoid ulcerations with purulent exudate in 8 children.

The main sites of involvement in children with Crohn's disease were both the small and large bowels in 7 (58%), small bowel only in 2 (16%), and colon only in 3 (25%). Terminal ileum involvement was seen in 75% of Crohn's disease cases. The main sites of involvement in children with ulcerative colitis were total colon in 4 (40%), up to the splenic flexure in 2 (20%), rectosigmoid in 3 (30%) and rectum only in one (10%).

Medical treatment including sulfasalazine, and systemic or topical steroid was administered initially in most patients. Seven of 12 patients with Crohn's disease and

Address for correspondence: *Jeong Kee Seo, Department of Pediatrics, Seoul National University, College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea Phone. (02) 760-3468, 3627, 3570*

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2 of 10 patients with ulcerative colitis were operated on. The mean follow-up period was 31 months (6 to 78 months). During follow-up, 70 procedures of fiberoptic endoscopy with multiple biopsies were performed to assess the disease process and the effect of the treatment. At the last follow up, a good state of health with almost no active disease was observed in 8, a fair state of health with mildly active disease in 10, and a poor state of health with limitations of daily activities in 3 patients with IBD. One child of Crohn's disease died.

Key Words: *Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Colonoscopy, Children*

INTRODUCTION

The incidence of inflammatory bowel disease (IBD) in children appears to be increasing in Korea whereas intestinal tuberculosis, which was the most frequent chronic intestinal disease in the past, has been decreasing.

A couple of reports demonstrate a significant delay between the onset of initial symptoms and the establishment of a diagnosis (Farmer and Michener, 1979; Michener et al., 1971). One of the major reasons for delay in establishment of diagnosis is unawareness that IBD occurs in children.

Since early diagnosis and the institution of therapy usually leads to an earlier recovery and a better quality of life for patients with IBD, pediatricians should be familiar with children with IBD. However, in our country, there have been very few papers dealing with IBD even in adulthood.

With the advent of floppy, small diameter pediatric colonoscopes, in Western countries, colonoscopy is now considered an essential tool in the diagnosis and evaluation of IBD.

If patients were suspected of having IBD by clinical symptoms and signs, we performed an endoscopic investigations. Colonoscopic biopsy, supplemented by radiologic and surgical examinations was most useful in assessing the diagnosis and the response to the management during follow up.

The aim of the present study is to analyze the clinical, endoscopic, radiologic, and histopathologic characteristics of IBD in Korean children and compare them with those of Western countries where the incidence is relatively higher. We also report data relating to medical and surgical management, and the outcome of the follow-up study.

MATERIALS AND METHODS

From Jan. 1987 to Dec. 1991, endoscopic, radiologic, histopathologic, and clinical investigations were performed on 22 patients with IBD who were admitted to the Seoul National University Children's Hospital. All the patients were referred from other hospitals for diagnosis and therapeutic evaluations.

Selected in this study were patients who were followed up for more than 6 months to observe episodes of remission and exacerbation, and a response to the steroid therapy. Infectious enterocolitis was excluded in the patients by negative stool cultures for Salmonella, Shigella, Yersinia, Campylobacter and Amoeba.

During this period, a standardized program for the study was used including endoscopy of the lower intestine with multiple biopsies and radiological investigations of the small and large bowels. Seventy procedures of fiberoptic endoscopy with biopsy were performed in 20 children with IBD to assess the disease and the effect of the medical treatment during the follow-up period.

Bowel preparation was done with a dulcolax or mineral oil administration 12 hours precolonoscopy and saline soap enema was administered one hour precolonoscopy. Sedation was achieved with systemic administration of diazepam (0.3mg/kg) and demerol (1mg/kg).

Endoscopy was not performed in 2 patients with Crohn's disease, who underwent surgical resection immediately after admission because of intestinal obstruction.

Small bowel series and barium enema were performed to investigate the extent of the lesions. Surgical biopsy specimens were obtained from laparatomy or surgery in 9 of the 22 children with IBD.

The final differential diagnosis of IBD was based on clinical features in combination with endoscopic and radiologic findings, also supplemented by histopathologic examination, either of specimens obtained endoscopically or at laparatomy.

Patients who fulfilled two or more of the following diagnostic criteria were regarded as having Crohn's disease. (1) Typical "aphthoid" ulcers detected on colonoscopic examination. (2) Operative specimen compatible with Crohn's disease. (3) Inflammatory disease present radiographically in the small bowel (4)

Microgranuloma present on biopsy specimens. (5) "Skip area", stricture formation and/or deep ulcerations present on X-ray examination (Hogan et al., 1980).

For the evaluation of growth failure, patients' body weight and height were compared with the growth percentiles of the Korean Pediatric Association study.

RESULTS

Age distribution in 22 children with inflammatory bowel disease are shown (Fig. 1). The mean age at diagnosis was 8.7 years (range 2 years to 14 years). Fifty nine per cent of children with IBD was diagnosed over 9 years of age. Two patients were diagnosed under 3 years of age. There were 13 boys and 9 girls.

Twenty two referred children had been treated under more than one clinical impression at other hospitals before referral (Table 1); chronic diarrhea in 11, irritable bowel syndrome in 5, colon polyp in 4, lymphoma in 3, intestinal tuberculosis in 2, amoebic colitis in 2, ulcerative colitis in 2 children and other diseases including periappendiceal abscess, fever of unknown origin, pseudomembranous colitis, yersiniosis and familial polyposis coli. All but two patients were diagnosed as IBD at our pediatric GI clinic. One of the two children who were referred with the impression of ulcerative colitis had the diagnosis changed from ulcerative colitis to Crohn's disease.

Table 1. Clinical impression before referral in 22 children with inflammatory bowel disease.

Clinical Impression*	Total No.(%)**	No. of UC	No. of Crohn's
Chronic infectious diarrhea	11(50%)	7	4
Irritable bowel syndrome	5(22%)	1	4
Colon polyp	4(18%)	4	0
Lymphoma	3(13%)	0	3
Intestinal tuberculosis	2(9%)	0	2
Amoebic colitis	2(9%)	2	0
Ulcerative colitis	2(9%)	1	1
Periappendiceal abscess	1(4%)	0	1
Fever of unknown origin	1(4%)	0	1
Pseudomembranous colitis	1(4%)	0	1
Yersiniosis	1(4%)	0	1
Familial polyposis coli	1(4%)	1	0

* Patients had been treated under more than one clinical impression at other hospitals before referral (Table 1)
** Percentages were calculated on the basis of 22 children.

Table 2 shows durations of symptoms before an established diagnosis of IBD.

The mean interval from the onset of symptoms to the diagnosis of inflammatory bowel disease was 18 months. Diagnosis of Crohn's disease was delayed for more than 13 months in 8(67%), whereas that of ul-

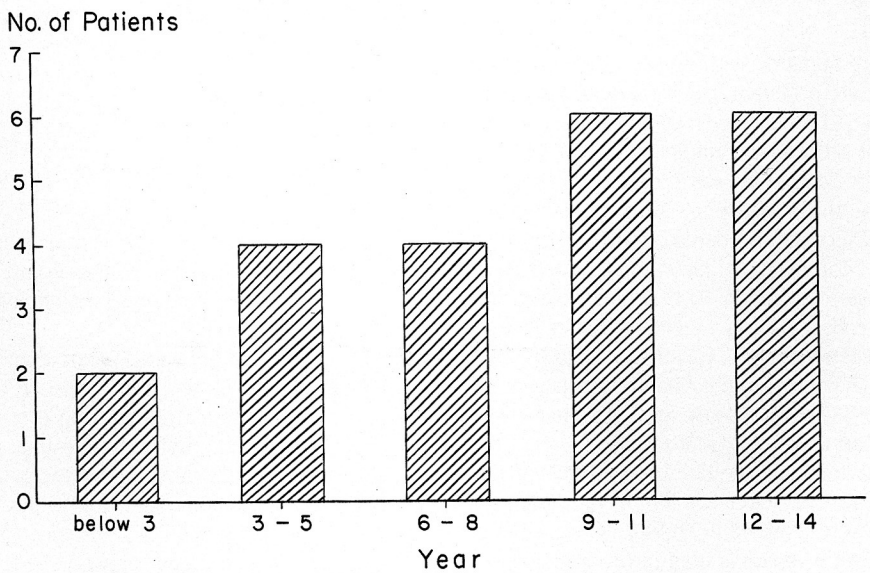

Fig. 1. Age distribution of 22 children with Inflammatory bowel disease

cerative colitis was delayed for more than 13 months in 4(40%). In 3 patients with IBD, diagnosis was delayed for more than 2 years.

Table 2. Duration of symptoms before diagnosis in 22 children with inflammatory bowel disease.

Duration	No. of Crohn's	No. of UC	Total No.	Cumulative No. (%)
0–3 mo	1	1	2	2(9%)
4–6 mo	1	2	3	5(22%)
7–9 mo	2	2	4	9(40%)
10–12 mo	0	1	1	10(45%)
13 mo–2 yr	6	3	9	19(86%)
>2 yr	2	1	3	22(100%)

Table 3. Chief complaints at admission in 22 children with inflammatory bowel disease.

Chief complaints	Total No.(%)*	No. of Crohn's	No. of UC
Chronic diarrhea	11(50%)	4	7
Abdominal pain	8(36%)	7	1
Rectal bleeding	8(36%)	1	7
Fever	2(9%)	2	0
Abdominal mass	2(9%)	2	0
Vomiting	1(4%)	1	0

* Percentage was calculated on the basis of 22 children.

Patients were admitted with one or two chief complaints as shown in Table 3. Diarrhea (50%), abdominal pain (36%) and rectal bleeding (36%) were the three most frequent presenting complaints of IBD. Moderately severe abdominal pain was a more common chief complaint in Crohn's disease (58%) than in ulcerative colitis (10%). Diarrhea and hematochezia were more common chief complaints of ulcerative colitis than of Crohn's disease; diarrhea in 70% of ulcerative colitis and 33% of Crohn's disease, hematochezia in 70% of ulcerative colitis and 8.5% of Crohn's disease.

Table 4 shows the gastrointestinal manifestations of 12 patients with Crohn's disease and 10 patients with ulcerative colitis during hospitalization.

Recurrent abdominal pain occurred in 95% of patients with IBD. Hematochezia (90% vs 17%) and moderately severe diarrhea (90% vs 75%) were more common in ulcerative colitis than in Crohn's disease. Palpable mass with vomiting, and fistula were noted exclusively in children with Crohn's disease. In 3 patients, palpable mass with vomiting and abdominal pain was an indication of laparatomy.

Table 4. Gastrointestinal manifestations of 22 children with inflammatory bowel disease.

GI manifestations	Total No.(%)*	No. of Crohn's	No. of UC
Abdominal pain	21(95%)	12	9
Diarrhea	18(81%)	9	9
Hematochezia	11(50%)	2	9
Vomiting	6(27%)	6	0
Protein losing enteropathy	3(13%)	2	1
Palpable mass	5(22%)	5	0
Anorexia	15(68%)	11	4
Anal lesions	9(40%)	5	4
Fistula	3	3	0
Fissure	2	0	2
Ulceration	2	2	0
Hemorrhoid	2	0	2

* Percentage was calculated on the basis of 22 children.

Table 5. Extraintestinal manifestations of 22 children with inflammatory bowel disease.

Extraintestinal manifestations	Total No.(%)*	No. of Crohn's	No. of UC
Oral ulcer	7(31%)	7	0
Arthralgia	11(50%)	6	5
Arthritis	4(18%)	3	1
Skin lesions	2(9%)	1	1
Eye lesions	2(9%)	1	1
Abnormal LFT	2(9%)	2	0
Anemia (Hb<11.0 g/dl)	13(59%)	7	6
Elevated ESR	11(50%)	8	3
Fever	12(54%)	8	4
Growth failure (<3% ile)	9(40%)	7	2

* Percentage was calculated on the basis of 22 children.

The associated extraintestinal manifestations are presented in Table 5.

Recurrent aphthous oral ulcerations were noted in 7 of 12 children with Crohn's disease during periods of active disease. Arthralgia with or without arthritis were the most common extraintestinal manifestations of IBD. Skin lesions developed in two patients with IBD; erythema nodosum in one child with Crohn's disease and pyoderma gangrenosum in one child with ulcerative colitis. Two patients showed eye lesions; keratitis in one child with Crohn's disease and chronic conjunctivitis in one child with ulcerative colitis. Liver involve-

Table 6. Growth failure in children with inflammatory bowel disease

Growth % ile*	No. of Crohn's	No. of UC	Total (%)	Mean age at diagnosis
< 3% ile	7	2	9(41%)	7yr 9mo
3–25% ile	5	4	9(41%)	8yr 6mo
25–50% ile	0	1	1(4%)	10yr 11mo
> 50% ile	0	3	3(13%)	11yr 3mo

* Growth percentile at admission calculated from the Korean standard growth chart.

Table 7. Duration of follow up after a diagnosis of inflammatory bowel disease.

F. U. period	Total No.	No. of Crohn's	No. of UC
6 mo–12 mo	3	1	2
13 mo–24 mo	7	5	2
25 mo–36 mo	4	3	1
37 mo–48 mo	2	0	2
49 mo–60 mo	3	2	1
>60 mo	3	1	2
	22	12	10

Table 8. Endoscopic, Radiologic, and Histopathologic findings in 12 children with Crohn's disease

Case No.	Involved bowel colon	Involved bowel SB*	Granul –oma	Cobble –stone	Aphthous ulcer	Skip asymm	Crypt abscess	Friab –ility	Muco –pus	Pseudo –polyp	Trans** –mural	Anal fistula
I	+	+	+	+	+	+	–	–	–	+	+	–
II	+	+	+	+	+	–	–	–	–	+	+	+
III	–	+	+	–	–	–	–	–	–	–	+	–
IV	+	–	+	–	+	+	–	–	–	+	ND***	–
V	+	–	+	–	+	+	–	–	–	+	ND	–
VI	+	+	–	+	–	–	–	–	–	–	ND	–
VII	+	+	–	+	–	–	–	–	–	–	+	+
VIII	+	+	–	–	+	–	–	+	+	+	ND	–
IX	+	+	–	+	+	++	–	–	–	+	+	–
X	+	+	–	+	+	+	–	–	–	+	+	–
XI	+	–	–	+	+	+	–	–	–	+	ND	+
XII	–	+	–	+	–	–	–	–	–	–	+	–

* SB: Small bowel
** Transmural changes were examined in the surgically resected specimens
*** ND: Surgery was not done.

Table 9. Endoscopic, Radiologic, and Histopathologic findings in 10 children with Ulcerative colitis

Case No.	Involved bowel colon	Involved bowel SB*	Granul –oma	Cobble –stone	Aphthous ulcer	Skip asymm.	Crypt abscess	Friab -ility	Muco –pus	Pseudo –polyp
I	+	–	–	–	–	–	+	+	+	+
II	+	–	–	–	–	–	+	+	+	+
III	+	–	–	–	–	–	+	+	+	+
IV	+	–	–	–	–	–	+	+	–	–
V	+	–	–	–	–	–	+	+	–	+
VI	+	–	–	–	–	–	+	+	+	+
VII	+	–	–	–	–	–	–	+	+	–
VIII	+	–	–	–	–	–	–	+	+	–
IX	+	–	–	–	–	–	+	+	+	–
X	+	–	–	–	–	–	+	+	+	–

* SB: Small bowel

ment indicated by persistent elevation of transaminases was noted in 2 patients with Crohn's disease. One of them underwent liver biopsy which disclosed fatty liver.

Growth failure was found in 40% of IBD. Table 6 shows that growth retardation was significantly more common in children with Crohn's disease than in ulcerative colitis (58% vs 20%).

The mean follow-up period was 31 months (range 6 to 78 months). In 55% of children with IBD, follow up period was more than 2 years (Table 7).

If patients were suspected of having chronic inflammatory bowel disease, endoscopic, radiologic, histopathologic investigations were done for a final diagnosis. Colonoscopy was superior to barium enema in demonstrating involvement of the large bowel and in differentiating Crohn's disease from ulcerative colitis. Seventy procedures of fiberoptic endoscopy with biopsy were performed to assess the disease and the effect of the medical treatment. Endoscopic biopsy specimens were obtained and examined histopathologically in all patients except two who underwent surgery and obtained resected bowels. Radiologic investigations of the small intestine were performed in all children with IBD.

Table 8 and 9 shows endoscopic, radiologic and histopathologic findings.

When the patients had findings of segmental narrowing or skip area, discontinuous asymmetric lesions (in 6 children), aphthous ulcerations (in 8 children), cobble stone appearance (in 8 children), and proximal inflammation without rectal involvement on endoscopic and radiologic examination, they were diagnosed as having Crohn's disease. Epitheloid cell granulomas either on endoscopic or surgical biopsy specimens (in 5) and transmural involvement or characteristic macroscopic findings of surgical specimens (in 7) were interpreted as having Crohn's disease. Crypt abscess (in 8), friability (in 10) or granularity, rectosigmoid ulcerations with purulent exudate with continuous distribution (in 8) were frequently found in children with ulcerative colitis. Pseudopolyps were found in 5 children with ulcerative colitis and 8 children with Crohn's disease.

Characteristic findings of endoscopic (Fig. 2, 3, 4, 5), radiologic (Fig. 6, 7, 8, 9) and pathologic (Fig. 10, 11, 12, 13) investigation of children in the present paper were shown in accompanying figures.

Table 10 and 11 show the involved site of IBD, type of management and outcome during follow up. The main sites of involvement in children with Crohn's dis-

Table 10. Involved site at admission, follow up period, types of management and the outcome in 12 children with Crohn's disease

Case No.	Site of involvement	FU (mo)	No. of procedures (Colono.)	No. of procedures (Gastro.)	Type of management	Outcome & present status
I	ileum, colon	50	(4)	(1)	PD+SSZ*	Fair, off PD now,
					Resection	Remission & exacerbation with PD
II	ileum, colon	78	(3)	(2)	PD+SSZ+Flagyl	Good, off PD now,
					Rt hemicolectomy	Remission & exacerbation with PD
VII	ileum, colon	19	(1)	(2)	PD+SSZ+Flagyl	Died,
					resection	UGI bleeding
VIII	ileum, colon	25	(3)	(0)	PD+SSZ	Fair, off PD now,
						Remission & exacerbation with PD
IX	ileum, colon	6	(0)	(0)	PD+SSZ	Good, no relapse till now
					resection	
X	ileum, colon	54	(0)	(0)	Rt hemicolectomy	Good, no relapse till now
VI	ileum, colon	12	(1)	(1)	PD	Poor, lost follow-up
XII	ileum	30	(1)	(0)	PD+SSZ+Flagyl	Fair, off PD now,
					resection	Remission & exacerbation with PD
III	jejunum, ileum	18	(1)	(0)	PD	Fair, lost follow-up
					resection	Remission & exacerbation with PD
IV	colon	15	(1)	(0)	PD+SSZ	Fair, low dose PD now.
V	colon	12	(1)	(1)	SSZ	Good
XI	colon	27	(4)	(0)	PD+SSZ+Flagyl	Poor,
						Remission & exacerbation with PD

* SSZ: Sulfasalazine

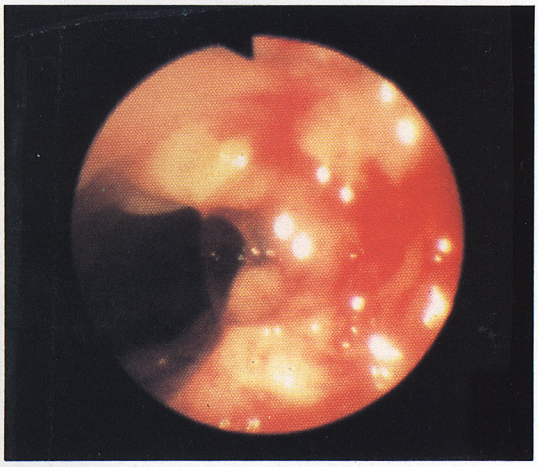

Fig. 2. Friability and ulcerations with hemorrhage in ulcerative colitis

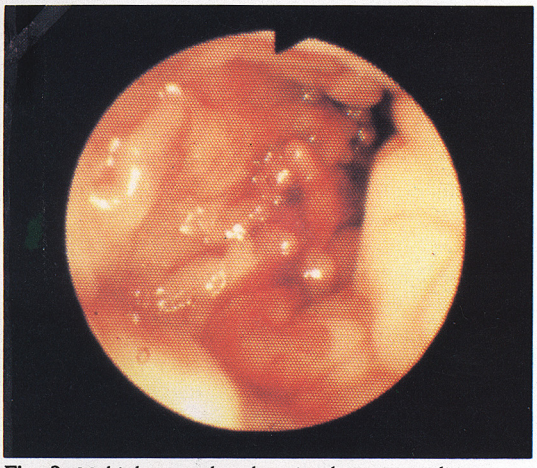

Fig. 3. Multiple pseudopolyps in ulcerative colitis

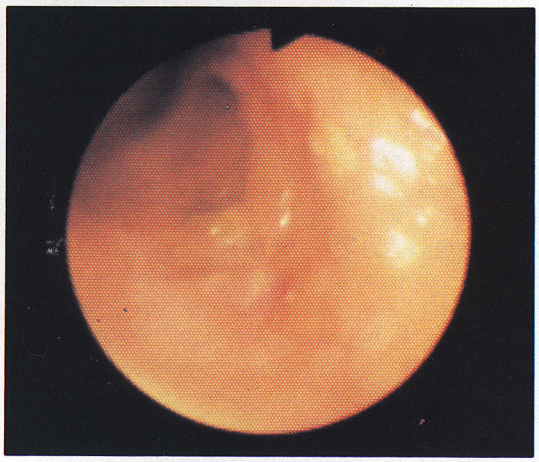

Fig. 4. Focal erythema with erosions and ulcerations in Crohn's colitis in the background of normal looking mucosa. Biopsy showed granuloma.

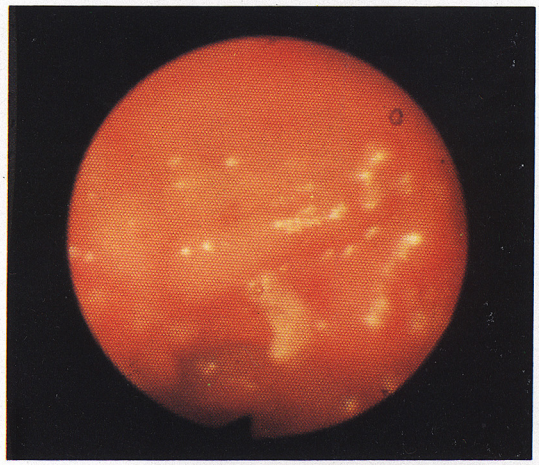

Fig. 5. Ulceration, focal erythema and nodular deformity of the thickened mucosa in Crohn's disease

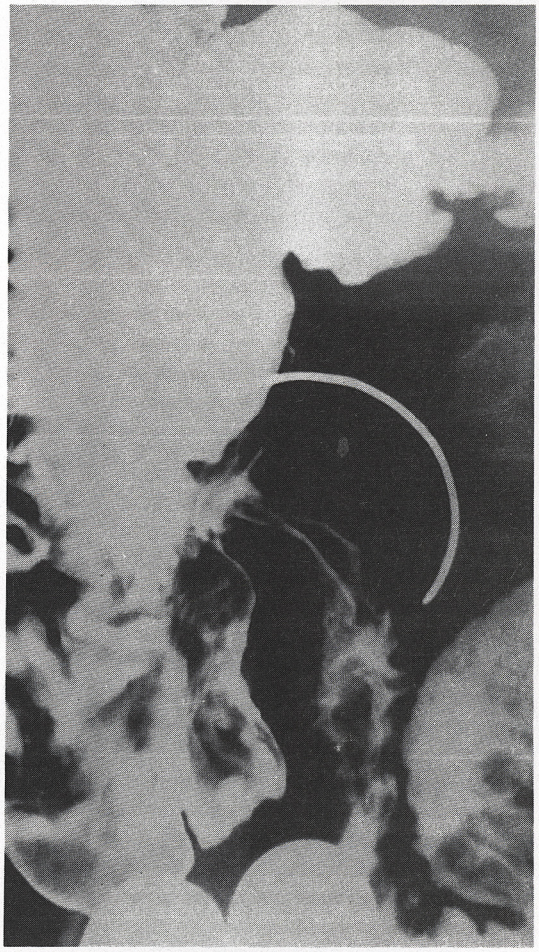

Fig. 6. Crohn's disease: Ileocolic involvement. There is submucosal edema, luminal narrowing and spasm in terminal ileum and medial aspect of cecum.

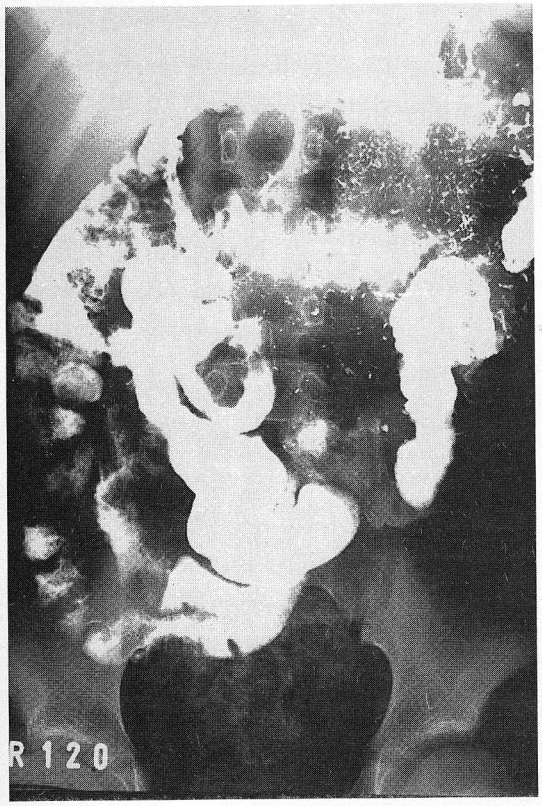

Fig. 7. Crohn's disease: Same findings as in Fig. 6, involving mid-ileum.

ease were both the small and large bowels in 7(58%), small bowel only in 2(16%), and colon only in 3(25%). The main sites of involvement in children with ulcerative colitis were total colon in 4(40%), up to the splenic flexure in 2(20%), rectosigmoid in 3(30%) and rectum only in one (10%).

Medical treatment including sulfasalazine, and systemic or topical steroid was administered initially in most patients. To assess the disease process and responses to the medical therapy, 36 procedures of colonoscopy and 7 procedures of gastrofiberscopy were peformed in 10 patients with ulcerative colitis. Twenty procedures of colonoscopy and 7 procedures of gastrofiberscopy were peformed in 10 patients with Crohn's disease.

Seven of 12 patients with Crohn's disease and two of 10 patients with ulcerative colitis were operated on.

The Status of the patients at last follow up were as follows; Good state of health with almost no active disease in 8(36%), fair state of health with mildly active disease in 10(45%), and poor state of health with limitations of daily activities in 3(13%). One child with Crohn's disease died of bleeding associated with hemorrhagic erosive gastritis and liver problems.

DISCUSSION

Chronic inflammatory bowel disease includes two chronic disorders of unknown etiology, nonspecific ulcerative colitis and Crohn's disease. The two conditions can be distinguished in most children with IBD after evaluating the clinical, endoscopic, radiologic, and histopathologic findings (Chong et al., 1985).

There have been very few papers dealing with IBD even in adulthood in our country. Intestinal tuberculosis was the most frequent inflammatory bowel disease in the past (Kim et al., 1988). In recent years, however, intestinal tuberculosis has been decreasing, whereas the incidence of inflammatory bowel disease in children appears to be increasing.

We experienced 22 children with IBD including 12 patients with Crohn's disease and 10 patients with ulcerative colitis during the last 5 years.

In Western countries, there has been a recent increase in the incidence of Crohn's disease in contrast with ulcerative colitis. Most pediatricians have now seen significantly more Crohn's disease than ulcerative colitis. Because of the very rare occurrence of IBD in Korea it is not certain that the incidence of Crohn's disease is higher than that of ulcerative colitis. Accurate diagnosis of IBD is often very difficult in our contury, for there is a rarer occurrence of IBD and a relatively higher incidence of inflammatory bowel disease of infectious origin such as common bacterial enterocolitis, intestinal tuberculosis and amoebiasis.

Twenty two children with IBD in the present study had been treated under more than one clinical impression at other hospitals before referral. One half of them had been treated under the clinical impression of infectious enterocolitis not responding to a couple of weeks of antibiotic treatment, as shown in other reports (Burbige et al., 1975). Twenty two per cent of patients were considered to have functional complaints (irritable bowel syndrome) for a couple of years before the proper diagnosis of IBD was established. Colon polyp was initially suspected in 18% of the patients, who showed intermittent hematochezia without systemic symptoms including fever. Lymphoma was the clinical impression before referral in 3 patients who presented with a palpable mass with obstructive symptoms. One of the most difficult diseases for differential diagnosis from Crohn's disease was intestinal tuberculosis, which was found in 2 patients who had been treated with antituberculous medication without response before referral. Yersiniosis which was known

Table 11. Involved site at admission, follow up period, types of management and the outcome in 10 children with ulcerative colitis

Case No.	Site of involvement	FU (mo)	No. of procedures (Colono.)	No. of procedures (Gastro.)	Type management	Outcome & present status
I	all colon	51	(2)	(2)	PD+SSZ* Total colectomy	Good, cured
III	all colon	39	(6)	(1)	PD+SSZ	Fair, off PD now Remission & exacerbation with PD
V	all colon	63	(3)	(1)	PD+SSZ+Flagyl Total colectomy	Good, cured.
VIII	all colon	75	(1)	(0)	PD+SSZ	Good, no medication now residual mild stenosis
IX	to splenic flex.	24	(3)	(1)	PD+SSZ	Fair, low dose PD, lost follow-up Remission & exacerbation with PD
X	to splenic flex.	6	(2)	(1)	PD+SSZ	Fair, on PD tapering
IV	rectosigmoid	18	(3)	(0)	PD+SSZ	Good, no PD now.
VI	rectosigmoid	6	(4)	(0)	PD+SSZ	Poor, lost follow-up, slightly improved on PD
VII	rectosigmoid	14	(4)	(1)	PD+SSZ	Fair, on PD tapering now Remission & exacerbation with PD
II	rectum	37	(8)	(0)	Steroid enema +SSZ	Fair, intermittent hematochezia

* SSZ: Sulfasalazine

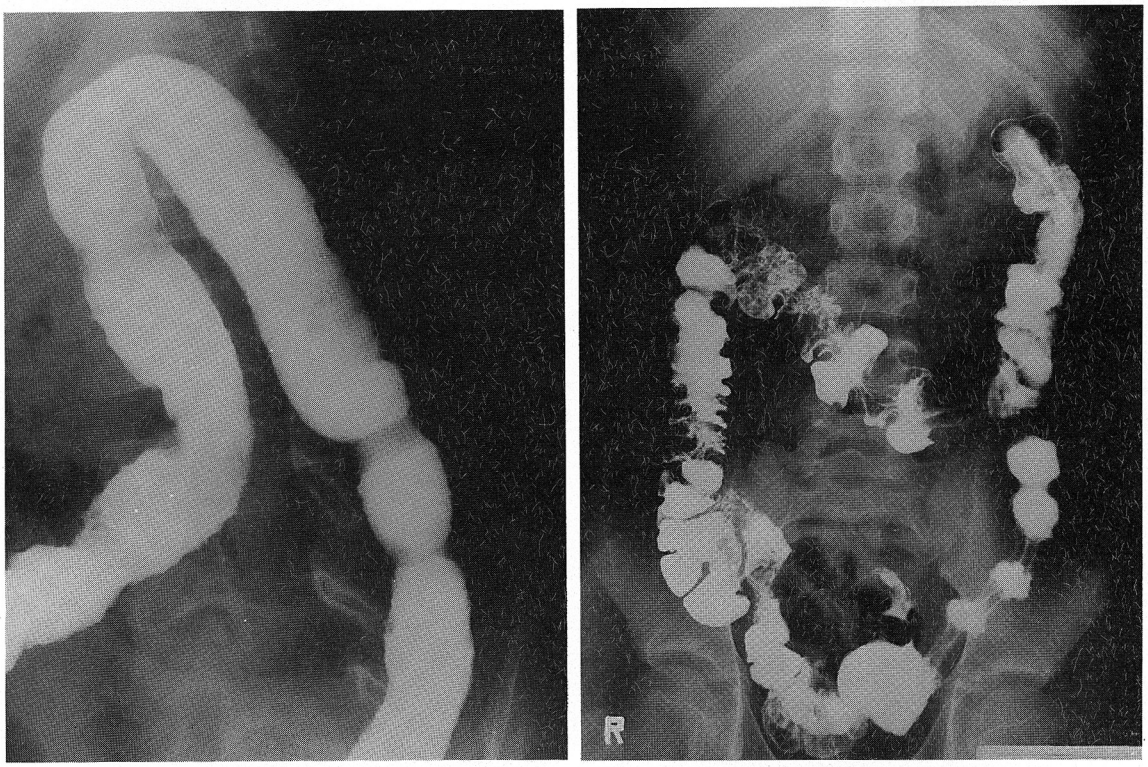

Fig. 8&9. Ulcerative colitis: Barium filled (Fig. 8) and postevacuation (Fig. 9) films show fine marginal irregularities with ulcerations and thickening of folds due to edema.

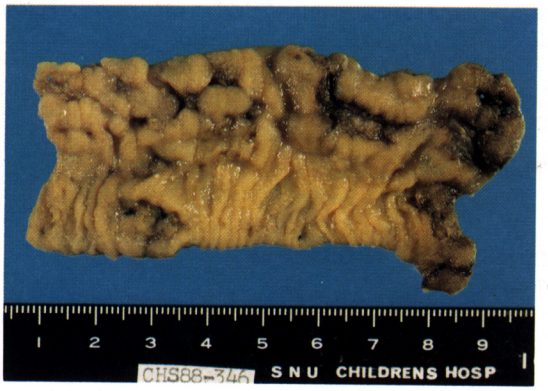

Fig. 10. Gross appearance of Crohn's disease. Multiple irregular ulcers and pseudopolyps are seen.

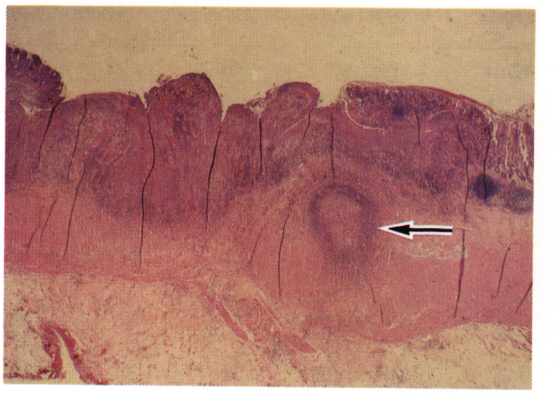

Fig. 11. Photomicrograph of Crohn's disease showing thickened wall, multiple fissures and a well-farmed granuloma (arrow) in the submucosa. H&E×40

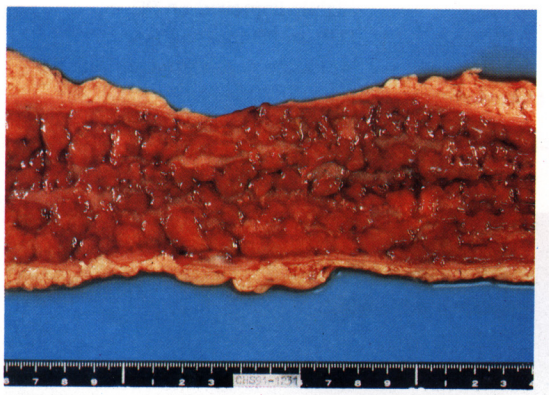

Fig. 12. Gross appearance of chronic ulcerative colitis, showing massive denudation of the mucosa. Remaining mucosa appears polypoid and deeply congested.

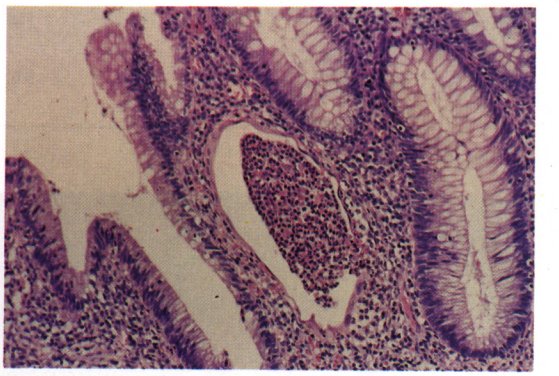

Fig. 13. Photomicrograph of chronic ulcerative colitis, showing an area of crypt abscess. H&E×250

to resemble Crohn's disease was suspected in one child, in whom symptoms relapsed one year later and a diagnosis of IBD was established.

The highest frequency of IBD was between the ages of 15 and 25 years. IBD is relatively uncommon in children particularly under the age of 6 (Whelan, 1990). In the present series of patients, the mean age of diagnosis was 8.7 years, range 2 years to 14 years. Two thirds of children with IBD were diagnosed over 9 years of age.

Major reasons for the delay in the establishment of a diagnosis of IBD were that pediatricians were not familiar with clinical profiles and diagnostic points, and were reluctant to use the diagnostic tools such as colonoscopy and radiology. In 3 patients with IBD in the present study, diagnosis was delayed more than 2 years.

Usually the onset of Crohn's disease is insidious and there is a delay between onset of symptoms and diagnosis compared with ulcerative colitis (Burbige et al., 1975; Gryboski and Spiro, 1978). In the present study, diagnosis of Crohn's disease was delayed for more than 13 months in 8(67%), whereas that of ulcerative colitis was delayed for more than 13 months in 4(40%). The three most frequent presenting complaints of IBD were diarrhea (50%), abdominal pain (36%) and rectal bleeding (36%). Moderately severe abdominal pain was a more common chief complaint in Crohn's disease (58%) than in ulcerative colitis (10%). Diarrhea and hematochezia were more common chief complaints of ulcerative colitis than Crohn's disease. Palpable mass with vomiting, and fistula were noted exclusively in children with Crohn's diesease. In 3 patients, a palpable mass with vomiting and abdominal

pain was the indication of laparatomy.

As in Gryboski and Hillemeier's series (1980), abdominal pain, diarrhea and growth retardation were the three most prominent symptoms of Crohn's disease; periumbilical abdominal pain was present in all patients, and failure to thrive was noted in 58 per cent of patients in the present study. Fresh rectal bleeding, which was one of the most frequent presenting features of ulcerative colitis, was less common in our Crohn's children.

However, colonic Crohn's disease may mimic ulcerative colitis with diarrhea, often containing blood, and pain prior to defecation. Differential diagnosis is often difficult between the two diseases. The presence of epithelioid granuloma or perianal fistula with sparing of rectal mucosa strongly suggests the diagnosis of Crohn's disease. In the present series of three children with colonic Crohn's disease, two showed granuloma with aphthous ulcerations and the other one showed severe perianal fistula. Perianal fistula occurs less frequently in ulcerative colitis than in Crohn's disease. Perianal fistula was noted only in 3 children with Crohn's disease (14%) in the present study. Marcowitz observed that 49% of pediatric Crohn's disease cases had perianal disease, including fissures and skin tags (70%), fistulas (14%), and abscesses (16%) (Marcowitz et al., 1984).

Exudative enteropathy may be a cause of hypoalbuminemia with protein loss (Steinfeld et al., 1969; Van Hees et al., 1980). Severe hypoalbuminemia was noted and protein losing enteropathy was suspected in our two children with Crohn's disease and one with ulcerative colitis.

Systemic complications or extraintestinal lesions in patients with inflammatory bowel disease are discussed less frequently in literature about children and adolescents than in literature dealing with adults (Allan, 1983; Greenstein et al., 1976; Kirsner and Shorter, 1982; Rankin et al., 1979; Smith and Winship, 1980).

The pathogenesis of extraintestinal manifestations in inflammatory bowel disease remains speculative. The most plausible explanation is that they are an immunologic phenomenon. This theory is supported by the presence of circulating immune complexes in the sera of many patients with inflammatory bowel disease with extraintestinal manifestations (Kirsner 1978; Korelitz and Coles, 1967; Rankin et al., 1979).

Arthralgias and arthritis are the commonest extraintestinal manifestations of inflammatory bowel disease in children (Ament, 1975; Burbige et al., 1975; Greenstein et al., 1976; Lindsey and Schaller, 1974; Passo et al., 1986). Usually, large joints are affected, especially knees, ankles, and hips. Ankylosing spondylitis occurs in a minority of children with Crohn's disease (Passo et al., 1986). Layden et al. (1976) and Passo et al. (1986) observed arthritis in 9 per cent of children with ulcerative colitis and 15 per cent of Crohn's disease. They described some instances, in which joint symptoms preceded intestinal complaints for years, leading to the erroneous diagnosis of rheumatic fever and rheumatoid arthritis. In IBD of adults, arthritis was also the most common, ranging in incidence from 5 to 25 per cent. Lindsley and Schaller (1974) reported a 17 per cent incidence in a study of pediatric patients, and Hamilton et al. (1979) found a fairly similar rate of 13% among youngsters with IBD. In the present study, we observed arthralgia in 50% and arthritis in 18% of children with IBD.

The main extraintestinal skin lesions are erythema nodosum and pyoderma gangrenosum. In the present study, erythema nodosum was noted in one child with Crohn's disease and pyoderma gangrenosum was noted in one child with ulcerative colitis. Pediatric series report incidences of 6 to 7 per cent while adults experience these complications in about 15 per cent of cases (Greenstein et al., 1976; Hamilton et al., 1979; Lindsley and Schaller, 1974). In Farmer and Michener's (1979) and Greenstein et al.'s (1976) reports, pyoderma gangrenosum is more frequent in ulcerative colitis (5%) than in Crohn's disease (1.3%). In contrast, erythema nodosum is seen more often in Crohn's disease (8 to 15%) than in ulcerative colitis (4%).

Episcleritis, iritis, and uveitis have been reported to occur in about 4 per cent of patients with inflammatory bowel disease. In children eye lesions are rarely reported. In three series that include over 300 children and adolescents, only one case of iritis was reported (Edwards and Truelove, 1964; Greenstein et al., 1976; Hamilton et al., 1979; Lindsley and Schaller, 1974; Patterson et al., 1971). Acute symptomatic uveitis occurs in only 0.5 to 3% of pediatric patients (Motil and Grand, 1988). We had two patients with eye lesions including keratitis and conjunctivitis.

Serious liver diseases including cirrhosis, sclerosing cholangitis, chronic active hepatitis have been associated about 3 to 7 per cent of the time with IBD. Reports in the pediatric age group are sparse (Greenstein et al., 1976; Kelts and Grand, 1980). Hepatic dysfunction is found in 8% of patients with IBD as determined by liver function test. In childhood, liver disease can be the sole presenting feature of IBD and therefore all children with liver disease of unknown etiology should be investigated with respect to possible IBD. We observed abnormal liver function tests in 2 patients with Crohn's disease. One of them disclosed fatty liver on liver biopsy.

Recurrent aphthous ulceration is the most common oral manifestation. Of our 12 children with Crohn's disease, 7(58%) showed recurrent oral ulcers. No children with ulcerative colitis showed oral lesions. In other series, oral lesions occur in IBD with a reported incidence of 6 to 20 per cent in Crohn's disease. Similar lesions in ulcerative colitis are less well documented, although Edwards and Truelove reported an incidence of over 8 per cent (Basu and Asquith, 1980; Edwards and Truelove, 1964). Greenstein et al. (1976) observed oral ulcers in 2 per cent of children with ulcerative colitis and in 9 per cent of children with Crohn's disease during periods of active disease. In our pediatric wards, the authors had no cases of recurrent oral ulcerations in 29 children with abdominal tuberculosis. The presence of recurrent oral ulcer is often useful in excluding tuberculosis (Kim et al., 1988).

Growth retardation is a major complication of IBD exclusive to children. It is estimated to occur in about 10 per cent of the children with chronic ulcerative colitis and in about 30 per cent of those with Crohn's disease. Bone age is usually delayed by at least 2 years. In our patients with IBD, 58% of Crohn's disease and 20% of ulcerative colitis showed severe growth retardation indicated by growth percentiles below 3. The greater frequency of growth failure in the present series of IBD children may be a reflection of the longer interval between the onset of symptoms and diagnosis and treatment of IBD.

Although malabsorption, zinc deficiency and corticosteroid therapy may play a part in the pathogenesis of growth failure, the most consistent explanation for the growth failure is chronic caloric insufficiency (Kelts et al., 1981; Kirschner et al., 1978; Kirschner et al., 1981; Layden et al., 1976; Strobel et al., 1979). Growth failure is now an established indication for surgical treatment that frequently leads to a growth spurt (Postuma and Moroz, 1985).

Colonoscopy is mandatory in the diagnosis and management of IBD in childhood and should be performed initially and during the follow up period. Even in endoscopically uninvolved intestinal segments, granuloma could be found in biopsy specimens of one of our patients. Multiple biopsy specimens should be taken from grossly normal mucosa. Thirty six procedures of colonoscopy and 7 procedures of gastrofiberscopy were peformed in 10 of our patients with ulcerative colitis. Twenty procedures of colonoscopy and 7 procedures of gastrofiberscopy were performed in 10 of our patients with Crohn's disease, to assess the disease process and responses to the medical therapy.

Aphthous ulcers, cobblestoning, ulcerations in an area of otherwise normal mucosa, asymmetric involvement, rectal sparing and granuloma are the most important endoscopic criteria which favor the diagnosis of Crohn's disease (Teague and Waye, 1981). Our children with Crohn's disease showed aphthous ulcers in 8, cobblestoning in 8, and perianal fistula in 3 patients on radiologic examinations and endoscopic biopsies repeatedly performed during the follow up period.

Tiny aphthous ulcers are seen early in Crohn's colitis; progression of the disease produces larger ulcers that coalesce, become longitudinal, and may extend for several centimeters with deep fissuring.

Cobblestoning is caused by submucosal involvement by Crohn's disease. Cobblestoning must be distinguished from multiple pseudopolyps projecting into the lumen; a pseudopolyp is characteristically taller than its base. Pseudopolyps are a common complication of long-standing disease and occur in both forms of colitis. Their presence does not favor the diagnosis of one or the other. In the present study pseudopolyps were noted in 8 of 12 Crohn's disease and in 5 of 10 ulcerative colitis. Endoscopists consider cobblestoning to be uniform nodulations caused by submucosal edema, although ulcerations may be present in the area recognized as cobblestoning.

Granuloma was found in the biopsy specimens, endoscopically or surgically in 5 of 12 Crohn's children. Granulomas are the hallmark of Crohn's disease but are not present in the majority of patients with this disease, occurring in less than 10 per cent of endoscopic biopsies (Geboes et al., 1978; McGovern and Goulston, 1968; Williams and Waye, 1978). Gastrofiberscopy was performed in some of our patients with Crohn's disease for the investigation of upper gastrointestinal tract involvement. No granuloma was found in the gastrofiberscopic biopsy specimens.

Transmural inflammation and involvement of the GI tract other than colon are the important points for the differentiation between two major idiopathic IBD. Transmural inflammation was noted on surgical specimens in 7 patients with Crohn's disease who underwent surgery. In contrast to ulcerative colitis, Crohn's disease can involve any portion of the gastrointestinal tract from the oropharynx to the perianal area. Radiologic investigation is the most useful method for the evaluation of the involved site. Examining the skip areas is helpful for excluding ulcerative colitis. The characteristic histopathologic lesions of Crohn's disease are small superficial ulcerations over Peyer's patch (aphthoid ulcer), with focal chronic ulceration extending into the submucosa, large lymphoid aggregates without ger-

minal centers and epithelioid granulomas with giant cells (Ament, 1975; Chong et al., 1985; Kirsner and Shorter, 1982).

Characteristically in ulcerative colitis, ulcerations are a manifestation of severe disease and do not occur in mild colitis. On the other hand, loss of vascular pattern and friability are features of relatively mild disease. Granularity and friability, continuous lesions with mucopus and crypt abscess are the endoscopic findings which favor a diagnosis of ulcerative colitis (Waye, 1988). In most instances of relatively early disease, endoscopic differences help in the differential diagnosis but the late stages of both types of colitis may resemble each other so closely that correct differentiation may not be possible endoscopically.

The characteristic histopathologic lesions of ulcerative colitis are: distortion of crypt architecture, polymorphonuclear leucocyte, lymphocyte, and plasma cell infiltration of the lamina propria, crypt abscesses and goblet cell depletion (Ament, 1975; Chong et al., 1985; Kirsner and Shorter, 1982). In the present study, crypt abscesses were found in 8, friability or granularity in 10, and rectosigmoid ulcerations with purulent exudate with continuous distribution were found in 8 children with ulcerative colitis.

The main sites of involvement in our children with Crohn's disease were both the small and large bowels in 7(58%), small bowel only in 2(16%), and colon only in 3(25%). Terminal ileum involvement was seen in 75% of Crohn's disease. Ileocolic Crohn's disease was the commonest localization. Farmer and Michener (1979) and Gryboski and Spiro (1978) reported that sites of involvement in children with Crohn's disease were diffuse small bowel in 20 per cent, terminal ileum in 20 per cent, ileocolonic in 34 to 52 per cent, Crohn's colitis in 10 to 30 per cent and anorectal in 6 per cent of children.

In 95 per cent of ulcerative colitis, the process involves the rectum with varying degrees of proximal extension, resulting in categories of disease: distal proctitis or rectosigmoid, left colon and extensive colitis that involves the transverse colon and pancolitis (Michener et al., 1979). The main sites of involvement in our children with ulcerative colitis were total colon in 4(40%), up to the splenic flexure in 2(20%), rectosigmoid in 3(30%) and rectum only in one (10%). Michener et al. (1979) observed that pancolitis was the most common form (62 per cent), while disease localized to the left colon (22 per cent) and rectum (15 per cent) occurred less frequently.

In general, children with pancolitis have a more severe course. Toxic megacolon, perforation and sepsis are the serious complications, which occur in only 2 to 4 per cent of children with pancolitis and are usually precipitated by procedures such as barium enema or extensive endoscopy. The prognosis of proctitis or proctosigmoiditis in children was not as favorable as for the patients who are adults at the time of onset of the proctitis or proctosigmoiditis. Approximately one third of the patients with childhood onset appear to have a much more chronic course, frequent exacerbations, and extension of disease (Gryboski, 1986; Mir-Madjlessi et al., 1986).

Prednisone (1 to 2 mg/kg/day) is the most effective form of therapy for small bowel and ileocolonic Crohn's disease, whereas the combination of prednisone and sulfasalazine (50 to 100 mg/kg/day) is the most effective in colonic Crohn's disease (Kirschner, 1988). After induction of remission and/or symptomatic improvement, the dose of prednisone is reduced over four to six weeks followed by a complete cessation if possible. Sulfasalazine is administered beginning at a low dosage, for one or two years, depending on the course of the disease.

Metronidazole was used in our 3 patients with Crohn's perianal lesions.

Since 1975, metronidazole has been successfully used to treat Crohn's disease. The usual dose in children is 20 mg/kg/day to a maximum dose of 750 to 1500 mg/day.

Azathioprine or 6-mercaptopurine have been used as adjunctive therapy in Crohn's children to maintain remission while weaning steroids. Azathioprine (50 to 100 mg/day) is usually continued for 3 to 12 months after steroids are tapered and then discontinued (Michener and Wyllie, 1990). Because of the potential risk of lymphoma, leukopenia, and pancreatitis, these medications are usually reserved for children who are steroid-dependent, those with extensive nonresectable disease, or those who have had prior resections (Kirschner, 1988).

In many respects management of ulcerative colitis in childhood present fewer problems than Crohn's disease, in that diagnosis is easier, proctocolectomy is curative, medical treatment is more clearly defined, and growth retardation much less common. Children are more likely to have active and more extensive diease than adults however, with 90% having moderate to severe disease (Ament, 1975).

For patients with mild ulcerative colitis, oral sulfasalazine (75 mg/kg/day, maximum 2 to 3 g/day) is an effective treatment. Starting dose is usually 25 mg/kg/day and is increased to the maintenance dose over several days to minimize potential side effects.

For patients with more severe disease, oral prednisone (1 to 2 mg/kg/day, maximum 40 to 60 mg/day) is effective. To minimize side effects, the dose can be given once a day in the morning if it is effective. We tried once a day steroid therapy in a few patients but it was ineffective. Steroids were administered on a divided dose basis. Tapering off steroids can be done by a reduction of 2.5 to 5.0 mg/week after remission is achieved. As the dose of prednisone is reduced, sulfasalazine is added for the maintenance of remission. Steroids are usually discontinued but there is some evidence that maintaining low-dose alternate-day therapy may be helpful in maintaining remission (Kirschner, 1988). In some of our patients, long term low dose therapy was needed to maintain remission after 4 to 6 weeks' steroid therapy and side effects could not be avoided, although alternate-day steroid was administered to prevent them. Administration of long term corticosteroids on an alternate day basis may lessen growth suppression but colectomy was recommended for a child requiring a dose sufficiently high to produce significant side effects.

Hydrocortisone enemas were beneficial as treatment for patients with the distal colon form of ulcerative colitis, whether proctitis or proctosigmoiditis (Truelove, 1956). More recently, 5-aminosalicylate (the active component of sulfasalazine) and tixocortol (rapidly metabolized steroid) enemas have undergone clinical trials in the treatment of left-side disease (Karp and Targan, 1988).

Seven of 12 patients with Crohn's disease and two of 10 patients with ulcerative colitis were operated on. During the last 30 years, one of the major advances in the therapy of inflammatory bowel disease has been the development of newer and better surgical operations. In ulcerative colitis, subtotal colectomy with an ileorectal or ileal anal anastomosis will make the patient well (Lavery et al., 1983). Our two patients with pancolitis who underwent total colectomy tolerated the frequent stool pattern remarkably well. Indications of surgery for IBD are complications such as obstruction, toxic megacolon, fistula, and abscesses. Surgery is indicated particularly in children who do not respond to medical treatment and show growth failure.

Younger patients have an increased rate of recurrence as defined by the need for a definitive surgical procedure, compared with adults. Those under 20 years of age have a probable recurrence rate of 70% compared with 30% over 40 years, showing the more aggressive nature of Crohn's disease in the pediatric population (Cooke, 1981).

The mortality of Crohn's disease diagnosed during childhood was 2.4 to 13% in other reports (Farmer and Michener, 1979; Puntis et al., 1984). Of 22 children with IBD in the present study, one patient with Crohn's disease died of bleeding associated with hemorrhagic erosive gastritis and liver problems during follow-up. At last follow up, a good state of health with almost no active disease was noted in 8(36%), a fair state of health with mildly active disease in 10(45%), and a poor state of health with limitations of daily activities in 3(13%).

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