INTESTINAL BIOPSY IN CHILDREN

Use of Crosby-Kugler Capsule on 62 Children

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The development of peroral biopsy capsules introduced an important and useful method for the diagnosis of gastrointestinal diseases.[1 - 3] Initially, biopsies were limited to the gastric mucosa, but rapid progress in this field and development of better equipment soon made intestinal biopsies by the oral route possible. Since Shiner's and Crosby and Kugler's descriptions,[4, 5] various other biopsy capsules have been described in an increasing number of papers.[6 - 13] Each new one claimed to be superior to the previous ones. Many of the new capsules have the advantage of being able to obtain biopsy specimens from various levels of the gastrointestinal tract with only one intubation. Use of these capsules in pediatric age groups, particularly in infants, seemed to be rather limited. However, the Crosby capsule has been used in many pediatric centers in studying intestinal mucosa of children and this is the type we used in this study. Our experience agrees with others in the practicability and easy use of this tool in well-trained hands.

Reports of complications following biopsy are rare in the literature.[14] The most serious ones are massive hemorrhage,[15, 16] perforation, and peritonitis.[17, 18] The others, such as failure to pass beyond the stomach, failure of the instrument to fire (due to kinking or plugging), loss of the instrument cap, temporary retention of the capsule due to failure of the knife to sever the mucosa completely, inability of the patient to swallow the capsule, hemorrhage, break in the tubing on extraction of the capsule, etc., are less serious ones.[14]

Since we have collected a fairly large number of biopsy specimens from children, we thought it would be worthwhile to review our experiences and results.

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Material and Methods

In this paper, we will summarize our experiences with 93 biopsy specimens obtained from 62 children seen at Hacettepe Children's Hospital from November 1963 to November 1965. We used eight and nine-and-a-half millimeter Crosby capsules, depending on the age and size of the patient. The smaller was preferred for malnourished children. The youngest patient was nine months old and the oldest 16 years. Table 1 is a tabulation of the age, sex, and diagnosis of the 62 children at the time of the first biopsy. Eleven children with malabsorption syndrome, 17 with malnutrition, 22 with pica and iron deficiency anemia, and, as controls, 12 children with diseases such as Gaucher's disease, mitral stenosis, rheumatoid arthritis, liver cirrhosis, xanthomatosis, and Hand-Shuller-Christian's disease all with some degree of anemia, were studied.

TABLE 1
DIAGNOSIS AND AGE AT THE TIME OF BIOPSY OF 62 CHILDREN

Age	Malabsorption (11 cases)		Malnutrition (17 cases)		Pica and iron deficiency anemia (22 cases)		Controls (12 cases)	
	Male	Female	Male	Female	Male	Female	Male	Female
Under 12 months	—	—	2	1	—	—	1	—
13 - 29 months	—	—	6	5	—	—	—	—
30 months - 7 years	3	1	1	1	6	1	2	—
Over 7 years	3	4	—	1	8	7	6	3
Total	6	5	9	8	14	8	9	3

Before biopsy, a period of fasting was imposed which varied according to the age of the patient: four to six hours for infants and eight to 12 hours for older children. No patients were acutely ill at the time of biopsy, and the infants were offered clear fluids in small amounts if the fasting period exceeded six hours.

Children over three years of age were given an explanation of the procedure before swallowing the capsule. Administration of sedatives (usually phenobarbital or a mixture of thorazine, phenergan and demerol as used in cardiac catheterization) to infants and younger children made the procedure easier. Infants were also wrapped in a large sheet during the biopsy period. However, after an adequate explanation and discussion, older children cooperated well most of the time. Preparation, winding and administration of the capsule was done in the same manner as decribed elsewhere.[19] A small rubber airway protected the polyethylene tube from being bitten by the patient. The children were kept resting in bed for at least half an hour after having swallowed the capsule, lying on their right sides, with their buttocks slightly elevated. Passage of the capsule into the duodenum was observed by fluoroscopy. If the capsule did not pass through the stomach of its own accord, it was led into the duodenum with the help of massage. This was not actually necessary in the majority of cases. When the capsule was seen to have reached the area of the duodenojejunal junction (the Treitz ligament), suction was applied immediately with a 10 and sometimes a 20 ml Luer-Lok syringe. Sudden withdrawal of the syringe was sufficient to fire the knife. Resistance to the injection of saline into the polyethylene tubing was considered proof of closure of the capsule. Then the capsule was pulled out gently and opened. The mucosa specimen was examined under a loop for shape and appearance of the villi before it was put on a card in ten per cent buffered formalin for fixation. After the usual fixation procedures, paraffin blocks were stained with hematoxylin-eosine and examined under the microscope. Special stains (PAS, alcian blue, etc.) were used for specimens requiring further study.

Repeat biopsy specimens were obtained from 26 of the 62 patients. Some of the patients with celiac disease had four biopsies done following a gluten-free diet. Complete details of each group will not be given here since they will be the subject of other papers to be published in the future.[20, 21]

Results

In our series, no serious post-biopsy complications occurred. However, in 32 of the patients, stool guiac tests were positive for occult blood during the 24 to 48 hour period following biopsy. This condition cleared up in two days. Other, less serious, complications were as follows: in three cases (five and six year old boys) the capsule did not go beyond the stomach because of agitation and aerophagia.

Kinking occurred in two cases (a 16 year old boy and girl) but successful biopsies were performed later. In two cases (a two year old boy and an 18 month old girl) the port of the capsule was plugged by mucus, and no specimen could be obtained. In the case of a six year old boy, a knot in the tubing in the stomach prevented a successful biopsy. The instrument fired without obtaining an adequate specimen in four instances. In the case of an eight year old girl with iron deficiency and pica, the capsule could not be removed because the knife failed to sever the mucosa completely. However, a successful biopsy was performed in this case 45 minutes later. The patient complained of some abdominal discomfort shortly after the biopsy was performed, and had a positive guaic test for two days following biopsy.

Our overall rate of failure in this series of 93 biopsies was about 14 per cent.

The following criteria were considered in the interpretation of the mucosa: thickness of the mucosa, villi (shape, range, crypts, mitotic activity and goblet cells), nuclei of the epithelial cells (position, shape, volume, staining properties), lamina propria (edema, degree of cellular infiltration, fibrosis, lacteals and capillaries), and submucosa (edema).[22, 23]

Normal jejunal mucosa contains tall, finger-like villi. The height of the villi is 60 to 80 per cent of the mucosal thickness. The epithelium is tall and contains an oval nucleus in the basal position. The nuclei at the tip of the villi tend to stain darker than those at the base. The lamina propria has capillaries, lymphatics and a moderate cellular infiltration made of lymphocytes, plasma cells, and eosinophils. Doniach and Shiner have shown that the average height of a villus is 470μ and the width is 70 to 150μ.[24] The glandular mucosa is 180μ thick. Today, abnormal changes in jejunal mucosa are divided into two categories, depending on the severity of the change. In *subtotal villous atrophy* the villi become completely flat and broad. Their height is shorter than 150μ, and is often unmeasurable. The epithelium is atrophied and the glandular mucosa is 300μ, or thicker. The lamina propria is edematous and infiltration of lymphocytes, plasma cells, and eosinophils is increased. The appearance is similar to that of glandular hypertrophy. The nuclei of the epithelial cells are irregularly lined and mitotic activity is increased. In *partial villous atrophy* these changes are less severe and the height of the villi varies between 150 and 300μ. Subtotal villous atrophy is considered to be the more advanced with more severe changes. Following

treatment of certain conditions exhibiting subtotal villous atrophy, such as tropical sprue, the mucosa becomes normal again. However, in gluten-sensitive enteropathies, the mucosa improves a great deal but never becomes histologically normal.

Histological examination of our specimens revealed that 14 of the biopsies were taken from the duodenojejunal junction, containing Brunner's glands, but most of the specimens came from the upper jejunum. Only one specimen contained material from the muscular layer; the rest were all of the submucosa.

Sixteen jejunal biopsies were performed on 11 children with a history of malabsorption, aged between four and 16 years. Subtotal villous atrophy was present in 12 specimens taken from seven children. Four had normal mucosa. Repeat biopsies were done on patients with known celiac disease in order to follow the mucosal changes after administration of a gluten-free diet (Figures 1, 2, and 3). Biopsy specimens from the children whose mucosa looked normal histologically will be subjected to enzyme studies in the future.

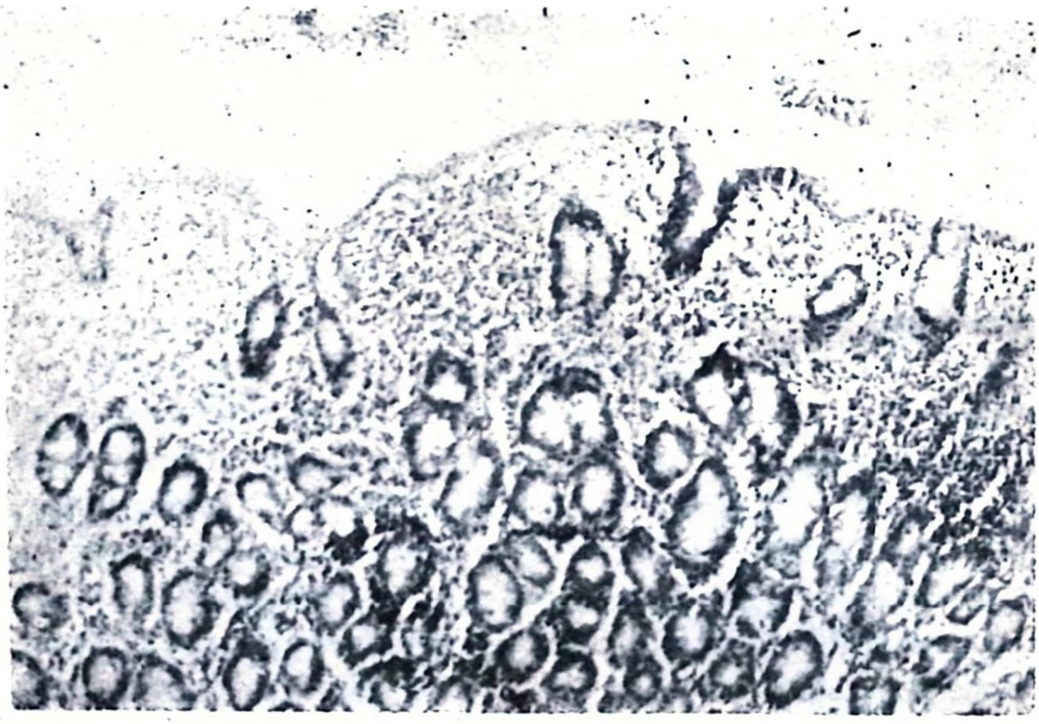

Figure 1. Subtotal villous atrophy in jejunal mucosa of a seven year old boy with celiac disease (hematoxylen-eosine 18 x 40).

A total of 23 biopsy specimens were taken from 17 children with first to fourth degree malnutrition,[25] aged between nine months and five years. Eight of these children had partial villous atrophy and nine were considered to be normal after the initial specimens were studied. Seven months later, four repeat biopsies were performed in

Figure 2. Biopsy specimen from the same patient taken after 18 months of gluten-free diet. Jejunal mucosa shows some degree of improvement. Villi are less broad, but the lamina propria still has increased cellular infiltration and many glands are seen (hematoxylen-eosine 18 x 2.5).

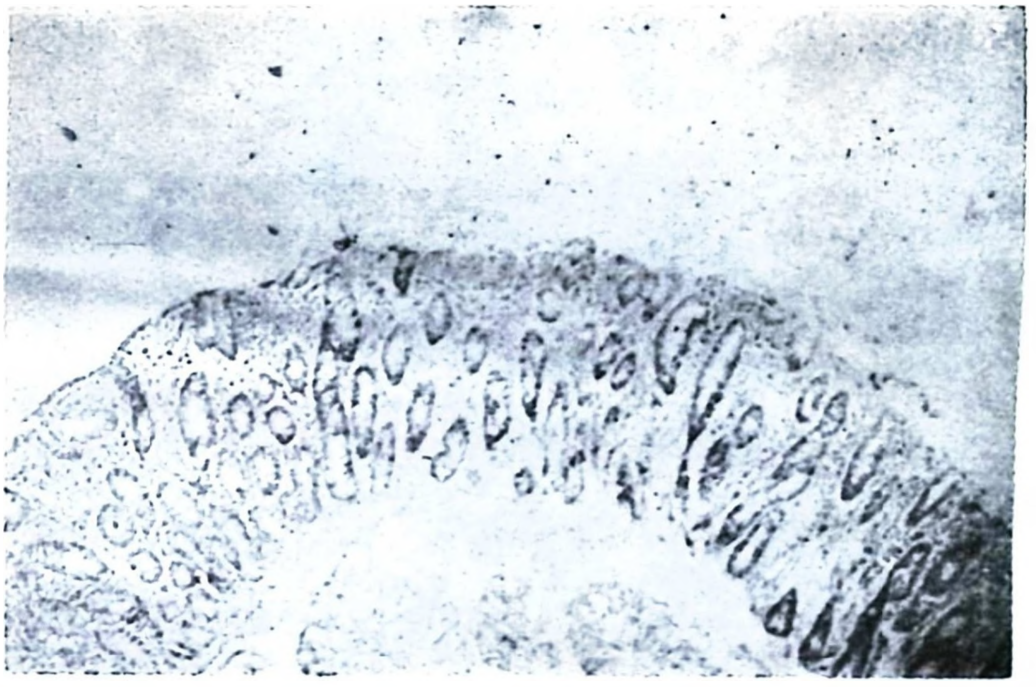

Figure 3. Biopsy specimen taken from the duodenojejunal junction in a four year old celiac patient showing subtotal villous atrophy. Villi are completely flat, glands are increased in number, and Brunner's glands are present (hematoxylen-eosine 18 x 2.5).

those instances where the specimen was histologically abnormal. These second specimens were histologically normal. Repeat specimens from these patients who were normal initially were found to be normal in two cases. Details of this study will be reported elsewhere.[20]

Forty jejunal biopsy specimens were obtained from 22 children with a history of pica and iron deficiency anemia. Their ages varied between 3.5 and 16 years. Seventeen of the specimens were taken after the treatment of their anemia. In the initial biopsies, two instances of subtotal villous atrophy and 11 of partial villous atrophy were observed. In nine cases, the mucosa was normal. Histopathologic examination of the biopsy specimens taken after the correction of anemia indicated that the intestinal mucosa had returned to normal in six patients and had not changed in one patient. Repeat biopsy specimens from children who had normal mucosa before therapy, were again found to be normal.

For control purposes, biopsy specimens were obtained from 12 children considered to be normal from the malabsorption point of view. Their ages varied from one to 12 years and the sections were found to be histologically normal. Specimens obtained from two of these children a year later were also normal (Figure 4).

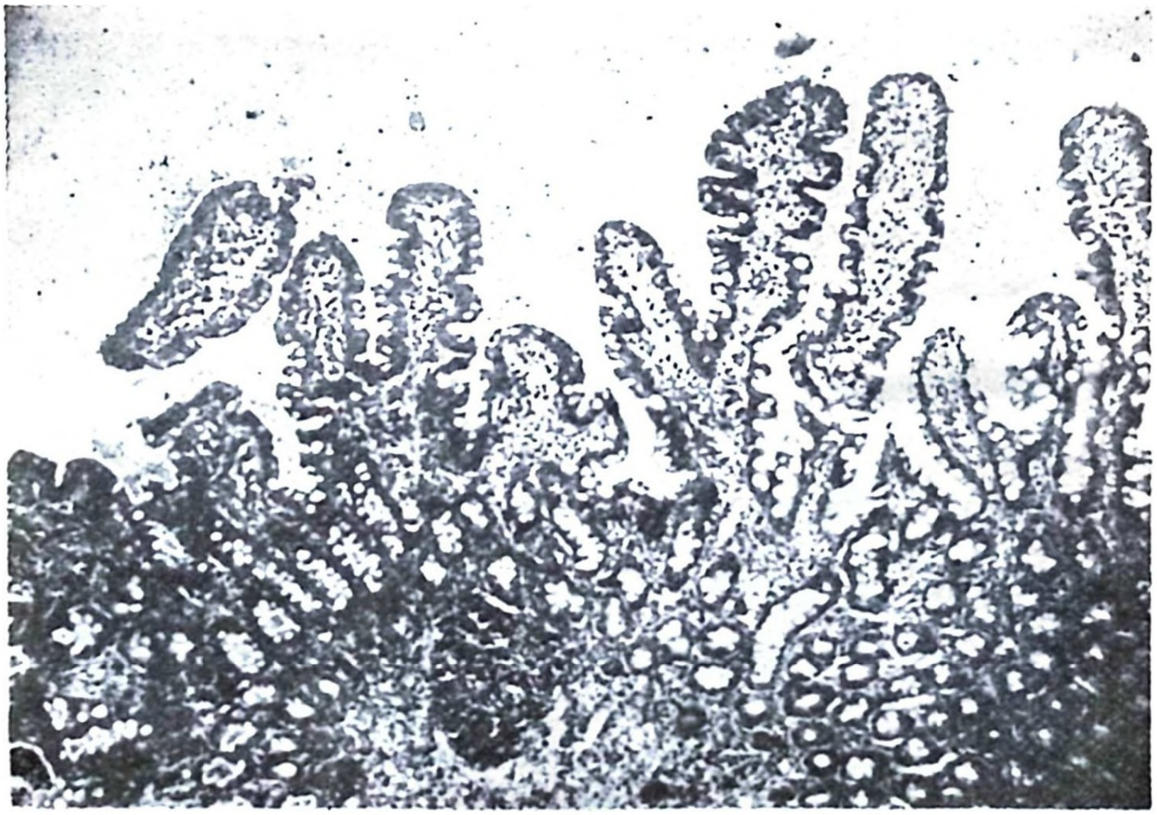

Figure 4. Normal mucosa of a 10 year old girl (hematoxylen-eosine 18 x 2.5).

Conclusions

Since 1956, intestinal biopsy has been increasingly used as a diagnostic method in gastrointestinal disorders such as celiac disease, idiopathic steatorrhea, tropical sprue, exudative enteropathy,

Whipple's disease, tumors and other conditions. Today it is widely used in pediatrics for diagnostic purposes and the number of articles describing its use is increasing daily.[13, 26 - 33] Also, the development of a small Crosby capsule has made it easier to perform biopsies in small children and infants.[33]

In a series of 62 children with diagnoses of celiac disease, malnutrition, pica and iron deficiency anemia, and other diseases, we obtained 93 intestinal biopsy specimens. Following treatment, abnormal mucosal changes disappeared in some patients of each group. This experience confirms that intestinal biopsy in children may be a valuable diagnostic method, and in experienced hands it is recommended without hesitation for pediatric patients.

Summary

Intestinal biopsy specimens obtained from 62 children with the Crosby-Kugler capsule are reviewed. Diagnostic use of the capsule, possible complications, and results are discussed.

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