CROHN’S DISEASE AND NEW ORLEANS
Since the early 1800s, signs and symptoms suggestive of Crohn’s disease have been reported by a number of European and American physicians. However, Dr Burrill Crohn first described the disease, as we know it today, in a presentation at the 83rd meeting of the American Medical Association in New Orleans on May 13, 1932. The paper, entitled “Regional Ileitis: A Pathologic and Clinical Entity,” was published later that year in JAMA under the authorship of Drs Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer. Little did these three pathologists at Mount Sinai Medical Center in New York know that this paper would become a classic. It is of interest that the surgeon involved in the study, AA Berg, declined to put his name to the published report.
The authors noted that patients with this disease commonly presented with diarrhea, fever, continuous weight loss, abdominal pain, and weakness. Certain physical findings characterize the disease, and the most common are:

1) a mass in the right iliac region,
2) evidence of fistula formation,
3) emaciation and anemia,
4) the scar of a previous appendectomy, and
5) evidence of intestinal obstruction.

Young adults were shown to comprise the largest number of patients who displayed the symptoms. Only two of the patients studied were over 40 years of age.

The authors in their presentation suggested that because “the disease simulates regularly the clinical characteristics of ulcerative colitis; the barium enema is first attempted.” However, they noted that the “barium meal,” when carefully interpreted gives definite positive findings of the disease. These usually consist of distended loops of terminal ileum, in which a fluid level is discernible, and a definite delay in motility of the meal through the distal end of the small intestine (Figure 1).

Crohn, Ginzberg and Oppenheimer suggested that medical treatment was palliative and supportive. “The diseased area cannot be reached by colonic irrigations or enemas, and any attempt by medical means to reach a necrotizing, ulcerating and stenosing inflammation of the terminal ileum is purely and essentially futile. But in general, the proper approach to a complete cure is by surgical resection of the diseased segment of the small intestine and of the ileocecal valve with its contiguous cecum.”

Subsequent findings and treatment
Since its description in New Orleans in 1932, Crohn’s disease has been found to be a panenteric process and may affect any part of the intestine from the mouth to the anus. However, the disease is characteristically segmental, with spared areas throughout the intestinal tract (Figure 2). The terminal ileum is the most commonly affected site.

On microscopic evaluation, Crohn and his collaborators noted mucosal changes resembling ulcerative or infectious colitis with infiltration of the intestinal crypts by polymorphonuclear leukocytes (cryptitis or crypt abscesses), and distortion of crypt architecture. However, the presence of fibrosis and histiocytic proliferation in the submucosa suggest the disease they described.

The pathologic hallmark of Crohn’s inflammation is transmural extension to all layers of the bowel wall and adventitia. Clusters of epithelioid histiocytes, or granulomas, are found in intestinal biopsy samples in about two-thirds of patients with Crohn’s disease. However, certain infections, such as tuberculosis and Yersinia enterocolitica, may also be associated with granulomas. Crohn’s disease may also have extraintestinal manifestations. The most common target organs after the intestine are the skin, joints, liver, eye, and bone.

There is no single test that can confidently diagnose the presence of Crohn’s disease. Complete blood counts, erythrocyte sedimentation rate, serum albumin, and C-reactive protein are all used to help establish the activity of the disease. Radioscopy and endoscopy are used to determine the nature and extent of intestinal inflammation (Figure 3).

Recently, antineutrophil cytoplasmic antibodies (ANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) have been recommended as tools to facilitate screening for inflammatory bowel disease with suggestive symptoms and to differentiate ulcerative colitis from Crohn’s disease. The ANCAs are immunoglobulin G antibodies directed against cytoplasmic components of neutrophils, originally described in Wegener’s granulomatosis and necrotizing vasculitis. Combined ANCA/ASCA testing has also been recommended to help differentiate Crohn’s disease from ulcerative colitis. Differentiation of Crohn’s disease from ulcerative colitis is clinically problematic only when inflammation is confined to the colon.
An exciting technology has recently emerged which may be helpful in the diagnosis of Crohn’s disease. In 1981, an Israeli physician, Dr Gavriel Iddan, began development of a video camera that would fit inside a pill. Technology was not ready, and the idea was put on hold. It took 20 years for technology to catch up with Dr Iddan. In 2001, the FDA approved the GIVEN® Diagnostic Imaging System. The 11 x 26 mm capsule weighs only 4 grams (about 1/7 of an ounce) and contains a color video camera and wireless radiofrequency transmitter, four LED lights, and enough battery power to take 50,000 color images during an eight-hour journey through the digestive tract. About the size of a vitamin, the capsule is made of a specially sealed biocompatible material that is resistant to stomach acid and powerful digestive enzymes (Figure 4). Another name for this new technique is Wireless Capsule Endoscopy.

Before the capsule is swallowed, it is suggested that the patient undergo an upper gastrointestinal barium study, which includes the entire small bowel. This allows the physician to eliminate a stricture of the bowel that could prevent the capsule from transversing the small intestine normally.

Patients report that the video capsule is easy to swallow. It seems that the most important factor in ease of swallowing is the lack of friction. The capsule is very smooth, enabling it to slip down the throat with just a sip of water. After the GIVEN M2A® Capsule Endoscope is swallowed, it moves through the digestive track naturally with the aid of the peristaltic activity. The patient goes about regular activities throughout the examination without feeling sensations resulting from the capsule’s passage through the bowel.

During the time the capsule is moving through the bowel, images are continuously transmitted to special antenna pads placed on the body and captured on a recording device about the size of a portable walkman, which is worn around the patient’s waist (Figure 5). After the exam, the patient returns to the doctor’s office for removal of the recording device. The stored images are then transferred to a computer, where they are transformed into a digital movie which the doctor can later examine on the computer monitor. The video capsule is disposable and does not have to be retrieved or returned to the physician. It is evacuated during a normal bowel movement.

Earlier this year, investigators published a study in the journal Gut, in which the video capsule was evaluated. Three seventeen patients with suspected Crohn’s disease fulfilled the study entry criteria: nine had iron deficiency anemia, eight had abdominal pain, seven had diarrhea, and three had weight loss. Small bowel X-ray and upper and lower gastrointestinal endoscop-
ic findings were normal. Each subject swallowed an M2A Capsule Endoscope. Recording time was approximately eight hours and the data collected was retrieved and interpreted the following day.

Of the 17 study participants, 12 were diagnosed as having Crohn’s disease of the small bowel according to the findings of the M2A Capsule. The authors concluded that wireless capsule endoscopy diagnosed Crohn’s disease of the small bowel (diagnostic yield of 71%). It was demonstrated as an effective technique for diagnosing patients with suspected Crohn’s disease undetected by conventional diagnostic methodologies.

Once diagnosed, the physician must explain to the patient and family members that the natural history and severity of Crohn’s disease varies greatly among patients. Exacerbations and remissions characterize the disease. The challenge in treating children and adolescents with the disease is to employ predominantly pharmacologic and nutritional therapy. The indications for surgical interventions for segments of diseased bowel include intraabdominal abscess, enterovesicular fistula, intestinal perforation, and intractable hemorrhage. However, drugs are the first line treatment for individuals with Crohn’s disease. Pharmacologic treatment can be broken into several groups: steroids, antiinflammatory drugs, antibiotics, immunosuppressive agents, and monoclonal antibodies directed toward inflammatory mediators (Table 1). The use of a chimeric monoclonal antibody (75% human/25% murine) is the first entirely new treatment for Crohn’s disease in the last 20 years.

Crohn’s disease and New Orleans today
The Gastrointestinal and Nutrition Group at Children’s Hospital follow a large number of children and adolescents with Crohn’s disease. We recently published a study of our experience with the new monoclonal antibody treatment of Crohn’s disease.4 The drug, infliximab, a chimeric monoclonal antibody, is directed against tumor necrosis factor. The concentration of tumor necrosis factor, a proinflammatory cytokine, has been found to be increased in the gastrointestinal mucosa of patients with active Crohn’s disease. Neutralization of tumor necrosis factor decreases the mucosal inflammatory response of adults with Crohn’s disease. Little information has been available on the use of this antibody in children and adolescents with Crohn’s disease. Our objective was to evaluate the clinical response and side effects of pediatric patients to this new drug.

A retrospective review was undertaken of data on 18 pediatric and adolescent patients with active Crohn’s disease (n=15) and ulcerative colitis (n=3) poorly controlled with conventional therapy. All patients received one to six intravenous infusions of infliximab (5 mg/kg) over a two-hour interval, while receiving their usual medications. All 18 patients experienced clinical improvement following treatment, including a decrease in the frequency of stooling and resolution of extraintestinal symptoms such as arthropathy, malaise, and skin manifestations. All but one patient had a documented decrease in the erythrocyte sedimentation rate. Prednisone dosage was tapered in all but two patients, and discontinued in seven patients.

The intravenous administration was well tolerated except for one patient who developed a
Table 1 Drug treatment of Crohn’s disease

<table>
<thead>
<tr>
<th>TREATMENT OF ACTIVE DISEASE</th>
<th>ACUTE DISEASE</th>
<th>REMISSION MAINTENANCE</th>
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</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Oral/IV corticosteroids (1 mg/kg/d up to 40-60 mg/d prednisone)</td>
<td>Not appropriate</td>
</tr>
<tr>
<td>Anti-inflammatory Drugs</td>
<td>Oral/rectal 5-aminosalicylic acid (50-100 mg/kg/d up to 4 g/d) (Pentasa most suitable for small bowel disease; Asacol or Dipentum most suitable for colonic inflammation)</td>
<td>Oral/rectal 5-aminosalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Oral sulfasalazine (20-60 mg/kg/d)</td>
<td>Oral sulfasalazine (20-60 mg/kg/d)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Oral/IV metronidazole (10-20 mg/kg/d up to 1 g daily)</td>
<td>Oral metronidazole (10-20 mg/kg/d up to 1 g daily)</td>
</tr>
<tr>
<td></td>
<td>Oral ciprofloxacin (20 mg/kg/d)</td>
<td>Oral ciprofloxacin (20 mg/kg/d)</td>
</tr>
<tr>
<td>Immunosuppressive Agents</td>
<td>not commonly used</td>
<td>Oral 6-mercaptopurine (1.5 g/kg/d)</td>
</tr>
<tr>
<td></td>
<td>not commonly used</td>
<td>Oral azathioprine (2 mg/kg/d)</td>
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<tr>
<td></td>
<td>Oral/parenteral methotrexate (up to 15 mg/per week)</td>
<td>Oral/parenteral methotrexate (up to 15 mg/per week)</td>
</tr>
<tr>
<td>TNF Monoclonal Antibody</td>
<td>IV infliximab (5 mg/kg)</td>
<td>not commonly used</td>
</tr>
</tbody>
</table>

rash several days after the infusion. Parenthetically, it should be noted that recently others have described serious anaphylactic reactions in pediatric patients with Crohn’s disease following infliximab infusion.3 Another one of our patients who received six infliximab infusions developed recurrent Staphylococcus aureus infections, as well as septic arthritis and chronic osteomyelitis during the follow-up period, raising the issue of the long-term safety of IV infliximab.

We concluded that the treatment of patients with refractory Crohn’s disease with infliximab was associated with remarkable clinical improvement. Although the drug may have an important role in management of Crohn’s disease and ulcerative colitis, further assessment of long-term safety and efficacy is needed.4

It is of note that one of our patients reported in the above published study, a 19-year-old New Orleans male with Crohn’s disease, developed fever and upper respiratory symptoms 10-14 days after receiving a second intravenous infusion of infliximab. He was admitted to Children’s Hospital where physical examination revealed fever and marked hepatosplenomegaly. The initial hemoglobin was 11.8 gm/dl, the white blood cell count 2.3 x 10 3/mm 3, and platelets 79.0 x 10 3/mm 3. Results of the following investigations were normal or negative: serum electrolytes, bilirubin and
The uric acid; urinalysis; chest roentgenogram; sputum and blood cultures; serologic tests for Mycoplasma pneumoniae, Epstein-Barr virus and cytomegalovirus; stool culture; and a PPD.

Because of progressive hepatosplenomegaly and pancytopenia, liver and bone marrow biopsies were obtained. Histopathology revealed noncaseating granulomas in both specimens and cultures were positive for Histoplasma capsulatum. Urine histoplasma antigen was weakly positive and anti-histoplasma IgM was elevated. Amphotericin therapy was given for two weeks followed by itraconazole. Eight months after the amphotericin, the patient was doing well on continued itraconazole therapy.

A number of patients nationally have developed disseminated Histoplasma capsulatum infection associated with IV infliximab therapy. Furthermore, infliximab may activate latent tuberculosis. Keane et al recently analyzed all reports of tuberculosis after infliximab therapy that had been received as of May 29, 2001 through the Med Watch spontaneous reporting system of the Food and Drug Administration. There were 70 reported cases of tuberculosis after treatment with infliximab. In 48 patients, tuberculosis developed after three or fewer infusions. Forty of the patients had extrapulmonary disease. The diagnosis was confirmed by biopsy in 33 patients. Of the 70 reports, 64 were from countries with a low incidence of tuberculosis. The reported frequency of tuberculosis in association with infliximab therapy was much higher than the reported frequency of other opportunistic infections associated with the drug.

The authors concluded that active tuberculosis may develop soon after the initiation of treatment with infliximab. Therefore, physicians should screen patients for latent tuberculosis or disease before prescribing the drug.

We now feel that although this new therapy for Crohn’s disease is highly effective in adults and children, infliximab and immunosuppressive therapy may increase the risk of uncommon infections.

In summary, this disease referred to as Crohn’s disease, regional ileitis, and granulomatosis colitis was first described in New Orleans. We hope that continued investigation will help us better treat the disease and improve the quality of life for the many children and adolescents with Crohn’s disease that we care for at Children’s Hospital in New Orleans.

About the authors
John N Udall, Jr, MD, PhD, received his BS from Brigham Young University, his MD from Temple Medical School, and his PhD from MIT. He is the Richard E L Fowler Professor of Pediatrics at Louisiana Health Sciences Center and practices at Children’s Hospital, both in New Orleans,
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Elizabeth Mannick, MD, received her BA from Harvard-Radcliffe College, her MS from Harvard School of Public Health, and her MD from Yale University School of Medicine. She is certified by the American Board of Pediatrics in general pediatrics and by the American Board of Pediatrics in gastroenterology. In addition, she is an assistant professor in the Division of Pediatric Gastroenterology and Nutrition at Louisiana State University in New Orleans, Louisiana.

References
1. Crohn’s disease was first described by Burrill Crohn in:
   a. 1912  
   b. 1922  
   c. 1932  
   d. 1942

2. Dr Crohn suggested that the most effective treatment for the disease he described was:
   a. good nutrition  
   b. anti-inflammatory drugs  
   c. immunosuppressive agents  
   d. surgical intervention

3. Which of the following organs can be involved in patients with Crohn’s disease?
   a. brain  
   b. eyes  
   c. adrenal glands  
   d. lungs

4. The most recent agent for treating Crohn’s disease is a chimeric monoclonal antibody to which of the following mediators:
   a. interleukin 1  
   b. interleukin 6  
   c. Cachexin  
   d. tumor necrosis factor

5. Granulomas, which are commonly seen in microscopic evaluation of intestinal biopsies are clusters of:
   a. neutrophils  
   b. histiocytes  
   c. lymphocytes  
   d. eosinophils

6. Surgery in Crohn’s disease is indicated for which of the following:
   a. gastrointestinal reflux  
   b. umbilical hernia  
   c. pancreatic cysts  
   d. intestinal strictures

7. Which of the following is a potential problem with capsule endoscopy:
   a. the capsule must be retrieved from stool  
   b. only large adults can swallow the capsule  
   c. the capsule may not transverse a narrowing of the small intestine  
   d. the transmitted signal can occasionally burn the mucosa

8. Which of the following antibiotics have been used to treat acute Crohn’s disease:
   a. metronidazole  
   b. penicillin  
   c. gentamicin  
   d. erythromycin

9. Which of the following anti-inflammatory drugs is most effective in treating Crohn’s disease of the small intestine:
   a. sulfuralazine  
   b. Aracol  
   c. Dipentum  
   d. Pentasa

10. Which of the following infections can be activated by infliximab therapy:
    a. mononucleosis  
    b. tuberculosis  
    c. Rocky Mountain spotted fever  
    d. lyme disease