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# Describing the Clinical Phenotypes of Crohn's Disease: Lessons from the Past

## Commentary on: *The Broadening Conception of Regional Ileitis*

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Although there remains some confusion regarding the original description of the clinical entity that is currently termed Crohn's disease, medical historians have cited clinical portrayals of what is likely the disease in the works of Hippocrates, Giovanni Batista Morgagni (1682–1771), John Abercrombie (1780–1844), Charles Combe (1743–1817), and William Saunders (1743–1817) [1–3]. In 1912, T.K. Dalziel of Glasgow described a disease of the intestine termed "chronic interstitial enteritis" in which chronic inflammatory changes associated with characteristic episodes of abdominal pain simulating intestinal obstruction were present [4].

Preceding its seminal description in the *Journal of the American Medical Association* (*JAMA*) [5], and references therein, a heterogeneous group of tumor-like inflammatory masses were documented by Tietze in an encyclopedic article in 1920 [6]. By 1923, Moschowitz and Wilenski from Mount Sinai Hospital in New York had described four cases of benign intestinal granuloma, with one having similarity to the original report of regional ileitis [7].

In the first of two presentations in May 1932, Leon Ginzburg presented, before a meeting of the American Gastro-Enterological Association and later published in an expanded form, a description of 52 cases of a granulomatous disease of the intestines without evidence of recognized diseases, including tuberculosis, syphilis, or actinomycosis [7]. A second presentation by Burrill Crohn entitled "Terminal Ileitis: Its Clinical Manifestations," was delivered to the Section on Gastro-Enterology and Proctology of the American Medical Association in New Orleans, describing 14 patients, predominantly young adults, with stenosis of the distal ileum and fistulous disease to the large intestine or abdominal wall. Clinical symptoms resembled the known entity ulcerative colitis, while pathology demonstrated subacute or chronic necrotizing inflammation beginning abruptly at the ileocecal valve and extending orally for 8–12 inches (c. 20–30 cm), involving the distal ileum alone. In short order, the presentation, entitled "Regional Ileitis," was published by Crohn, Ginzburg, and Oppenheimer to a wide audience in *JAMA* on October 15, 1932 [3, 5].

The original description of regional ileitis was timely and accepted by the medical community with immediate additions to the 14 original cases. J.A. Bargen from the Mayo Clinic offered the term "regional" as opposed to "terminal" ileitis, recalling similar cases and recognizing the "agonal" connotation of the descriptor "terminal" [5]. Julius Friedenwald of Baltimore and Louis Hirschman of Detroit added anecdotal cases similar to the descriptions of Crohn, with the addition of a relationship between a previous diagnosis of ulcerative colitis and granulomatous pathology of the terminal [5].

In Volume 1 of the *American Journal of Digestive Diseases and Nutrition* (and reprinted in part in this issue), Crohn describes in detail three cases of regional ileitis in his publication "The Broadening Conception of Regional Ileitis," in an attempt to revise and expand the initial concepts of the diagnosis in the face of growing clinical experience [8].

The original article *The broadening conception of regional ileitis* by Burrill B. Crohn published in *American Journal of Digestive Diseases and Nutrition*, April 1934, Volume 1, Issue 2, pp. 97–99. Springer.

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# THE BROADENING CONCEPTION OF REGIONAL ILEITIS*

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WHEN the original observations on ileitis were made, about three years ago, (1) the disease was considered to be one which involved only the terminal ileum. In fact, in the fourteen cases which were published as the original report, the terminal ileum was the seat of election of the disease in practically all instances. The degree of involvement of the terminal ileum averaged usually from eight to ten inches. There were however, instances of twelve, fourteen and sixteen inches involvement. On the other hand, there was one patient in which the diseased area, actually only an inch wide (2.5 cm.), had created an obstructive stenosis of the small intestine. In the original group reported there was one exception. This unusual case was one in which a terminal ileitis had been found at a previous operation and an ileo-transverse-colostomy had been performed. Symptoms recurred and on re-operation another and probably a new area of the ileum *proximal* to the anastomosis was discovered to be the seat of an identical pathological lesion. This was a clear warning that the disease could involve other segments then the terminal ileum. The term, "regional ileitis," suggested by Dr. J. A. Bargen, was adopted in preference to "terminal ileitis."

About two years have elapsed since our original description of this disease. The fundamental considerations and characteristics detailed hold good. In special particulars, as our clinical experience broadens, we are electing to enlarge, and in a small way, amend the first concepts. Some of these suggestions will be mentioned in the discussions of the following cases:

## MULTIPLE INTESTINAL FISTULAE: A MUCH OPERATED PATIENT

CASE 1.—A. B., a 40-year old Pole, a salesman by occupation, with a past history which is irrelevant and of little significance. Venereal infection was denied; the patient had suffered from an attack of nasal sinusitis seven years previously. In 1917, or 17 years ago, he entered Mt. Sinai Hospital, New York City, with a *complaint of epigastric pain* of three months' duration; the pain radiated to the left flank and the left iliac fossa. The onset of his illness seemed rather acute and well defined; it was characterized by severe abdominal pain or cramps without vomiting or fever. Later however, the attacks of cramps became almost continuous and were associated with vomiting. There was a loss of 6 pounds of weight in 6 weeks.

*The physical examination* (in 1917) was negative. A slight anemia was present (hemoglobin 72%). White cell count was 14,000 of which the polymorphonuclears represented 80%. There was normal gastric acidity. The gastro-intestinal radiographs were, at that time, described as being negative. However, there was *pain on deep pressure over the right iliac region.*

*Operation:* The patient's abdomen was explored, an uninvolved appendix removed, and no evidence of other disease detected. Following operation, the patient continued to be troubled with epigastric and lower abdominal pains. Three years later, at a quite different hospital, (1920) he was *reoperated* because an abscess had formed under the scar of the initial operation. The opening of this abscess disclosed fecal material, which *fecal fistula* now became a permanent feature, draining profusely and giving discomfort. Shortly thereafter, the patient was once more operated upon; an ileo-transverse-colostomy was performed. A year later he underwent a *fourth operation*, at which time a resection of part of the cecum and ascending colon was performed (1921). The data concerning these operations is meagre, but apparently in spite of four laparotomies, no one had yet discovered the nature of the underlying disease. Following the fourth operation an uneventful recovery was made and for a period of nine years (until 1929) the man felt well and gained more than 60 pounds in weight.

*Four years ago, pain reappeared* in the right lower quadrant at the site of the old fistula. Shortly, the skin became red and swollen and in a few days an abscess broke, re-establishing the old fecal fistula.

An exploratory laparotomy, (*the fifth operation*) performed at a third hospital, was made and an attempt to close the fistula carried out. This was unsuccessful; the fistula persisted and with it attacks of abdominal pain. The failure of the fistula to close suggested partial or sub-acute intestinal obstruction. Five months after this fifth operation, *another short-circuiting operation* was performed at the same institution. This last operation probably was in the nature of an anastomosis between the proximal ileum and the sigmoid, since, by this time, it was apparent that the small intestine was the cause of the obstruction, but the nature of the lesion in the ileum still remained an enigma. *Following the sixth operation*, the wound again broke down with the re-formation of a fecal fistula and with the recurrence of abdominal pain and vomiting (partial obstruction).

A year and a half ago (1932) another attempt was made to close the fistula, this was again unsuccessful and still another attempt, one year ago (1933) was made; this latter attempt again was unsuccessful. All in all, there were *eight laparotomies* before the patient was admitted to Mt. Sinai Hospital for the second time.

*On re-admission*, the general condition of the patient was fair. He had pain, some loss of weight, a slight anemia; the abdomen was soft, but not distended. There were multiple abdominal scars: three lower left quadrant rectus scars, two lower right quadrant rectus scars, and in addition, two small puckered scars of old sinuses, all healed. *There were four right lower quadrant fistulae* exuding thin fecal matter and surrounded by a zone of moderately inflamed skin. Hemoglobin was 55% but the blood chemistry not abnormal. There was a *positive guaiac reaction* for occult blood in the stool at all times.

*A barium enema* showed the presence of two fistulous openings, one from the sigmoid toward the cecum, and the other from the sigmoid toward the small bowel. These findings were confirmed by a barium meal by mouth.

In the face of these enormous difficulties further operation did not seem feasible, yet it was impossible to allow the patient to remain in his sad plight. *A ninth operation* was performed by Dr. A. A. Berg. This consisted of a resection of the terminal ileum, of the ascending colon and the hepatic flexure; disconnection of a double ileo-signoidostomy; closure of a proximal sigmoidal stoma; an end-to-side implanting of the proximal end of the resected ileum into the distal sigmoidal stoma; closure of the cut end of the transverse colon and drainage of retroperitoneal space for abscess. There were resected 152 centimeters of small and large bowel. (Figure 1). The patient made an uneventful recovery—*mirabili dictu!*

### PATHOLOGICAL REPORT

The specimen consisted of small intestine, the ascending colon and hepatic flexure anastomosed by an ileo-ascending-colostomy. From the ileo-colostomy there were four or five fistulous tracts, about which there was dense scar-tissue. At two and at eight centimeters from the stoma in the small intestine, were transverse ridges of elevated, pale mucosa consisting of bands completely annular. At various areas along the ileum there were patches of elevated, injected, raised and thickened mucosa. *The microscopic examination* of these scattered areas of sub-mucosal inflammation were reported as "annular ulcerations with non-specific, chronic inflammation of the ileum; no tuberculosis in the specimen submitted."

### COMMENT

Of course, the outstanding and most striking feature of this case is that surgeons of repute overlooked the underlying pathological condition. Until recent years, before attention was called to the distal segment of the ileum, it was common during the course of an exploratory operation to observe carefully the appendix, gall-bladder, stomach, kidneys, pancreas and colon; the small intestine was supposed to be exempt from disease, or involved so rarely as to demand very little consideration.

That, *in three years*, we have accumulated experience with between 30 and 40 cases is evidence that the affection being discussed is not rare. Hereafter, pain in the right lower quadrant associated with temperature, distention and tenderness on palpation, calls for close scrutiny of the coils of the lower ileum.

We have also remarked on the number of cases of ileitis which have been appendicectomized at some time. At

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[1]Crohn, Burrill B., Ginzburg, Leon, and Oppenheimer, Gordon, from the Mt Sinai Hospital, New York. Regional Ileitis. *J. A. M. A.*, 1932, XCIX, 1323-1328.

First, is a case of a 40-year-old male initially undergoing appendectomy for abdominal pain with weight loss, followed by eight operations for recurrent fistulous disease. Crohn comments on the nature of the newly-described disease of the small bowel, focusing on surgical resection as the most appropriate durable therapy. In doing so, he raises concern for appendicitis in the differential diagnosis of the initial clinical manifestations of the disease. Appendectomy and inflammatory bowel disease have continued to be associated to the present day, with some data supporting prior appendectomy as a risk factor [9]. In the single case report, Crohn also describes surgical sequelae, such as the development of recurrent disease and the spontaneous healing of internal fistula following resection, foreshadowing current concepts of the management of post-operative Crohn's disease [10].

In the second case, Crohn describes the presentation of a 24-year-old attorney with mild diarrhea and weight loss. Following exclusion of ulcerative colitis with sigmoidoscopy, and without the commonly described tender right lower quadrant mass, diagnosis was confirmed by radiographic examination in which rounded and oval ulcerating lesions of the distal ileum were reported. Understanding the role of surgical resection in the management of disease, an exploratory operation was performed based on the radiographic findings, after which the patient expired. On the basis of pathologic examination of the resected intestine and colon, ulcerations and longitudinal ridges with areas of spared mucosa extending from jejunum to distal ileum were described for the first time.

In 1934, the definition of regional ileitis expanded to include not only ileojejunitis but also colitis, although Crohn himself refuted the notion that the colitis and ileitis were of similar etiology. The definition further extended to the duodenum by 1937, and to the stomach by 1949 [11]. Outside of individual cases, the typical radiographic appearance of regional ileitis was described by Kantor in 1934, who first coined the term "string-sign" [11].

The final case describes a 32-year-old female, a sister of a patient in the originally described cohort. While symptoms of generalized and related right upper quadrant pain suggested disease of the gallbladder, development of intestinal obstruction led to resection of the distal ileum, cecum, and ascending colon, with regional ileitis reportedly affecting the distal 8 inches (c. 20 cm) of ileum. In describing this, the first familial involvement of regional ileitis, Crohn suggests a congenital predisposition or transmissible causative agent, although further data supporting a hereditary influence would not be described until 1960 [12].

From the original descriptions of chronic inflammatory changes of the small intestine, to benign granulomas of the gastrointestinal tract, and ultimately the account of regional ileitis, significant advancement has been made in the documentation of the of the clinical manifestations of Crohn's disease, as highlighted in the early pages of the *American Journal of Digestive Diseases and Nutrition.* Initial attempts at characterization of the disease entity constricted its phenotypic description. Nonetheless, the heterogeneous clinical manifestations of the disease were soon recognized, necessitating amendments to the original disease description to include post-operative recurrence and familial inheritance, all of which are active topics of research interest today. Although we still think of treatments in non-specific ways among patients with intestinal inflammation, we are moving away from such "lumping" of all the inflammatory appearances of the intestine into "Crohn's disease" towards more detailed description of phenotypes and the increasing recognition of genetic, serologic, and even microbiome-related distinctions between disease types. Underlying this progress are careful observations and detailed descriptions of individual patients suffering from enigmatic conditions, which is well illustrated with Crohn's description, republished in this issue [8].

**Conflict of interest** None.

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