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Regional enteritis

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REGIONAL ENTERITIS

SENIOR THESIS PRESENTED TO THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

OMAHA 1939

ROBERT E. LLOYD
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INTRODUCTION

"We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by subacute or chronic necrotizing and cicatrizizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

The disease is clinically featured by symptoms that resemble those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine; the constant occurrence of a mass in the right iliac fossa usually requires surgical intervention (resection). The terminal ileum is alone involved. The process begins abruptly at and involves the ileocecal valve in its maximal intensity, tapering off gradually as it ascends the ileum orally for from 8 to 12 inches (20 to 30 cm.). The familiar fistulas lead usually to segments of the colon, forming small tracts communicating with the lumen of the large intestine; occasionally the abdominal wall, anteriorly, is the site of one or more of these fistulous tracts."
Thus, in 1932, did Crohn, Ginzburg, and Oppenheimer (40) recognize and describe a specific entity which must have existed for centuries. It seems incredible that the condition could have defied recognition for so long. The literature prior to 1932 does make reference to a heterogeneous group of cases under various terms, e.g., benign granulomas of the intestine, infective granulomas, varioc carcinomas and tumors in the abdomen, and non-specific granulomas of the intestine. The concept of early writers of regional ileitis was a tumor-like mass characterized by piling up of granulation tissue and exhibiting varying stages of necrosis, fibroblastic changes, and scar tissue. Many recognized the masses as non-specific tumors but were much confused as to classification. This error was based on the similarity to other tumor masses due to tuberculosis, actinomycosis, Hodgkin's, and lymphosarcoma. The very word, granuloma, is confusing. The only distinctive differentiation of these masses from tumors made by early observers was the use of the term "infective granuloma", conveying the idea of an inflammatory mass.

Crohn, Ginzburg, and Oppenheimer deserve much credit for the first clear-cut description of this clinical entity which has resulted in the reporting of nearly 600 cases within six years of the original report according to Clark (24).

Fate decreed that these three men should get the
credit for presenting a masterpiece of medical literature to which essentially little has been added. Over a century ago, on July 4, 1806, Charles Combe and William Saunders, a fellow of the Royal College of Physicians of London, reported a case of terminal ileitis under the title, "A Singular Case of Stricture and Thickening of the Ileum". They reported the case as follows: "The patient was William Payne Georges, Esq. of a very nervous and delicate habit-----at necropsy (Monday, Feb. 10, 1806), ---it was found that the stomach, duodenum, the jejunum, and the upper part of the ileum, liver, spleen, and kidneys were in a natural and sound state. The lower part of the ileum as far as the colon, was contracted, for the space of three feet, to the size of a turkey's quill-----".

John Abercrombie (2) who lived from 1780 - 1844, tells of a 13 year old girl, who about a year before her death, began to be affected with pain of the abdomen and frequent vomiting. "The lower end of the ileum, to the extent of about 18 inches was distended, thickened in its coats, externally of a reddish colour, and internally covered by numerous well-defined ulcers, varying in size from the size of a split pea to a six-pence." The lungs and all other organs were healthy.

Mock (104) and Lick (94) state that Braun (17) presented one of the first clinical reports of the dis-
ease as an entity in 1909. Moynihan (107) in 1907 operated on six cases of ileal granuloma under the mistaken diagnosis of malignancy. The clinical and gross appearance supported such a diagnosis but microscopic sections proved the process to be non-malignant in character.

Mayo Robson (97) in 1908 called attention to the not uncommon occurrence of non-malignant tumors of the gastrointestinal tract. Dalziel (45) in 1913 published an article entitled, "Chronic Interstitial Enteritis", in which he presented several cases which resembled those which we now call regional enteritis. One of his cases as a physician who died in 1901 and presented a fixed small intestine, omental mesentery, and enlarged glands. The pathological report was chronic inflammation.

Moschowitz and Wilensky (106) described in 1923, four cases of non-specific granulomata of the intestine of which one case was very suggestive of our present conception of regional enteritis. They insisted that the thickening was neither tumor nor specific infection.

Mock (104) called attention to the frequency of infective granulomata and the inadequacy of the literature of our own country in dealing with this field. He recognized that these tumor-like masses were due to low grade inflammatory causes. He preceded Crohn in recognizing the lesions as non-specific, sharply differentiated from specific or true granulomas.
In 1920, Tietze (140) presented one of the first reviews of benign granulomas.

Mock (104) cleared the confusion somewhat by for the first time differentiating true granulomas represented by tuberculosis and lues from the infective lesion which simulate them. However he did not recognize the definite entity.

Crohn and associates finally swept away all confusion regarding the classification.

Harris, Bell, and Brunn, in the year following the original description, disputed Crohn and associates' contention that the condition was limited to the terminal ileum. In their article (71) they state,"One of our cases, and another case we are not reporting in this paper, clinically and microscopically showed the characteristic lesions described by Crohn and associates, and involved mainly the jejunum- -". Crohn (34) in 1934, fell in line with their conception of the extent of the process. He said, "Within a year we were beginning to see higher lesions of the ileum, involving the upper ileum and -------. I was at first inclined to deny that jejunitis and ileitis were the same disease; since that time, we have had three instances of involvement of the upper ileum and jejunum, so that we are anxious to add to our original description of the disease, the fact that the whole ileum and jejunum may participate in the process."
Harris, Bell and Brunn suggested the name "chronic cicatrizing enteritis" since the disease was not limited to the ileum. Bell (10) again suggested this term in 1934. Corr and Boeck (32) in 1934 suggested "chronic ulcerative enteritis" since ulceration was such a constant feature and was found in both early and late phases of the disease, whereas cicatrization appeared in the later stages only.

Colp in 1934 (29) reported a case in a young medical student in which the disease extended beyond the ileocecal valve into the cecum. He stated that the ileocecal valve did not arbitrarily limit the progress of the disease. Crohn and Rosenak (42) in 1936 recognized the necessity of presenting another addition to the original concept in their article, "A Combined Form of Ileitis and Colitis." In presenting 60 cases of regional ileitis of which 9 involved the cecum or colon in addition, they extend credit for the original report of such a form to Colp. However, in the same year of Colp's important discovery, Brown, Bargen, and Weber presented a series of 18 cases of which 1 involved the cecum and 5, the cecum and ascending colon as well as the ileum. In addition they had 3 cases which involved the jejunum alone, a worthy support to Harris and associates contention.
ETIOLOGY

Most authorities agree that the cause of regional enteritis is obscure. In efforts to establish the cause of regional enteritis, varied explanations have been offered, which to their proponents, leave little room for doubt. Efforts to corroborate the findings, however, leave little definite proof of the etiologic factors.

It generally is accepted that tuberculosis, amebiasis, chronic ulcerative colitis, diverticulitis, foreign bodies and disturbance of the blood supply can cause granulomatous lesions of the bowel. Pumphrey (121) undertook investigation of 13 cases of granulomata of the bowel in an attempt to add to our knowledge of the etiology. Ten were of the regional ileitis type and the other three were lesions of the cecum and ascending colon. Many organisms were recovered none of which could be said to be predominant throughout the series. In no instance was he able to isolate an organism belonging to the dysentery group. Of the organisms recovered, none caused agglutination regularly; that is, an organism recovered might cause agglutination of the serum of the patient from whom it was recovered, but not of the serum of the other members of the series. Thirteen rabbits were injected intravenously; in one rabbit a diffuse thickening of the small bowel about eight inches long situated about twelve inches above the junction of the small and large bowel was noted. None of the other rabbits gave
any evidence that gastrointestinal disease was present. In two cases in which foci of infection in the upper respiratory system were suspected, cultures were made and Streptococcus viridans recovered. Injected into rabbits, this material failed to produce evidence of gastrointestinal disease.

Inoculation of laboratory animals has showed no evidence of tuberculosis. Romans and Mass (76) injected macerated tissue from lymph nodes and from the serosa of the ileum into animals. They also made cultures under anaerobic and partially anaerobic conditions. The animals all remained healthy and ten weeks after injection were examined and found to have no pathological lesions. In addition, no growth could be cultured.

Wasserman reactions have been repeatedly negative. Mock (104) thinks the cause of infective granuloma is a low grade infection causing an impairment to the circulation or to an impairment of the circulation followed by a low grade infection. Moschowitz and Wilensky (106) as early as 1923 that some low grade bacteria must be the cause.

Woolsey (144) calls attention to the abundance of lymphatics in the ileocecal region. Reichert and Mathes (126) produced chronic lymphedema in various regions of the gastrointestinal tract. They reported their findings in chronic lymphedema of the ileum and colon which was
secured by injection of sclerosing materials into the mesenteric and subserosal lymphatics. The injections produced a sclerosis and thrombosis of the lymphatics which led to a chronic lymphedema. Thickening and edema were most marked in the submucosa and muscular layers. The injection of bacteria intravenously in conjunction with this lymphedema produced the greatest thickening of the wall. The lymphedema persisted for ten months and appeared to be permanent. These findings paralleled those of regional cicatrizing enteritis. They state, "The more extensive stenosis and mucosal ulceration in regional enteritis might be attributed to the persistence of a chronic low grade infection. The two dominant features of regional cicatrizing enteritis seemed to be a low grade chronic inflammation with a concomitant chronic lymphedema."

Mixter (103) states that the observations of Homans, Drinker, and Field support the findings of Reichert and Mathes,

Jackson (80) states that "---the etiological factor in some cases may be a fungus organism similar to the Streptothrix."

Razzaboni (125) suggests a virus as the causative agent.

Erdemann and Burt (51) believe that toxins in contact with a broken mucosa may precipitate the condition.
Pupini (122) reports a case of stenosis of the small bowel following trauma two months before. Leonardo (92) attributed the cause in his case to the trauma following operation for adherent retrocecal involvement ten days before the onset. The pathological report was early appendicitis. The ileocecal region was normal at the first operation. At a second operation a combined form of ileitis and colitis was found.

Most observers agree the appendix is innocent. Crohn (39), reporting his personally observed series of 110 cases, says that 33% of the cases had had their appendix removed with no affect on the course of the disease or with no typical changes in the appendix. Nevertheless, several have advanced the appendix as an exciting factor. Among them, Donchess and Warren (48) report a case apparently developing from appendicitis. Molesworth (105) suggests that stenosis, in his case, was due to appendicitis and appendectomy, thus embracing the traumatic factor as well. Ravdin and Rhoades (124) have ventured a common etiological factor between regional enteritis and fibrinoplastic appendicitis. They have observed six cases of the former, two of the latter, and have noted a marked similarity in their pathology.

Specific infections as etiological factors have gained little support. Halligan and Halligan (70) obtained a pure culture of Aerobacter aerogenes, and sug-
gest that this organism's usually mild pathogenicity may be altered under favorable conditions. Fetterman and Lerner (59) report a case of ileitis associated with a fatal tularemic pneumonia. Barber and Stokes (5) advance the possibility of Giardia infection as the causative factor, this organism being a recognized invader of the small intestine. Their patient had a G. lamblia infection which remained until the time of his death. Mixter (102) obtained anaerobic streptococci in pure culture from the peritoneal fluid and the cut surface of mesenteric glands. However, with these organisms, the lesion could not be reproduced in laboratory animals. Mailer (96) found Strep viridans in the blood.

Perhaps the most interesting claims for a specific infection as being the etiological factor in regional ileitis have been introduced by Felsen (54), (55), (56), (57), (58), who is certain that the blame lies with the dysentery bacillus. He contends that bacillary dysentery, distal ileitis, and non-specific ulcerative colitis are merely different stages of the same disease process. He (54) classifies terminal ileitis as one of the atypical forms of acute bacillary dysentery, viz., the "appendicular type". Felsen and Gorenberg (58) having studied several hundred cases of acute bacillary dysentery (Flexner type), state that 90% of the patients recover but the remaining 10% develop chronic forms more
generally known as regional ileitis or ulcerative colitis. Felsen's conclusions have been drawn from a study of 553 cases of acute bacillary dysentery, distal ileitis, and chronic ulcerative colitis; he calls attention (57), to the absence of positive agglutination in many recovered cases of known bacillary dysentery, thereby seeking to explain the absence of positive titers noted by other observers. Studies made in the Metropolitan area between December of 1933 and December of 1934 of the Sonne-Duval and Flexner types of dysentery showed a 3% frequency of the "appendicular" form in both types (55).

Paulson (113) supports Felsen's views.

Pumphrey's (121) failure to find dysentery has been reported above.

Bisgard and Henske (13), in discussing their case, assumed that the dysentery bacillus which was present in the urine, might have played a part in the inflammatory process in the ileum, and a$reptococcus hemolyticus isolated from the peritoneal cavity and a mesenteric lymph node, might have been a secondary if not a primary invader of the bowel wall.

Bargen (6) states that agglutination titers in a large series of intestinal conditions exhibited a positive result just as frequent, and in as high a titer, in cases of of cancer of the intestine as in cases of regional ileitis. Most other authorities hold Felsen's views in disregard also.
In the absence of a known etiological agent, other reasons for the predilection of the disease for the ileum have been considered. It is possible that some peculiarity of the anatomy of the terminal ileum, its mesentery, or its blood supply may predispose toward the development of a chronic granulomatous inflammation of this region. Bell (10) has been unable to produce a cicatrizing stenosis, ulceration of the mucosa, or any other lesion simulating the condition by experiments dealing with the interference of blood supply.

An arrangement which would permit of twisting, angulation, and partial intermittent intussusception or volvulus has been considered. Ginzburg and Oppenheimer (64) mention the possible role played by a disturbance of the vascular mechanism. They referred particularly to repeated and self-reducing intussusception or recurrent partial volvulus at the ileocecal valve, and emphasize the inability of differentiation, in the end stages, granulomatous lesions due to primary vascular insufficiency from those due to primary infective agents. Jackman (77) describes his first impression of two cases seen on the operating table, "At first sight the appearance of deep congestion in the gut and its sharply limited extent strongly suggest that there has been some strangulation. An internal hernia, strangulation by a band, or a volvulus might each cause this appearance of abruptly
limited strangulation, or a thrombosis of one of the terminal branches of the ileocolic artery might have produced the same apparent result." Bockus (15) states that the ascending branch of the ileocolic artery, which supplies the cecum, is more or less fixed in most anatomic specimens, whereas the terminal branch of the same artery, which supplies the terminal ileal segment, might by twisting or pinching the terminal branch of this artery, tend to devitalize the part in much the same way as an intussusception.

Bockus also claims the abrupt cessation at the ileocecal valve could be explained on the basis of recurring self-reducing intussusception and adds, by way of support, that regional ileitis patients are youthful as are those with intussusception and that the terminal ileum is involved in both instances.

Woolsey (144) expresses his beliefs thusly, "The ileocecal valve gives a normal slowing of the intestinal content and sphincteric reaction from stimulation or irritation can become more spastic and give increased stasis. It is of interest that the majority of individuals seen by us have been of the vagotonoc or very active involuntary nervous system type where there is less inhibition of peristalsis and presumably a more spastic sphincter action."

Lewisohn (93) remarks that the ileocecal valve is
the only barrier between the pylorus and the anus and suggests that there may be a relation between the temporary stagnation of the intestinal contents and the production of the inflammatory tumor.

Berg (11) and Lewisohn (93) are not convinced that regional enteritis and ulcerative colitis are unrelated diseases. Lewisohn says of regional enteritis, "---with accumulated experience during the next few years, this lesion may turn out simply to represent a milder form of ulcerative colitis."

Crohn (39) has noted the disease in siblings, the most recent appearance in two brothers simultaneously affected by a rather acute process suggesting a common infecting agent rather than a mere familial tendency to the disease. Lewisohn considers the familial angle an accidental one; he had two sisters as patients who had not lived together for years. This fact would tend to dispute the belief of Crohn's.

Powers (118) compares the process to peptic ulcer when he remarks, "Pathological lesions are prone to occur in the gastrointestinal tract just at or proximal to points of constriction."

Corr and Boeck do not consider their finding of amebiasis as significant (32).

Pemberton and Brown (114) found a pleomorphic Gram positive strep in one case. They think the more active lymphoid tissue of the young an important factor.
PATHOLOGY

The concept of the pathology has changed very little since the original description (40), except for the more tolerant interpretation of the extent of the process. The steps of the broadening conception have been traced under the section of Etiology. Suffice it to say that the process now not only involves the terminal ileum, but may involve the cecum and colon distally, and the higher ileum and the jejunum proximally.

An idea of the extent of the pathology can be gained from the following table prepared by Clark and Dixon (25).

<table>
<thead>
<tr>
<th>SITE OF PATHOLOGICAL PROCESS IN 44 CASES</th>
<th>NO. OF CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum alone ---------------------------</td>
<td>20</td>
</tr>
<tr>
<td>Jejunum &amp; ileum -----------------------</td>
<td>1</td>
</tr>
<tr>
<td>Jejunum, ileum, &amp; cecum-----------------</td>
<td>1</td>
</tr>
<tr>
<td>Ileum &amp; cecum--------------------------</td>
<td>14</td>
</tr>
<tr>
<td>Cecum-----------------------------------</td>
<td>1</td>
</tr>
<tr>
<td>Ileum, cecum, ascending colon----------</td>
<td>2</td>
</tr>
<tr>
<td>Ileum, cecum, ascending &amp; transverse colon-</td>
<td>2</td>
</tr>
<tr>
<td>Ileum, cecum, ascending, transverse &amp; descending colon-</td>
<td>2</td>
</tr>
<tr>
<td>Ileum, cecum, transverse, &amp; sigmoid flexure</td>
<td>1</td>
</tr>
</tbody>
</table>

Crohn (39) has noted in a study of 110 cases that the majority showed an involvement of from 2 to 12 inches of the terminal ileum. He has seen as much as 36 to 50 inches of continuous involvement. In 6 patients, the whole upper and lower ileum was involved and in 2 of
these the jejunum was probably involved. One post-mortem case showed the entire small intestine including the duodenum to be affected by the inflammatory process.

"Skip areas" are a prominent feature of the disease; perfectly normal segments of intestine may separate areas of pathological tissue. Barbour and Stokes (5) tell of a case with multiple constrictions in 21 inches of small intestine. The constrictions were present in 13 places of thickening while 7 intervening portions of ballooned, thin walled intestine bore no constant relation to the constricted points. Crohn (39) found these "skip areas" to range from 2 to 12 inches in most instances but one case "skipped" 18 inches. These skip areas are significant in the treatment of the disease, for if they are not found and removed, they remain as a focus of further trouble.

From Crohn (39).

In all of the combined types, the terminal ileum seems to be the place of origin and the seat of the more severe process. Lest the reader be confused it is well to explain the pathological differentiation of ul-
Cerative colitis and regional ileitis about the ileocecal region. A fact that everyone concedes (42, 38, 11, 94) is that in severe diffuse ulcerative colitis as well as in localized segmental colitis and cecitis, the ileum may be involved by retrograde extension of the process. There is probably a 25% involvement of the ileum in the severe types of ulcerative colitis. This process in the terminal ileum in ulcerative colitis is destructive and denuding, as it is in the colon, but is not hyperplastic and granulomatous, as in primary ileitis. The mucosa only is involved, the walls are not thickened, fistulas do not form, obstruction does not occur, extension upward into the more proximal ileum is not seen—the amount of ileum involved as a result of the backwash is between 3 and 6 inches of the most terminal portion. The ileal pathology is not only secondary but minimal and may be ignored.

The pathological process is generally thought to begin as small oval ulcers along the mesenteric attachments of the ileum. Adams (3) feels that the infective agent whatever it may be, attacks the submucosa first and produces ulceration of the mucosa secondarily. He based his belief on the observation of an intact mucous membrane in an early case which revealed tiny submucosal abscesses.

Considerable attention has been paid the acute
phases which in the earlier reports were not so often studied. They are considered to be abortive stages of the hyperplastic and chronic termination. The acute pathology is responsible for the clinical resemblance to appendicitis. The terminal ileum is found to be thickened, soggy, and edematous; the serosa is blotchy red, rough, and tends to bleed easily. The mesentery is edematous, greatly thickened, and contains many enlarged hyperplastic lymph nodes. These nodes may be complicated by abscesses. Intermittent sections of normal bowel, if present, are indicated by absence of enlarged nodes parallel to the normal section of bowel. The involved mesentery is fan shaped and tapers toward its root. Plastic lymph on the bowel wall is noted; free serosanguineous or turbid peritoneal fluid is present in small quantities. Few cases have been resected in the acute stages, so that this phase has not had a thorough study of the mucosal and muscular layers. Woolsey remarks (144) that the bowel section of the acute stage exhibits edema and spotty ulceration of the mucosa. Jackman's information (77) concerning a thorough examination of the acute phase is of interest. "The mucosa over a wide area had been replaced by a firm hemorrhagic exudate with a roughened surface. The transition between the diseased and healthy segment was somewhat abrupt. The mucosa was severely ulcerated along the mesenteric side of the bowel. Micro-
scopic examination revealed a condition of simple intestinal ulceration. The mucosa throughout the affected area had been completely destroyed and replaced by a thick fibropurulent exudate. In the bowel wall generally, there was an acute inflammatory reaction lessening in degree toward the subperitoneal layer which showed congestion, edema, interstitial hemorrhage, but few polymorphonuclear cells. This was in marked contrast to the condition in the submucosa and muscle layers where in places, the degree of polymorphonuclear cell infiltration approached abscess formation. Evidence of previous acute inflammation was present in the form of dense scar tissue.

Sproull (136) in discussing a subacute phase of regional enteritis, reveals a striking feature which is seldom mentioned by other authors but which can be noted in illustrations of their articles. He observed that edema and inflammation of the mesenteric fat produced a seeming overgrowth of this tissue as is evidenced by its extension upon and almost complete encirclement of, the bowel wall (normally the mesenteric fat does not extend beyond the mesenteric border of the small intestine).

The acute phases of the disease gradually progress to the fully developed hypertrophic process in which the bowel is firm, ropy, and fibrotic in distinction to the heavy, wet, soggy ileum of the acute form. The most advanced pathologic changes are present at the
valve, which in some instances becomes converted into a rigid diaphragm with a small opening barely capable of admitting a probe. Typically, the severity of the disease gradually abates proximally, shading off into normal mucosa. "Skip areas" however, must not be overlooked. Normal intestinal folds are broken up and distorted by the destructive ulcerative process and rounded and blunted by edema, giving a bullous structure to the normal mucosal aspect of the intestine, or frequently a cobble-stone appearance of the surface may result. Occasionally well formed polyps develop. A series of small linear ulcerations with their long axis parallel to that of the ileum lie on the mesenteric side of the bowel as a rule. Whether these are the remnants of the original ulcerations or whether they are mechanical erosions due to the formation of a "darmstrasse" by the shortening of the fibrotic mesentery, has been a matter of conjecture but since reports such as those of Jacmans (77), they have been accepted as early phenomena. Ulcerations along the mesenteric side of the bowel have been seen in early acute cases.

The submucosal and, to a much lesser extent, the muscular layers of the bowel are the seat of marked inflammatory hyperplastic and exudative changes. As a result of these, the wall of the bowel becomes enormously thickened, frequently reaching two or three times its normal
density. The lumen of the bowel is greatly encroached on, becomes irregularly distorted, and, at times, is only large enough to admit a medium sized probe. Intestinal loops proximal to the involved segment frequently, but not invariably, become greatly dilated and may show superficial irregularly placed tension ulcers. When seen at the operating table the involved loop has been likened to a hose-like mass (Crohn, et al. 40), a heavy snake (Lick, 94), and a soft lead pipe. The latter description is hardly adequate as the loop is truly much more flexible, elastic, and softer than the term would indicate.

In the latest phases of the disease, the exudative process is replaced by a fibrostenotic reaction, and the mucosa appears atrophic with occasional superficial erosions and islands of papillary or polypoid hyperplasia. The serosa loses its gloss and frequently exhibits tubercle-like structures on its surface. The mesentery of the affected segments is greatly thickened and fibrotic, as is the subserosal intestinal fat.

Microscopically, no specific features can be demonstrated. The stained histologic sections show various degrees of acute, subacute, and chronic inflammation, with variation in the predominance of polymorphonuclear, round cells, plasma cell, and fibroblastic elements. In the early stages the lesion is a diffuse one, involving
mainly the mucosa and submucosa, with the presence of some inflammatory serosal reaction. The mucous membrane shows areas of marked destruction, and at times the glandular structure is almost completely gone, leaving an atrophic layer of epithelium, the result of a regenerative process. In later stages of the disease the inflammatory reaction is more focal in character. These focal areas of inflammation give the appearance on gross examination, of tubercles; they are, however, merely subserous collections of lymphocytes.

The presence of giant cells, in most cases, together with these tubercles is the basis of an erroneous diagnosis of tuberculosis.

Fig. 18. Foreign body giant cell containing particles of crystalline material (x200); b, subserous collection of lymphocytes. (x30).
Special stains have occasionally demonstrated the presence of large pale cells, or groups of cells, probably vegetable in nature, in the vicinity of the giant cells. They are demonstrated in all layers of the intestine. These and the giant cells are probably not an essential feature of the pathologic changes in this condition. They are, more likely, accidental findings due to the inclusion of small particles of vegetable matter which have become trapped in the ulcers, entered the lymphatics and become encapsulated in the process of healing. The resultant foreign body reaction around these non-absorbable particles results in the presence of the giant cells.

There is a marked tendency to perforation in regional enteritis. The process is usually slow enough to permit of walling off by adhesions to a neighboring viscus, to the parietal peritoneum, or to the omentum. These walled off abscesses resulting from slow perforation into the peritoneal cavity are, as a rule, considered appendicular in origin and hence, are drained with a resultant persistent fistula. Acute perforation is rare and when it does occur seems limited to the upper small bowel, according to Mixter(102). Halligan and Halligan (70) first noted acute free perforation as the first sign of clinical regional ileitis in 1937. Before then only Arnheim (4) had recorded a spontaneous perfor-
ation and his case had had symptoms for ten years.

Fistulas are common pathologic manifestations of regional enteritis in the chronic stages. Binney (12) reported an incidence of 15% of 26 cases. Meyer and Rosi (99) found an external fistula in one of their eight patients. Dixon (47) noted 10% of 30 cases had internal fistulas— one patient between the ileum and urinary bladder, two between the ileum and the lower sigmoid. Three of eleven cases of Lewisohn (93) exhibited fistulas. Coffey (27) notes that of 21 cases at Mayo’s, there were 6 external fistulas and 2 internal fistulas.

External fistulas are very common following previous operations, as has been pointed out elsewhere. The combination of an old appendectomy scar and a persistent fistula is very suggestive of regional ileitis.

Crohn (39) considers the perianal, rectal, and rectovaginal fistulas very common, basing his assertion on a collection of 20 cases of this type.

Diagram showing the course of fistulous tract via the ischiorectal fossa from diseased ileum to the perineum.

Crohn (39)
Diagram showing the course of fistulous tracts from diseased ileum to various points in the perineum.

Crohn (39)

His concept of the pathogenesis is as follows. The diseased heavy terminal loop lies on the pelvic floor near the Douglas pouch, ascending at an acute angle to the junction. Infectious pus and other material escapes from the porous terminal ileum, seeps downward, infecting the pelvic peritoneum and retroperitoneal fat, and burrows thru the pelvic fascia by a fistulous tract which tends downward. This tract may exit into the rectum above the sphincter; or, piercing the sling like attachment of the levator ani, may exit at the perianal margin. If the infectious fistula pierces the fibers of the levator ani laterally, the ischiorectal fossa is contaminated and the abscess formed will exit as a pararectal fistula. In the female, the fistulous tract may traverse the recto-vaginal septum and exit in the perineum, vagina, rectum, or rectum and vagina.
Fistulas, single or multiple, persist as long as the ileitis is present and active; they close on resection of the ileum, occasionally heal after a short-circuiting operation. The rectovaginal variety, in the estimation of Crohn and Penner (41), are the most persistent and require surgical removal.

Fissure-in-ano is common in all diarrhea diseases; Bargen has revealed an incidence of 3.7% in a series of 697 cases of non-specific ulcerative colitis. The non-infectious diarrheas do not produce perianal fistulae. Tuberculosis causes only 1% of perianal fistulas contrary to popular belief.

The fistulous tract originating in the ileum is seldom direct in its course but more typically tortuous. The tracts become secondarily infected and from low grade abscesses frequently.

Internal fistulas are a result of the diseased segment becoming adherent to contiguous structures; the colon is frequently involved in this manner.

Crohn and Penner (41) report the occurrence of multiple fistulas in the lumbar region, the openings being arranged in a vertical line, in a patient with no intestinal symptoms. They tell of a similar case of Snapper's of Amsterdam who had a perinephric abscess exit in this region.
CLINICAL FEATURES AND COURSE

The prevalence of the disease for Jewish patients in the early reports apparently is explained by the fact that such reports originated from the Eastern seaboard or from large cities with a large Jewish population. Also many of the authorities found their material in Jewish hospitals. Crohn (39) does not now think the problem is a racial one, as Gentiles in Sweden, Africa, Holland, and England as well as other countries, have been afflicted. Colbeck, Hurst, and Lintott (28) consider the disease not uncommon in the British Isles. They state that the condition has remained unrecognized on the continent except in Holland. Among the British reports are those of Jackman (77), Maier (96), Molesworth (105), Barbour and Stokes (5), Barrington-Ward (9), and Colbeck, Hurst, and Lintott (28). Australia recognizes the condition as attested by Kinsella (87), Skewes (135), and Ross (130). Regional enteritis is found in all sections of the United States as is evidenced by reports in the various state and sectional journals. Barning and Dixon (8) of the Mayo Clinic reveal that many patients who appear at the Clinic are from the Middle West, and the various sections of the country are all represented. Only Stafford (137) has reported the disease in a negro. Chapin (23) has obser-
ved that persons of Irish descent or with old American names are scarcely affected. He believes the longer a family has been in the United States, the less liable are its members to have this condition; Jewish people are the most prone to develop regional ileitis, in his estimation. Of Chapin's 5 cases, 3 were of Polish, Italian, or French extraction. That there does seem to be a tendency for Hebrews to acquire regional enteritis, is evidenced by the 20% Jewish incidence in a series of 44 cases at the Mayo Clinic as revealed by Clark and Dixon (25). These figures possess some significance when it is remembered that the Clinic obtains as its patients, a cross-section of the American melting pot.

For all practical purposes the sex ratio may be considered equal. Crohn and associates originally thought the ratio of males to females to be 2:1; he now, (39), considers the ratio 6:4. Similar ratios have been noted by other observers. At the Mayo Clinic, (24) men and women were equally represented in a series of 30 cases. Adam's 15 cases showed females predominating 9:6.

The disease is still, as was originally reported, a disease of youth. There is a definite predilection for the third and fourth decades. Crohn's large series of 110 cases (39) reveals an average age of 27.8 years. Clark and Dixon's review of 44 cases (25) shows an average age of 27.3 years at the time of onset of symptoms.
Adams' (3) cases averaged 36 years. Of Mixter's 20 cases (102), 55% were under 25 years of age; 90% were under 35 years of age. Binney's review (12) of 26 cases showed the greatest incidence in the third decade. Pemberton and Brown (114) note that the age distribution parallels that of ulcerative colitis.

The old and the very young do not escape entirely, however. Erb and Farmer (50) reported cases of ileocolitis in children aged 8 3/4, 10, 2 1/2, and 3 years respectively. Holman (75) had a case of regional enteritis in a boy of 6 years. Rosenblate (129) reports a case in a boy 4 1/2 years old. Brown, Bargen, and Weber (18) treated a patient 9 years of age. Binney (12) reports a case of regional ileitis in a 5 year old.

Adams' (3) oldest case was 69 years old. Binney has reported one 64 years of age. A 62 year old patient appeared at Mayo's (18). Crohn's oldest patient had seen 58 winters, Mixter's 56.

Most authorities reveal that a respectable percent age of their patients have had a previous futile appendectomy because of the acute symptoms. Of Crohn's 110 cases, 33% had had appendectomies with no affect on the course of the disease. Clark and Dixon (25) found 24 of 44 cases had previous appendectomies. Adams records the fact that 8 of his 15 had previous operations.

Crohn (39) has seen regional enteritis three
times in siblings and Lewisohn (93) once.

Regional enteritis is characterized by a chronic course and a remission of symptoms. As time progresses and the disease is more readily recognized, the duration of symptoms will undoubtedly be decreased. Crohn's series (39) showed 62 patients or 56% with a history of one to five years; 15 patients or 13% had symptoms from five to ten years; 8 patients or 7% had been troubled for over fifteen years. The following table of Clark and Dixon (25) illustrates the duration of symptoms in 44 cases.

<table>
<thead>
<tr>
<th>DURATION OF SYMPTOMS IN YEARS</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 1 or less</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>5-10</td>
<td>7</td>
</tr>
<tr>
<td>10-15</td>
<td>2</td>
</tr>
<tr>
<td>20-25</td>
<td>1</td>
</tr>
</tbody>
</table>

Their series showed an average duration of symptoms before being seen at the Clinic, of 4.1 years.

An epitome of symptoms is presented by Clark and Dixon as follows:

Series of 44 Cases

<table>
<thead>
<tr>
<th>Signs or Symptoms</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>43</td>
</tr>
<tr>
<td>(average loss 21.9 lbs.)</td>
<td></td>
</tr>
<tr>
<td>Palpable mass</td>
<td>32</td>
</tr>
<tr>
<td>(positive roentgen)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
</tr>
<tr>
<td>(average no. stools, 3-6)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>28</td>
</tr>
<tr>
<td>Obstruction</td>
<td>28</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>25</td>
</tr>
<tr>
<td>Anemia</td>
<td>18</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>18</td>
</tr>
<tr>
<td>Pain other than cramps</td>
<td>12</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>7</td>
</tr>
<tr>
<td>Fecal fistula</td>
<td>9</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3</td>
</tr>
<tr>
<td>Tarry stools</td>
<td>1</td>
</tr>
</tbody>
</table>
Jellen (82) reviewed 50 cases, presents the following epitome:

- Abdominal pain ------- 72%
- Weight loss---------- 60%
- Palpable mass-------- 58%
- Diarrhea------------- 52%
- Anemia------------- 42%
- Fever--------------- 38%
- Fistula------------- 36%
- Vomiting------------ 28%

Twenty three of thirty cases reported by Dixon (47) showed a definite history of remission of symptoms lasting two to four weeks.

Diarrhea, a fairly constant feature, falls short of the number of movements and intensity of the actions which are characteristic of a true colitis. As Musick (110) points out, diarrhea varies with the location of the lesion. Ulceration in the ileocecal region causes from two to four bowel movements daily, whereas the same process in the left bowel, sigmoid, and rectum, may cause as many as 15 to 20 movements a day. Similarly, pus and blood are present only in small quantities when the ileocecal region is involved, the presence of pus being impossible to detect without a microscope as a rule; bloody, purulent, mucous containing movements are typical of involvement of the left colon. Stools may vary from a mushy to a liquid state. With extreme ulceration, a pancreatic like stool may result. This is a large bulky stool which shows an increase of undigested fat. As Musick (109) notes, this type of stool occurs only
when a great deal of the absorptive surface of the bowel wall is destroyed. Tenesmus is usually not present, but Bissell (14) tells of a case with tenesmus which resulted from irritation of the rectum due to a loop of ileum bound down in the cul-de-sac. Irritation also was responsible for the urinary symptoms which he found. Clark and Dixon observed that the diarrhea associated with intense colicky spasms was of a disturbing nature, necessitating frequent bowel evacuations sometimes accompanied by tenesmus. Prouty (120) states that diarrhea is not common in the acute phase unless a large area is involved or unless the colon is affected.

Vomiting is a characteristic of the stenotic or obstructive phase, is never marked or persistent and usually is accompanied by abdominal pain and peristalsis. According to Prouty (120), vomiting is more common when the jejunum is involved, and the pain in such an instance is at a higher level.

Leukocytosis, if present, is always mild. Pember- ton and Brown (114) had only one case of remarkable leukocytosis and this was proved at autopsy to be due to peritonitis.

Pain is probably the chief complaint of the patient. The pain, other than the cramping pain of the obstructive phase, is of two main types (1). One type is not dissimilar to the distress of peptic ulcer, being situ-
ated in the epigastrium. It is dull and intermittent in character and usually is precipitated or exaggerated by eating; gaseous distention is a usual accompaniment. (2) The other type generally occurs in the right lower quadrant in severe episodes of a few moments to a few hours duration and is relieved on occasion by catharsis or by nausea and vomiting. The patient with this type of pain is generally free from any cramps or diarrhea.

When cramps become severe, periods of diarrhea may alternate with periods of constipation. The colicky spasm passes across the lower part of the abdomen and seems to reach a maximal intensity in the right lower quadrant. It is accompanied by, or alleviated by, passage of a loose watery, mucous-containing stool and much gas. The concomitant symptoms of malnutrition, obstruction, with a palpable mass in the lower right quadrant are more pronounced in those patients who give as their chief complaint, abdominal cramps with diarrhea.

Halligan and Halligan (70) have noted a lumbar distribution of pain which they believe is a result of mesenteric involvement. Clute (26) agrees with this contention.

The anemia of regional enteritis is typically hypochromic and mild. The lowest hemoglobin recorded by Pemberton and Brown (114) in their findings of secondary anemia, was 8.5 grams. Anemia is related more to the du-
ration of the disease and the deficiency of the diet than to actual blood loss. This is contrary to what occurs in cases of ulcers of the ileum or of Meckel's diverticulum in which hemorrhage is common. Butt and Watkins (20) found 6 of 7 cases of proved regional ileitis with a macrocytic anemia. They concluded, "Regional ileitis may produce a macrocytic anemia which apparently is independent of the amount of involvement of the ileum." This anemia responded not to administration of the antianemic principle effective in pernicious anemia, but recovered spontaneously after resection of the diseased bowel segment. Their findings have not been verified. The majority of observers have noted a slight secondary anemia in roughly one-half of their patients, a normal blood count in the other half. The sedimentation rate is characteristically increased according to Clark and Dixon. Even in stenotic cases, the blood plasma findings that are seen in marked obstruction of the upper alimentary tract are rarely seen.

Musick (109) states that the patients are usually highly nervous and unable to sleep, complaining of body aches, hyperesthessias, parasthesias, chilly sensations, hot flashes and the like. He has noted that the patients have not always appeared very ill and may be found in the psychopathic wards.

Until Halligan and Halligan (70) reported their case in 1937, the occurrence of acute free perforation
as the first sign of regional ileitis had never been clinically noted. Arnheim (4) in 1935, had reported the only other known case of free perforation, but it followed a history of abdominal pain and diarrhea for ten years.

Certain physical signs characterize regional enteritis, the more constant findings being (1). a mass in the right iliac fossa (2). evidences of fistula formation (3). emaciation and anemia (4). the scar of a previous appendectomy (5). evidences of intestinal obstruction.

(1). The mass is usually found in the right lower side, and, in patients with much weight loss, is sometimes visible. The mass is usually the size of a small orange, tender, firm, irregular, and only slightly movable. It is without the nodular hard consistency of cancer, and does not cause reflex rigidity of the abdominal musculature. It is composed of the tremendously hyperplastic ileum, the stenotic inflamed ileocecal junction, which may and often does, assume a size from two to five times that of the normal valve of Bauhin,(Crohn (40)), and frequently an adherent section of the colon or sigmoid to which a fistulous tract has been created, or adherent coils of small gut. The mass may indicate a walling off of a perforation, according to Crohn (39). When the sigmoid is adherent and involved, the mass may lie more to the left; when the ascending colon, cecum, or
hepatic flexure constitutes the distal end of the fistulous tract, the mass may lie more to the right and higher in the abdomen. The tumor is usually palpable per rectum, especially if the boggy ileum has settled and become adherent in the cul-de-sac; otherwise, it is felt by the examining finger very high in the rectum. Occasionally matted coils of the intestine can be felt vaginally. Clarke and Dixon (25) reveal that a mass is not infrequently the first warning to the patient.

(2). Fistulae and sinus tracts are one of the most common manifestations of regional ileitis. They have been discussed in greater detail under Pathology. Crohn (39) reminds us that fistulas may be one to fourteen years prodromal. Fistulae terminate on a body surface be it internal or external. Most common of sites is the abdominal wall, the sinus burrowing thru the scar of a previous operation. Accordingly an appendectomy scar with a draining sinus is a not infrequent occurrence. Often the first clinical manifestation of regional enteritis is a perianal fistula. The cecum, ascending colon, ubiquitous sigmoid loop of the pelvic colon, the vagina, rectum, bladder and ureters, and the lumbar region are all sites of fistulas.

(3). Evidence of emaciation and anemia is common and is a result of the long course and marked weight loss.

(4). The frequencies of appendectomy have been
discussed before.

(5). In those cases in which the process has progressed to a stenotic stage, the physical findings are those of intestinal obstruction. Loops of distended intestine may be visible thru the emaciated abdominal wall, and puddling is frequently observed in the X-ray plates. Visible peristalsis is not uncommon, and is accompanied by borborygmus and the passage of gas with evident relief. The visible loops of the distended intestine are usually localized to the lower mid-abdomen. General distention and ballooning of the whole abdomen are unusual. Lesions higher in the intestinal tract tend to give symptoms of intestinal obstruction more frequently and more rapidly than lesions in the ileum or colon.

Adams (3) warns us that abdominal tenderness and spasm are minimal with the exception of early acute cases and abscesses.

Crohn, Ginzburg, and Oppenheimer originally typed the clinical course into four groups; (1). acute intra-abdominal disease with peritoneal irritation (2). symptoms of ulcerative enteritis (3). symptoms of chronic obstruction of the small intestine (4). persistent and intractable fistulas in the right lower quadrant following previous drainage for ulcer or abscess. These four group continue to embrace the majority of instances of regional ileitis.
(1). **Signs of Acute Intra-abdominal Inflammation**—

It is extremely difficult to distinguish this form of acute regional ileitis from the acute appendix preoperatively. There are generalized colic, pain and tenderness in the right lower quadrant and a fever which may be 101 or 102 F. The white blood count may be elevated also. The associated symptoms of nausea and vomiting are often present to confuse the diagnosis. The development of symptoms does seem slower in most cases in regional ileitis. The presence of a mass is a fairly constant feature. It is this confusion of diagnosis which has resulted in such a large percentage of appendectomies prior to realization of the true pathology.

(2). **Symptoms of Ulcerative Enteritis**— This stage is a progression of the acute cases which have failed to subside. The patients complain of colicky periumbilical or lower abdominal pain. There is a tendency toward looseness of the bowels (three to five movements a day). The stool is usually liquid or mushy and may contain pus, mucous, occult or visible blood. There is no gross melena. Fever is constant but is rarely above 100 F. As the disease progresses a secondary anemia develops. Weakness and weight loss become more marked. Malnutrition and anemia may become prominent features as a result of the great loss of food and fluids because of the
diarrhea, and because the intake may be greatly limited due to the persistent nausea and vomiting. In the earlier phases there may be long periods of remissions from any trouble but as the disease progresses, the remission become less frequent or of shorter duration and symptoms of intestinal obstruction are superimposed on those of chronic enteritis.

(3). **Stenotic Phase**— This type is very commonly seen first as the condition may have progressed from the earlier stages which had been featured only by an occasional bout of pain. The symptoms of this stage are those of a subacute intestinal obstruction of varying severity. The obstruction is not complete. Violent cramps, borborygmus, occasional attacks of vomiting and constipation are the characteristics of the phase. A palpable mass is usually found, and visible peristalsis and intestinal erection are common. Fistulous communications with the colon or sigmoid may mask the true nature of the disease by simulating a colitis.

(4). **Persistent Fistulas**— These often develop a few months after the original drainage operation for appendiceal abscess, the wound meanwhile having healed and having remained healed for a few months. An abscess then develops in the wound; when this abscess is investigated a communication with the intestine may be demonstrated. The fistulas of regional ileitis can be distinguished from those of an appendiceal abscess by the fact that
the latter tend to close spontaneously or tend to be susceptible of closure by excision of the tract and inversion of the stump; the presence of ileal, not cecal origin can be demonstrated. Removal of specimens from the sinus tract will fail to reveal evidence of tuberculosis or other specific disease.
DIFFERENTIAL DIAGNOSIS

The X-ray plays an essential part in the diagnosis of this condition; accordingly, it has been discussed under a different section. No attempt will be made to bring the roentgenological phases into the present discussion.

Calambos and Mittelmann have emphasized the need for early recognition of regional ileitis because (1) early resection leads to cure, and (2) incorrect diagnosis often leads to unnecessary appendectomies which frequently result in persistent fistulas.

A preoperative diagnosis is not so imperative, but when operation is performed for an acute appendix or other pathology in the region, it is necessary to bear in mind the possibility of regional enteritis and to look for the disease if other pathology is not found. Prouty (120) emphasizes this point.

Jackson (78) has the following to say, "As one becomes familiar with its characteristic symptoms, he is inclined to conjecture how many such cases he may have overlooked prior to 1932. Even now, undoubtedly many innocent appendices are being removed while the real source of the discomfort is overlooked. If more need to be said as to the inadequacy of the formerly popular button-hole incision, it might be urged that
even the remote possibility of ileitis demands an adequate abdominal exploration when conditions permit it. Regional enteritis, mesenteric lymphadenitis, a diseased Meckel's diverticulum, and lesions of the gall bladder and pelvis are but a few of the pathological entities which through inadequate exposure may escape the surgeon's eye.

Suffice it to mention the more common conditions which need differentiation. Ulcerative colitis, in the largest percentage of cases, can be differentiated by sigmoidoscopy and the barium enema. A few cases of ulcerative colitis involve only the proximal segments of the colon, the rectum and sigmoid escaping. This type again is diagnosed principally with the aid of roentgenology. Fistulas except of the rectum and anus, milder diarrhea, rare appearance of blood, mass in the right ileac region abdominal cramps, and eventually ileal stenosis, argue against colitis.

Ileocecal tuberculosis as a primary process is very rare. In 15 years at the Mt. Sinai Hospital, only 4 cases of primary tuberculosis in this region have been diagnosed! (39).

Sarcoma of the intestine is usually multiple, causing dilatation at various levels, and in general occupies higher levels of the intestine. Exact clinical differentiation is impossible until operation. The conditi-
on is rare and may be featured by gross hemorrhages, Hodgkins may give its characteristic monocytic blood picture, or a regional node may reveal the true nature of the disease. Findings elsewhere may suggest the diagnosis.

Actinomycosis with fistula formation to the external abdomen must always be borne in mind. The condition is not common in this region of the body. Examination for the actinomycete is important in eliminating this possibility.

Carcinoma can not be clinically differentiated definitely until operation.

Crohn (39) considers the differentiation of nontropical sprue and high regional enteritis the most difficult. The sprue X-ray is not characteristic nor constant, and consists of puddling and delays in the higher loops of ileum and jejunum without constant anatomical deformity. The stools are frothy, abundant, and are without a constant positive test for occult blood. Anemia is very severe and often is of the hyperchromic type; glossitis is typical, and there are signs of avitaminosis.

A search for organisms of amebic dysentery and giardial flagellates may be necessary.
ROENTGENOLOGY

The use of X-ray in the diagnosis of regional enteritis is of such value as to warrant a special discussion. Whereas one hesitates to diagnose the condition from the clinical findings alone, the correlation of these findings with those of a properly taken roentgen series will in most cases clinch the diagnosis. Pember-ten and Brown (114) state that "---a typical, pathognomonic clinical syndrome of regional enteritis has not been elaborated, in fact, the clinical diagnosis remain conjectural or tentative until roentgen evidence of the disease is adduced." The almost pathognomonic "string sign" can alone make the diagnosis in some cases. Despite the fact that most observers depend greatly on the X-RAY, Adams (3) found in his series of fifteen cases that preoperative X-rays had been of aid in only five. The value of X-ray in instances where clinical diagnosis has not been made due to the variable clinical picture of regional enteritis is well illustrated by a case of Crohn's (29) who for two years had had a mild inoffensive diarrhea with several watery movements a day and weight and strength loss. In the face of the extensive involvement of the ileum the valve of which would barely admit a lead pencil, the clinical picture was amazingly mild and indefinite. As Crohn points out "---the diagnosis was a roentgen diagnosis first and
In Crohn's personally observed series (39) of 110 cases with regional enteritis, only one failed to show a positive roentgenology.

Crohn, Ginzburg, and Oppenheimer in their original article (40) stated that the value of the barium enema rested in the negative report alone, recognizing that any colonic pathology indicated the absence of regional ileitis. They placed the greatest faith in the barium meal, the importance of which is appreciated by all present observers. However, the enema has gained considerably more respect than was shown it at the time of the original description of the disease.

In 1934, Kantor (85) first discussed in detail the part of X-ray in the diagnosis of terminal ileitis, his observations being based on a series of six cases. He emphasized the necessity for examination at proper time intervals after the barium meal ingestion, the time of observation corresponding to the interval between the periods just before the cecum fills, to the normal period of ileal emptying. This meant from 3 to 9 hours after ingestion and he recommended hourly observations during this period. Crohn, and associates (40) originally suggested examination at 4, 6, and 9 hour intervals. Galambos and Mittelmann (63) in 1935 were of the opin-
ion that one of the causes for failure to recognize the ailment was due to the fact that X-ray examination of the ileocecal region is performed **routinely** six hours after the barium intake "---at a time when the terminal ileal coils in that particular region are as a rule empty anyway." An X-ray report with such a routine procedure would reach no conclusions and a "negative" finding would be reported in a case which could have been readily diagnosed with the proper procedure. They suggest that instead of the usual routine of fixed 6 and 24 hour intervals, it would be more correct to have studies at varying times and with varying technic dictated by the individual needs of the case. As a rule they considered the 2, 3, or four hour exposure the most valuable. Jellen (82) believes the narrowing of the ileum is best demonstrated at 4, 6, and 8 hour observations. Prouty (120) maintains that the roentgenologist should be informed of the suspected condition since the usual gastrointestinal examination will overlook regional ileitis.

As to technic, Kantor (85) uses the standard opaque meal on an empty stomach and prefers the roentgenograms to be taken with the patient in the prone position because in the erect position the ileal loops are not as widely separated and hence not as easily visualized. A normal meal may be taken after the barium ingestion.
Weber (143) says, "It may be assumed that the completely performed roentgen examination of the small intestine can be made to deliver diagnostic evidence as early as symptoms producing and signs producing morphological changes develop".

In discussing the use of the enema which serves to promote visualization of the terminal ileum by reflux of opaque material thru the ileocecal valve, Prouty (120) states that in cases where a low lying ileum is obscured by the sigmoid loop, the patient by expelling the enema will allow of visualization; the cecum and terminal ileum will rise out of the pelvis unless held down by adhesions and "permit palpation for pliability and study of the mucosal pattern".

In general and as all authorities will agree the roentgen manifestations of regional enteritis vary somewhat as the pathological manifestations. The X-ray reflects not only the site but the kind, the intensity, and the extent of the pathological changes. If the hyperplastic character of the pathological process is in predominance, then the roentgenological manifestations will be such as are directly or indirectly attributable to hyperplasia. Such changes are narrowing of the lumen due to encroachment on it by the thickened intestinal wall, shortening of the affected segment due to contraction of the hyperplastic tissue, loss of normal pli-
ability and motility as noted by manipulation of the segment during the roentgen exam. If ulceration is the dominant feature of the pathology, then it will be seen as such on the film. Narrowing, shortening, and rigidity of the affected segment will not be so manifest but revealing changes are to be looked for in the pattern of the mucosal relief of the ulcerated segment. Weber (142) describes the relief as shown by X-ray following denudation of the intestinal surface as flat, moist, and stippled. Weber (143) says that the early relatively unpronounced degree of submucosal infiltration may be manifested roentgenologically only by flattening of the normally high mucosal relief pattern; if ulceration has taken place the relief pattern is irregular and is jagged, not smooth and flat. Prouty (120) states that the early diagnosis may have to be made on a persistent irritability and lack of filling of the involved segment and hypomotility above the site of the lesion. He describes an occasional polypoid appearance of the mucosa.

Galambos and Mittelmann (63) had a case which showed a 36 hour delay in passing the barium due to the complicating affect of adhesions around the ileocecal juncture.

Kantor describes colonic changes due to secondary spasm, the spasm being most marked in the cecum; the
sphincter of Busi (a sphincter separating the cecal tip from the cecum above it) as well as the cecal tip often become spastic and the cecum assumes a "teat-like" appearance. Most cases of functional spasm are intermittent and fill out well with the barium enema. The colon may be involved directly by adhesions or fistula formation. Lewisohn (93) suspected primary lesions of the sigmoid in 2 cases and with barium enema found fistulae between the sigmoid and the ileum.

Jellen (82) has classified the X-ray findings into 5 groups as follows:

I. **Regional ileitis.** Caliber is reduced to 1/2 or 1/3 of normal. Narrowing is usually irregular; margins are usually smooth and obliterated of normal mucosal markings. Changes are constant even on later reexamination. Ulcerations may cause irritability so that barium is not retained; however a normal terminal ileum may not be visualized. Expected dilatation proximal to the narrowed ileum is seldom seen on X-ray.

II. **Cecal deformity with regional ileitis.** This is occasional and in some cases is due to spasm. More often is a smooth "moon" defect on the medial aspect of cecum from pressure of the mass. Changes also may be due to adhesions, fistulae, walled-off abscesses; if fistulae and abscesses are present, cecum is often constricted and irregular in outline. No Stierlin's sign in this group.
III. **Regional ileitis with colitis.** May be cecum, colon or both. Stierlin's sign usually present. Cecum and proximal colon show marginal irregularity and often appear contracted. Ulceration noted by spasm, irritability, local hypermotility of involved segment so that very little barium is retained. These findings also are characteristic of ileocecal tuberculosis.

IV. **Nonspecific jejuno-ileitis.** Uncommon, may or may not involve terminal ileum.

V. **Fistulae.** Intestinal fistulae are difficult to demonstrate by barium meal or enema.

The important changes as seen in the ileum by Kantor (85) are of the most value to the uninitiated interpreter of the films of regional enteritis. Since the terminal ileum is constantly involved whether or not other areas of the intestinal tract are similarly affected, the following points as listed by Kantor are of diagnostic value:

I. A filling defect, the extent being dependent on the extent of the stenotic process.

II. Abnormal contour of the ileum proximal to the defect.

III. Evidence of obstruction as shown by stasis of contents and dilatation of loops proximal to the filling defect.

IV. The striking "string sign", a thin, slightly irregular linear shadow suggesting a cotton string in appearance and extending more or less continuously from the
region of the last visualized segment of the ileum thru the entire extent of the filling defect and ending at the ileoceleal valve. It represents the attenuated barium filling of the greatly contracted intestinal lumen. Multiple or branched "string signs" he attributed to multiple areas of involvement or to fistula formation.

Weber has referred to the "string sign" as the "twisted cord" appearance.

Meyer and Rosi (99) have used X-ray films to follow up their cases of acute regional enteritis which spontaneously subsided. One month after operation, they found that the terminal ileum showed signs of intermittent passage of barium only. Three months after operation the involved ileum appeared normal in every respect. One acute case became chronic and this showed a typical filling defect just proximal to the ileocecal valve.

Kantor (85) and Lewisohn (93) have called attention to the possibility of confusing the "string sign" with the normal filled appendix dipping into the pelvis. Kantor also adds that the line of the right sacroiliac synchondrosis may be misleading. The appendix shadow is likely to be more homogeneous in density and its outline more uniform than that of the "string sign". The synchondrosis may be identified by careful comparison with its fellow of the opposite side. The "string sign"
may also have to be differentiated from the streak-like filling of abnormally contracted (spastic) segments of the small intestine. In the case of the latter, the lumen is wider, the shadow denser, and the outline smoother, and, more important still, the location of these loops may vary from one exposure to another because of the freer motility of such bowel segments. It is characteristic of regional ileitis that the "string sign" remains hour after hour and even day after day in practically the same relative location in the right lower quadrant.

In the differential diagnosis by X-ray, intestinal neoplasms merit little consideration because the deformities produced by the two processes have so little in common. Unless perforation has taken place, the neoplasm deformity is comparatively short and abruptly demarcated above and below. The mucosal pattern within the filling defect is entirely deleted. The lesion is mobile, and when palpable, its knotty type of induration gives an eloquent clue to its neoplastic nature. Perforation of such a lesion tends to obscure these stigmata of neoplasm but even so, the painstaking examination can as a rule elicit enough of them to recognize the perforated neoplasm for what it is. Non-neoplastic processes deform segmentally, but more widely. Demarcation between diseased and healthy tissue is gradual, no
not abrupt. When palpable, the consistency of the lesion is not as hard and resistant as is a neoplastic lesion. Also, the mucosal markings may be obliterated in spots, and definitely abnormal in appearance throughout the diseased area, the mucosal pattern still remains recognizable.

Tuberculous enteritis has so much in common morphologically with the nontuberculous form with which we are primarily concerned here that the two are not always readily distinguishable from each other even at gross pathological examination. Does the roentgenological examination have anything to offer to this diagnostic problem? Criteria for an unfailing roentgenological distinction between the two forms of enteritis are frankly lacking, yet there are some evidences which when elicited make at least a good presumptive diagnosis possible. General contraction of the diseased segments, which implies diminished caliber and length, mucosal changes, loss of pliability, and an ileocolic distribution of the pathological process are features of both forms. The tubercular form however, has been observed to have a different roentgen "look" from the nontubercular form. Comparing one to the other, the contours of the tubercular form have rougher more corrugated appearance, corresponding to a more irregular development of the ulcerative-hyperplastic process. In its roentgen manifestations, the nontubercular form of
regional enteritis imitates thrombo-ulcerative colitis more closely. The contours are characteristically smooth and the narrowing is uniform, corresponding to the diffuse even development of the underlying process. In addition the important differential point of tubercular lesions in other localities must not be forgotten; calcified glands in the mesentery, positive Mantoux, and the finding of tubercle bacilli in the stools point to a tubercular process.
TREATMENT

The treatment is essentially surgical with resection of the diseased segment the rule; medical regimens have proved of no value in curing this malady.

Spontaneous cures have been recorded by the majority of observers who have had wide experience. However, the probability that these individuals may later experience a relapse and that the disease will progress to its later stages is something which can be determined only by the passage of time. Certain it is that among those individuals who have experienced progression of the disease to the extent that there is ulceration, stenosis, malnutrition, obstruction, fistulas or abscess formation, surgical intervention is the only means of combatting the irreparable damage to the intestine. Spontaneous healing in the chronic case has not been observed (39).

The acute phase may result in subsidence or progression. Crohn (39) had 11 acute cases of which 3 have at least undergone recession if not spontaneous cure. Of the 11, 8 did poorly and 6 were eventually operated upon. Koster, et al. (88) reports 8 cases who without operative procedure have apparently been cured. In 6 others failure of operation led to progression and ev-
eventual operation. De Courcey's case (46) with 12 inches of involved ileum completely recovered without surgical intervention. Dixon (47) has recognized spontaneous resolution. Berg (38) refused to operate 3 acute cases and as a result the three are apparently well several years later. Meyer and Rosi (99) found 3 of 4 cases which involved only the ileum, the mesentery being clear, spontaneously subsided. They feel that recession will not be forthcoming when more than the bowel itself is involved, and therefore advocate surgery if the mesentery is involved.

Mixter reminds us that operation performed in the acute stage may disseminate infection (102). Not so much as an incidental appendectomy should be done in his estimation, since the appendix is not a causative factor and the risk of external fistula formation is great. Crohn (36) says resection in the acute phase can be successfully accomplished without too much risk; yet, in another article (38) he warns against the use of severe surgical procedures in acute ileitis. Woolsey (144) feels that in the very early stages a bland diet, mineral oil, a probable smooth muscle antispasmodic, and periodic observations are in order. If a real acute stage is present, he believes that a two stage operation is the procedure of choice with resection at a later stage if
there seems to be progression. He prefers to wait at least six weeks between stages. Lehman (91) is of the opinion that the first attack is not the time for radical resection; he suggests that radical surgery can follow if resolution does not occur. In general, the treatment of the acute case seems to be dependent on the merit of the individual case; operation can be performed with little risk but there remains the possibility of spontaneous resolution without operation. The choice of operation lies between the conservative and the radical. Kross (89) advocates a conservative measure such as ileocolostomy or enterostomy in an attempt to rest the diseased segment in the hope that resolution will occur. Later, if necessary, a second stage resection can be done at a more propitious time. Clark and Dixon (25) are of the same opinion, pointing to the low mortality of the short-circuiting operations. Leonardo's (92) patient was apparently cured by a simple ileostomy in an early "stage".

Lewisohn (93) in considering the surgeon of the smaller communities who may not care to risk the removal of the lesion in toto, suggests that under the circumstances a relatively simple sidetracking operation be performed.

Everyone agrees that surgery is the only method
of choice in the advanced cases. After surgical intervention has been decided upon, much further thought and consideration will be required to determine the exact procedure most suited to the case. Should one attempt resection and anastomosis in one stage which will save the patient time and money, or would it be more judicial to approach the problem conservatively by making a simple ileocolostomy as a primary process, carrying out a resection only after a period of observation? Curiously, experience has led to the practice of employing the more radical procedure in those cases in which the pathological process is most advanced and in which, from a theoretical standpoint, the operation is not likely to be tolerated well. Surprisingly, however, the patient with regional enteritis tolerates the radical surgery remarkably well. Primary radical extirpation of the diseased segment has much to offer in the advanced case. This is true particularly if only the terminal ileum is involved or at the most the terminal ileum and its adjacent colonic segment. In these instances there is the choice of performing ileocolostomy with or without division of the ileum and of making a resection at that same time or at a subsequent time. In the advanced stages of the disease such as is present in the majority of the cases, obstruction, fistulas or both have developed and side to side ileocolostomy without transection of the ileum would
only partially deviate the fecal current, and the cramping pain, reflex nausea and vomiting and even the diarrhea would not be completely relieved. With this situation obtaining, the patient can make very little headway in preparation for the second stage of the operation. Furthermore one is frequently disappointed if it is expected that with the involvement only partially at rest the infection will subside and will permit resection to be made more easily. If ileocolostomy alone is to be employed, it is true, that the fecal current can be sidetracked completely by transecting the ileum proximal to the diseased region and by inverting the distal stump. However, if the obstruction is severe an almost "blind segment" obtains and there is the possibility that a blowout of the closed stump will occur. Also, reflex disturbances and toxic manifestations continue unabated in some of these cases. Extension of the disease has been known to occur between the two stages of the operation with ensuing involvement of the region of anastomosis. Should the disease extend after ileocolostomy, which has been accomplished by transection of the ileum in an uninvolved proximal segment, it would seem highly probable that the spread occurred by way of the diseased mesentery and lymphatic structures which were left in situ. [Clark and Dixon, 25]

When the ileocolostomy is made to prevent the flow of feces thru a fistulous tract, it is evident
that the entire fecal current must be side-tracked. Even then, altho the feces no longer extrude thru the abnormal opening, the origin of the tract in the infected segment of the intestine has not been disturbed and will not close. Occasionally when a large quantity of fluid and unabsorbed elements of food are being lost thru an external fistula and there is severe excoriation of the abdominal skin, it would seem logical to precede resection by diversion of the intestinal contents as described. Thus rehabilitation in this way undoubtedly would make the risk of resection less. However, it is unusual for the fistula of regional ileitis to be that extensive.; the debilitation which is present is generally that occasioned by the presence of the disease, rather than by loss of the substances mentioned. For this reason very little is obtained by a simple short-circuiting procedures.

What may one expect from resection and anastomosis in one stage when the disease has already progressed to a late phase? It will be found the patient obtains relief from his discomfort, that extensive progress of the disease toward an uninvolved segment is obviated as nearly as possible, that fecal fistulas are eliminated if present, and that the likelihood of occurrence of a fistula postoperatively is extremely remote. Also the return of the patient to his normal pursuits is hastened by many months. The only question then is: Does an oper-
ation in one stage subject the patient to an unjustifiable and avoidable risk? Observations do not warrant such a conclusion if one considers the results obtained in properly selected cases. Also the attending circumstances seem to militate against the likelihood of the occurrence of that most dreaded and very frequent complication of intestinal surgery, viz., peritonitis. The infection of the wall of the intestine has exposed the peritoneal cavity to contamination for such a long period of time in most cases, that considerable immunity to subsequent infection has apparently ensued. Peritonitis as a cause of death in regional enteritis is a rarity.

Among older patients in the upper age limits and especially among those with involvement of several segments, the conservative procedure would seem to be a necessity. This is especially true if abscess has formed.

Holm (74) has pointed out that the sidetracked loop of ileum does not fare well in lateral ileo-ileo-stomy or ileocolostomy; he remarks that an enteral loop may develop elongation, dilatation, and ulceration. He suggests resection and in cases where this is inadvisable, a second stage with removal of the segment.

Haymond has collected 257 cases of massive resection of the small bowel and, discounting dangers of
the operation and its concomitant complications, finds 
that a patient can withstand a massive resection of 33% 
of the length of the small intestine and expect the di-
gestive tract to return to normal function; 50% removal 
constitutes the upper limits of safety in extensive 
enterectomy.

Clark and Dixon have summarized the results of 
surgical treatment in 44 cases as follows:

<table>
<thead>
<tr>
<th>Status</th>
<th>Ileocolostomy</th>
<th>1 stage</th>
<th>2 stage</th>
<th>Exploration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>5</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persis.</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fistula</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
| Not repor-
| ted       |               |         |         | 1           |
| Total     | 14            | 14      | 15      | 1           |

The report is based on knowledge possessed 6 months to 
2 years postoperatively. The average time between the 
stages was 3 months. The entire operative mortality 
was 11.5% - based on the number of operations it was 
8%. Four died after short-circuiting operations, 3 as 
the first stage of a two stage operation and 1 as a pal-
liative ileostomy. Two died after anastomosis and resec-
tion in the second stage- both had extensive recurrence 
and progression between stages. One died after a one 
stage operation. All the dead were at the extreme ends 
of the age limits. The authors conclude that both the
old and young are particularly susceptible to the dis-
when once afflicted or are less prone to develop resis-
tance and immunity to the disease than are the middle-
aged. Also 3 of their deaths followed recurrence or ex-
tension of the process with marked involvement of the
colon. They consider such an eventuality a grave one, th
outlook being poor and surgery being fruitless.

Mixter (102) sent questionnaires to prominent
surgeons and clinics of the United States. Of 363 cases
thus collected, he found 278 had been operated upon with
a mortality of 14%. Twenty five of the twenty seven sur-
geons considered radical resection in one or more stages
the treatment of choice. In a period from 4 months to 6
years there was a 20% recurrence; this recurrence was fo
found to be more liable to appear in the most advanced
cases.

Crohn (39) found that short-circuiting operations
entailed a risk of only 10.5% but that 50% of the cases
needed eventual resection. The others were apparently
well after 2 to 3 years. Primary resection entailed a
risk of 15% on a larger series of patients but the
chances for cure were better; 7.7% recurred and he laid
this to a failure of recognition of the upper limits of
the process. Resection after recurrence from short-cir-
cuiting operations introduce an increased risk.
Koster, et al. (88) collected 126 cases from the literature, found a mortality of 15% in cases with resection, a general mortality of 14%.

Oppenheimer (111) expresses the general belief when he says that recurrences after primary resection are due to (1) true recurrence of a previously uninvolved ileum, or (2) persistence and progression of the overlooked area of disease which has not been removed. In 1938, he reported a recurrence of one of the original 14 cases reported in 1932. He advises division of the ileum 8 to 12 inches above the visible or palpable involvement, and emphasizes the search for "skip areas".

Extensive involvement, recurrence of the lesion, and involvement of the jejunum are unfavorable factors as far as prognosis as to life is concerned according to Koster, Kasman, and Sheinfeld (88).

Shearer and Jackson (134) report a two-time recurrence in a patient over a period of 12 years; wide resection had been resorted to with no benefit.

Mixter (100) had 4 deaths in 11 cases, 3 of them being due to peritonitis and the other to pulmonary embolism.

The failure of medical treatment is realized when we see that 32 of 44 cases (25) had undergone a course of medical care for a period of years with no
results. Almost every conceivable mode of attack had been tried faithfully to no avail. Anyone who has seen the irreparable state of the intestine will agree that no known medical treatment will prove of value. Medical treatment as an adjunct to surgery is of recognized value.

Clark and Dixon point out that a severe deficiency in nutritional elements has occurred as a result of the inroads of the disease and for several days post-operatively the patients can take nothing by mouth to replenish these deficient stores. They recommend the use of crystalline vitamins in solution to be given intravenously, restoration of the basic elements by intravenous administration of NaCl and CaCl₂, replacement of the serum protein and of hemoglobin by transfusion, Prevention of post-operative distention, retention, and ileus also have a prominent place in therapy. Transduodenal continual aspiration is performed at the earliest indication. (Daine and Wangensteen, 112). A rectal tube is inserted at regular intervals to relieve accumulation of colonic pressure (25). Boothby, Lovelace, and Bulbulian have devised an oxygen apparatus of great value (16, 95, 19). Fine, Sears and Banks recognized the value of a high oxygen percentage in the decompression of the bowel (60). Pfeiffer (124, pg. 405) caused a case to subside with X-ray.
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