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Regional enteritis

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REGIONAL ENTERITIS

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by

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INTRODUCTION

Regional enteritis, although a rather new disease entity, no doubt has been affecting the human body along with other disease processes since the beginning of mankind.

It is the object of the writer of this paper to review the literature on this subject and to present a clinical picture of this disease entity in divisions. Each division is presented as far as possible in a chronological form, reviewing the important literature pertaining to each aspect of the disease as well as to noting progression of thought and work on the subject from the time it was first described up to the present.

It has been a source of considerable pleasure and interest to the writer to assemble what to him seems the selected literature on the subject of regional enteritis and present the same in a thesis to the University of Nebraska College of Medicine.

DEFINITION

Benign or non specific enteritis or ileitis, localized chronic cicatrizing enteritis, infectious or non specific granuloma of the ileum, regional ileitus or enteritis are terms variously applied to the clinical entity terminal ileitis, first described as such by Crohn, Ginzburg and Oppenheimer (15) in 1932. Regional enteritis is now favored as the most inclusive term in view of the broadening interpretation of this disease. The magnitude of the disease to intestinal involvement differs only in that described by Crohn (15) as terminal ileitis in 1932.

We may define regional enteritis, Lewisohm (36), as a subacute or chronic, nonspecific inflammatory disease of unknown etiology which does not elect and affect the ileum alone, but may attack other parts of the small intestine as well as the cecum and other areas of the colon. The inflammatory process, being of an exudative hyperplastic type, eventually resulting in stenosis and obstruction of the bowel and, not infrequently, in internal or external fistulas.

HISTORY

Regional enteritis was not named such until 1932 when Crohn, Ginzburg and Oppenheimer (15) described the disease. Out of a group of nonspecific granulomatous diseases they described a disease which they called regional ileitis. The name regional ileitis was given the disease because at that time Crohn and his co-workers thought only the ileum was involved in this new disease entity and the terminal ileum being the most often involved.

Dalziel (21) in 1913 noticed a condition in a which he called chronic interstitial enteritis, after observing several other such cases of the same nature.

Tietze (47) in 1920 described a benign granuloma but did not come close to the description later given by Crohn in his description of regional ileitis.

A very good account of what they named "non-specific granulomata of the intestine" was given in 1923 by Moschowitz and Wilensky (42). They failed to discover any characteristic clinical signs or clear cut pathological picture. They insisted that the thickening was neither a tumor growth nor a specific infection, but that some low grade sort of bacteria must be presumed to be the cause.

So it was now for Crohn and his co-workers to isolate from a large group of non-specific granulomata a clean cut disease entity which they named regional ileitis.

ETIOLOGY

The etiology of regional enteritis is still as obscure as when Crohn (15) first described the disease entity as regional ileitis in 1932. Dalziel (21) in 1913, even before the disease had been shown to be a distinct disease entity, described a similar condition and mentioned the possibility of a tubercular origin but no bacilli could be found on examination. Johne's disease, a chronic bacterial enteritis of cattle which was pseudo-tuberculous, he thought might have been the same as found in man in the cases which he described. Again the absence of the acid fast bacillus suggested a clear distinction, but the histological characters were so similar as to justify a proposition that the disease might be the same. Dalziel made the statement, "as far as I know the disease has not been described, but must have been seen and diagnosed as tuberculosis and nothing done for its relief."

Ginzburg and Oppenheimer (27) have given a classification of lesions which they thought might be responsible for regional enteritis.

1. Extra or peri-intestinal granuloma secondary to sealed off perforation.

A. Response to some irritation, i.e., fish bones, toothpicks, as the cause of perforating of intestines which were sealed off by Omental adhesions, thus producing a

palpable fibrotic mass even leading to calcification (two cases seen).

2. Granuloma secondary to known vascular disturbances, as in compressed guts after hernia operations (strangulation). Five cases reported where this has happened. All segments involved were segments that previously had been strangulated.

3. Localized hypertrophic colitis, with or without low grade generalized colitis.

4. Localized hypertrophic ulcerative stenosis of the terminal ileum.

5. Simple penetrating ulcers of the colon.

6. Lesions secondary to inflammation of the appendages of the bowel such as appendicitis, diverticulitis, and typhlitis.

Felsen (24) believes, if his interpretation of the pathology of the dysenteries is correct, the lesion seen may be the earliest stage in terminal ileitis in as much as the infection precedes symptoms by a week or so. It is reasonably certain in some patients the acute lesion may fail to heal, secondary nonspecific infection occurs, B. dysenteriae and the specific agglutination titre having disappeared. Felsen (24) states that in his experience, the sharply segmental nature of the lesions and general pathology speak for the common pathogenesis of terminal ileitis, idiopathic ulcerative colitis and bacillary dysentery. The lesions in the chronic stage of terminal ileitis are the same as seen in acute bacillary dysentery, except that

owing to the long duration of the disease, extensive fibrosis and intramural infection is present.

Mock (41) in 1931 had the idea that, with the presence of a tumor mass in the abdomen, the possibility of infectual granuloma should be considered. He thought at this time some specific bacterial infection as bacillary dysentary, protozoal infections as amoebic dysentary, and metazoal infections as worms, and diverticulitis and ulcerative colitis sometimes precede a localized granuloma.

Sanders (44) suggests a theory which centers around the perforation of a bowel. A tumor-like mass then surrounds the perforation. In such cases the intestine may show only a few changes from the normal although the peri-intestinal tissues are extensively infiltrated by the inflammatory process. Blood supply impairment has been followed by formation of granulomatous masses at the affected area. Such lesions have been seen to follow intestinal obstruction, intussusception, mesenteric thrombosis, and hernial incarceration.

Bockus (9) thinks a virus may be the cause of regional ileitis as in lymphogranuloma, but this has not been proved. Tuberculosis and amebiasis have been disposed of as an etiological factor.

Schapiro (45) describes a case that was suggestive of tuberculosis of the jejunum instead of hypertrophic jejunoileitis because of the numerous typical anatomical tubercles in the

adjacent lymph nodes, however, it was impossible to demonstrate the tubercle bacillus by direct examination or by guinea pig inoculation.

Barbour and Stokes (3) thought the foreign body factor might be the cause of regional ileitis, then preceding operations were stressed as a possible etiological factor. Even suture material was incriminated. More recently these factors have been found inadequate and suggestions have been made that mechanical factors operate either directly on the gut or its blood supply. Chronic recurrent self-reducing intussusception at the ileo-caecal value or upset in local blood supply by an appendix might cause terminal ileitis, but they would not account for lesions higher up in the intestine.

Barbour (3) recorded a case that gave a history of alimentary infection by Entamoeba histolytica, B. Typhosis, B. paratyphosis, and Giardia lamblia. There was no evidence of foreign body or abdominal operation . The involvement of small intestine alone would tend to exclude Entamoeba histolytica. The wide spread involvement of the small intestine is against B. typhosus and B. paratyphosus. The Giardia infection was present and found in the stools. In view of the work of Lyon (37), Barbour (3) thinks the Giardia infection was the primary cause of the granulomata found in the case he describes.

Homans (30) believes the appendix may be implicated in some cases of regional ileitis. He presents two cases under his

observation. One showed ulceration and the other was partially destroyed by fibrosis. He maintains the vascular relation of the appendix is more favorable to ileal than cecal involvement. Furthermore, removal of the appendix frequently proceeds the onset of regional ileitis.

Mixter (35) in his experience says Homan's (30) impressions are erroneous because the true pathologic condition is unrecognized at the time of operation. In none of the cases described by Mixter (35), where no appendectomy had been done, was there evidence suggestive of primary appendiceal involvement or ulceration of the mucosa. Usually the lesion was so chronic at the time of operation, a mixed culture was reported bacteriologically. The only bacteriologic findings were in early cases and a culture of anaerobic streptocuccus in all the cases. Repeated tuberculosis cultures have proved negative along with guinea pig inoculation.

Lewisohm (36) thinks the cause of this lesion may turn out simply to represent a middle form of ulcerative colitis. He finds that many of these cases have a very acute onset with fever, diarrhea, and with mucus and blood in the stools. These cases may belong to a group in which segmental enteritis represents a lesion caused by a less virulent virus of the same nature which in its more toxic state produces the well known clinical picture of an ulcerative colitis. However, segmental enteritis presents two pictures seldom seen in ulcerative colitis: one, fistulous

communication between the lesion and other parts of the intestinal tract; two, symptoms of incomplete intestinal obstruction.

Crohn (19) in some of his recent work on the etiology believes the appendix may be a possible cause. This area at the ileocecal junction is rich in lymphatics and a lymphatic block may be a cause. A type of lipin absorption being the provoking agent in a mononucler cell type of infiltration that is seen. The disease process at higher levels after lower resection speaks loudly against lymphatic block, however, and in favor of a residual infective agent. Crohn (19) has never been able to recover a dysentery organism from a speciman. The agglutination reaction against dysentery organisms is uncertain. The reaction is too general and too nonspecific to be of great significance.

In conclusion it can be stated that granulomatous lesions of the bowel may be caused by many different agents. The etiology of such granulomatous lesions which present a uniform picture and most frequently involves the terminal portion of the ileum is unknown.

PATHOLOGIC MANIFESTATIONS OF REGIONAL ENTERITIS

Prior to the description of ileitis in 1932 by Crohn and his co-workers (15), all granulomas of the small and large bowels were considered in a nondescript group, the etiology of which commonly was assumed to be tuberculosis.

Dalziel (21) in 1913 had several cases which he called chronic interstitial enteritis and realized it to be a condition not previously fully described. The pathological report on several specimens from ileum, jejunum and colon showed much in common in all specimens. All stages from acute to chronic inflammation were seen. The earliest change in the bowel appeared to be acute congestion with much edoma of the submucosa. Polymorphs were thick in the vessels and also a marked infiltration of the same type of cells within the tissues. There had been irregular hemorrhages here and there in the mucosa. The mesentery was also involved much the same way. The next phase seemed to be a cellular and fibrinous exudate within the gut lumen. Still later in the picture the mucous membrane was denuted of epithelium. In one specimen the regeneration process was somewhat evident. The muscle layer had a definite outer limit of a broad zone of granulation tissue which was replacing the layer of purulent exudate within the gut lumen. A still later phase was seen in a section, a fibroblastic transformation well seen in the gut lumen. There is less edema of the tissues in the more chronic form. Research failed to reveal any micro-organisms in the specimens. The works

of Moschcowitz and Wilensky (42), in 1923, conclusively established that these lesions of the ileum were rarely tuberculous.

It remained for Crohn and his co-workers (15), in 1932, to segregate the confused category of intestinal granulomas, a distinct clinical entity, which he then called terminal ileitis. He described the pathology as a subacute or chronic necrotizing and cicatrizing inflammation which frequently leads to stenosis of the lumen of the intestine and associated with formation of multiple fistulas. The terminal ileum is alone involved as he described the disease entity at that time, but his later works have corrected that statement. Crohn describes the terminal ileum as a thickened, soggy, and edematous tissue. The serosa is red and the mesentery of the terminal ileum is thickened and contains numerous hyperplastic glands. The inflammatory process is not, however, a static one nor is the entire diseased segment affected at one time. The oldest lesions begin apparently at or just oral to the ileocecal valve and the more recent ones are situated proximally. In some of the cases he describes, isolated involved areas were found. The characteristic lesion was usually limited to the distal 25 to 35 cm. (10 - 14 inches) of the terminal ileum. The most advanced pathology was situated at the valve and in most cases had become a rigid diaphragm, with a small irregular opening. Proximal the disease process gradually abated, shading off to normal mucosa. The normal intestinal folds were distorted and broken up by the destructibe ulcerative process. Much edema being present.

Crohn also describes a series of small linear ulcerations lying in a groove on the mesenteric side of the bowel which is nearly always present. The cause of the above, he thought, might be remnants of the original destruction or mechanical erosions due to the formation of a darmstrasse by the shortening of the fibrotic mesentery. The submucosal, and to a lesser extent, the muscular layers showed marked inflammatory, hyperplastic and exudative changes thus causing the bowel to become thickened, perhaps several times its normal size. The lumen of the bowel becomes closed or nearly so. The proximal bowel to the affected segment frequently becomes dilated and may show tension ulcers. In the older phase of the disease the exudative reaction is replaced by a fibrostenotic phase and the mucosa is atrophic with occasional erosions, and islands of papillary or polypoid hyperplasia. The serosa loses its gloss and may exhibit tubercule like structures on its surface. The mesentery is likewise involved.

In the fourteen cases, which Crohn (15) described in 1932, there was a marked tendency toward perforation into the peritoneal cavity. In the chronic perforations the omentum had time to wall off the leakage. There was a marked tendency to form internal fistulas, the sigmoid being the seat of fistulous involvement in four cases and the ascending colon and cecum once each.

Microscopically no specific features could be demonstrted. The stained histologic sections showed a various degree of

acute, subacute and chronic inflammation with variations in the predominance of polymorphonuclear, round cells, plasma cells, and fibroblastic elements. In the early stages of the disease the lesion is diffuse mainly in the mucosa and submucosa with some serosal inflammation. The mucous membranes show marked destruction and the glandular structure partly destroyed. Later in the disease the inflammatory condition is more focal in character.

Harris, Bell and Brunn (29) in 1933 pointed out that jejunal involvement did occur but could not add to the description of the pathology given by Crohn.

Bockus (9), trying to find a reason for the known predilection of regional ileitis to involve the terminal ileum, finds it to be a matter of speculation. Some anatomical factor may be the cause. Microscopical appearances of nonspecific ulcerative lesions are the same and appear any where in the G. I. tract and so far no reasonable conclusions have been reached as to why ulceration occurs at one place more than at another in the G. I. tract.

Crohn (19) in 1939 again describes the pathology of this disease entity and about the only difference was the possibility of various locations in which the nonspecific granuloma might be found. The main blunt is on the terminal ileum beginning abruptly at the ileocecal valve and extending up the small intestine for a variable distance. In one case even the jejunum and duodenum were involved. The extent of the involvement is

is usually shown by enlarged mesenteric lymph nodes adjoining the mesenteric attachment of the affected segment. The nodes are never calcified nor do they break down. There may be areas or skip areas, varying from 2 to 12 inches of uneffected bowel. The terminal ileum as well as some of the colon may be involved. The colon involvement will often regress while the ileum keeps on in its involvement. The terminal ileum may be excised.

In ten cases reported by Stafford (46) the terminal ileum was involved in five cases. In the other five the segment was located from one to three feet above the ileocaecal valve. None of the ten cases had multiple lesions, and no involvement of the colon. The mesenteric glands draining the area were involved in each case. Grossly the specimens were thickened, hoselike with a roughened serosal surface. Ulceration of the mucosa was present in every case. Under the microscope various stages of inflammation and scarring of the intestinal coats could be seen. In several instances giant cells were seen, but no true tubercles or tuberculous bacilli were found.

Coffey (12) at the Mayo Clinic describes the pathology in twenty-one cases. The only cases included in his report, however, were those in which the ileum was involved predominantly by a hyperplastic stenosing inflammatory process.

The typical appearance of the involved bowel was seen. The ileum was greatly thickened, its lumen narrowed, and the mesentery edematous. The inflammatory process was usually more

severe toward the distal end of the lesion and, not infrequently, the ileocecal valve would barely admit a large probe. Oval, shallow, ulcers were usually present above the stenosed portion of the bowel. The mucosa was marked by longitudinal ulcerations, usually at the point of mesenteric attachment. The mucous membrane usually had a cobblestone-like appearance and occasionally well-formed polyps were present. Extreme thickening and edema of the submucosa were seen constantly. In some specimens the muscular layers were conspicuously hypertrophied.

The microscopic finding showed exudative, proliferative, subacute and chronic inflammation. Cells of the lymphoid series appeared to be predominant and submucous lymphoid follicles appeared invariably numerous and enlarged.

Coffey (12) states the erroneous diagnosis of tuberculosis in this disease is chiefly based on two findings. In the first place, giant cells are usually present, but these multinucleated cells very frequently contain particles of a crystalline or lipoid nature which undoubtedly represents food remnants which lodge in the ulcerated mucosa. The true tubercles, with the epithelioid reaction, central caseations and giant cells, were encountered only in the material from patients who had active pulmonary tuberculosis. The second feature that suggests the tuberculous nature of regional ileitis is the frequent occurrence of tubercule-like spots on the serosa of the bowel. However, these are seen to consist of focal collections of lymphocytes and

are in no way tuberculous.

A study of the pathology in twenty-one cases of regional enteritis:

Extent of involvement	(Ileum: terminal in 16 cases; discrete (patches in 5 cases. (Cecum: involved in 10 cases.
Fistula	(External: 6 cases. (Internal: 2 cases.
Histologic changes	(Nonspecific granulomatous: 16 cases. (Typically tuberculous: 3 cases. (Lymphogranulomatous: 2 cases.

Roentgenographic evidence of active pulmonary tuberculosis: recovery of tubercle bacillus from sputum in the three cases which were typically tuberculous.

The above study as described by Coffey (12) indicates: (1) that regional enteritis or regional ileitis is a subacute or chronic granulomatous inflammatory process with a pronounced tendency to stenosis of the bowel and formation of fistula; (2) that, although the terminal portion of the ileum is always predominantly and usually solely involved, the bowel above or below may be affected; and (3) that evidence of any tuberculous nature for the disease is lacking, except in those cases in which an active pulmonary focus is demonstrable.

CLINICAL COURSE

The clinical course of this disease is pretty well known and a good many workers interested in the disease entity agree it can be divided into four stages as originally outlined by Crohn (15) in 1932 and also in his articles since then on the subject. These different stages and phases are named various things, but each phase as described by different writers are some what similar in character.

The first stage or phase according to Crohn (15), Crohn, Ginzburg, Oppenheimer (16), Corr and Boeck (14), Ginzburg and Oppenheimer (27), is an acute stage giving signs of acute intra-abdominal inflammation with peritoneal irritation. Before operation the diagnosis is rarely regional enteritis, but usually appendicitis. Meyer and Rosi (38) confirm the above and particularly if the lesion is of the ileum the symptoms nearly always simulate an acute appendicitis. There are generalized colic, pains and tenderness, fever 101° to 102° F. The white blood count is elevated. Crohn and Rosenak (18) point out the onset of symptoms are usually slower than in appendicitis, however. The presence of a mass is rather common. At operation the involved segment is found to be thick red, blotchy with a marked edema of surrounding tissues. There is an exudate on the involved segment. The mesentery is thickened and edematous and contains many large glands. Usually a clear fluid is found in the abdomen. The future course of the disease from here cannot be told. Some resolve while others pass

into one or other of the chronic states, or if drained may produce intractable fistulas.

The second phase or stage as described by the same workers for the first phase gives symptoms of an ulcerative colitis. The patient complains of colicky periumbilical or lower abdominal pain. There is a tendency toward looseness of the bowels, usually three to five times per day. The stool is usually liquid or mushy, containing mucus and occult or visible blood. A constant fever is present, but not high. A secondary anemia developes together with a loss of weight and strength. This process may continue for as long as a year when the stenotic phase gradually sets in. It is during this stage colitis is blamed but bacteriological examinations are negative.

The stenotic phase is the most often encountered and here symptoms of intestinal obstruction are seen. Violent cramps, borborygmus, and occasionally attacks of vomiting may be seen. There is usually visible peristalsis and a palpable mass is nearly always present in the right lower quadrant. It is to be noted a patient may pass through any of the above stage without symptoms or a previous history of trouble and then start having intestinal obstruction symptoms due to the stenotic condition of the involved segment. In this stage of the disease fistulous communications with the colon or sigmoid may lead to signs and symptoms of colitis and mask the true nature of the disease.

The fourth stage is characterized by peristent fistulae which occur spontaneously between loops of bowel, or appear late

postoperatively, as abdominal fistulae such as may follow an appendectomy. The feature of the fistulas formation is of interest. They may develop a few months after a drainage or operation, the wound having already healed and an abscess then develops in the wound. When this abscess mass is investigated it is found to communicate with the intestine. Barrington, Ward and Norrich (5) call this stage of the disease one of adhesions as well as fistulae formations. Halligan (28) reports two atypical cases in their clinical course. There was an absence of symptoms previous to perforation in contrast to the pathology found. The onset of pain was in the back. There were organisms found in pure culture from the peritoneal fluid. Whether this was an etiological factor wasn't known. The various phases of the disease occurred within a short time and finally ended in complete resolution.

Felsen (23) feels that bacillary dysentery, distal ileitis and nonspecific ulcerative colitis are merely different stages or manifestations of the same disease. Since a good many other workers have failed to confirm this idea altogether the above four stages seem to be the accepted clinical course of regional enteritis today.

CLINICAL FEATURES

The clinical features of this disease as described by Crohn (15) and others are of interest. Crohn (15) found that young adults were most often affected in the original group of cases he described. The average age incidence being thirty-two years. The youngest being seventeen and the oldest fifty-two years of age. Males being effected two to one over females.

Most patients were ill for several months to two years, before coming under observation. During that time the outstanding symptoms were fever, diarrhea, continuous loss of weight and progressive anemia. The clinical picture resembled a nonspecific ulcerative colitis. The fever was rarely high, and long periods of apyrexia being interspersed with shorter and irregular cycles of moderate temperature. The temperature may go to 103 degrees in one patient and the next patient may never have a fever.

Diarrhea was usually an outstanding feature, but seldom approached that of a true colitis, the average number of stools per day being two to four. These are loose or semi-solid, sometimes with blood and always with mucus. When stenosis has taken place constipation may take the place of the diarrhea.

Vomiting characterizes the stenotic type of the disease. This is never very intense however and there is usually abdominal pain and visible peristalsis.

Pain over the lower abdomen is common. This pain is dull, cramp-like and is accompanied or followed and relieved by

defecation. The pain is usually in the right lower quadrant. When the sigmoid if it does become adherent to the necrotizing ileum, fistula formation occurs between these two hollow viscera. The pain is then in the left abdomen and a mass may be felt abdominally and per rectum.

The general symptoms are weakness, loss of weight and anemia. All the above varying per patient. The appetite is poor expecially during the febrile bouts. A moderate leukocytosis may be seen, but usually it is about normal.

The most common findings in the physical examination are, (1) a mass in the right iliac region, (2) evidences of fistula formation, (3) emaciation and anemia, (4) the scar of a previous appendectomy and (5) evidences of intestinal obstruction.

The mass is usually moderate size, tender, firm, irregular and only slightly movable. When the sigmoid is involved the mass may lie more to the left. When the cecum or ascending colon or hepatic flexure constitutes the distal end of the fistulous tract, the mass may lie more to the right and higher in the abdomen. When the fistulous tract burrows into and through the mesentery, the necrotic process may cause a diffuse mesenteric suppuration which participates in the formation of a mass. The tumor is usually palpable per rectum.

Fistula formation is most often seen in the sigmoid, then cecum, ascending colon and occasionally the hepatic flexure.

There are evidences of emaciation and anemia.

In half of Crohn's (15) first cases the appendix had been removed and in half of these the ileum had been noticed to be in question at the time of the operation. The appendix is always free of guilt in this disease.

The stenotic type show evidences of intestinal obstruction. Loops of distended intestines may be visible through the abdominal wall and puddling is frequently seen in flat x-ray films. Visible peristalsis is not uncommon and is accompanied by borborygmus and the passage of gas with evidence of relief. General distention and ballooning of the whole abdomen are unusual.

The new data on regional ileitis is supplemental rather than contradictory to the postulations of Crohn and his associates (15) in their description of the fourteen cases in 1932 of a pathological and clinical disease entity. The only contradictory attack upon Crohn's first postulations being the location of the disease. It is generally known now among the investigators of this subject that any portion of the large or small intestine may be involved. The terminal ileum being by far the most often involved.

Mixter (39) in eleven cases finds the age incidence twenty to thirty years to be the most frequent. Males being involved more than twice as often as females. The youngest of his cases was fourteen and the oldest fifty-six years. The highest incidence was among the Hebrews. Brown, Philips, Bargen and Arnold (10), in eighteen cases they followed, found the age

incidence to be from nine to sixty-one years, with the most frequent involvement between the ages of twenty and thirty years. The locations of the lesions are of interest; in nine of their cases the ileum alone was involved; three cases had jejunal involvement alone; one case had the terminal portion of the ileum and a small portion of the cecum involved; and five cases had the terminal ileum, the cecum and part of the ascending colon involved.

The gross description of the lesions at operation varied remarkably among the different surgeons. The noted inflammatory process, rather sharply localized in area and involving all layers of the intestinal wall, associated with hypertrophy and its similarity to a stiff rubber hose were usually noted. Subserous tubercles were not observed. Enlargement of lymph nodes along the mesentery was encountered. The detailed pathologic study failed to add anything to the original description by Crohn and his associates (15).

The preoperative histories of the patients are of some interest. Most of the patients had been ill for years with symptoms running a specific progressive course. Several had been ill for ten years or more, some for as long as twenty years. Only five had symptoms for less than one year. Ten of these patients had previously undergone operations. Seven cases had been diagnosed as appendicitis, and had been operated for that trouble. Six cases had abnormal conditions of the ileum or colon thought to be tuberculosis, Hodgkins disease or some intestinal inflammation of unknown cause. In one case appendicectomy had been

followed by a resection of the obstructing part. One patient had had a spleenectomy because of an unexplained anemia. The anemia continued and it was finally found the patient had an ulcerating lesion of the lower ileum. The rest of the patients had previously undergone resection of the ileocecal portion of the gut and later the disease had spread to distal portions of the ileum.

The clinical symptoms and physical findings were not unusual in respect to those already mentioned in this paper.

Crohn (19) in 1939 in a discussion of symptomatology finds the onset of this disease is usually slow, but may be acute. Usually the patient has occasional spells of discomfort or diarrhea, which later may be followed by continuous intestinal frequency, fever and pain. Sixty-two patients had histories of such symptoms from one to five years; fifteen patients five to ten years. During this long period of the nonrecognized disease various things, for example nervous diarrhea with a psychoneurotic background, food allergy and undulant fever, were the diagnosis.

The appearance of a mass in the lower right quadrant or across the lower abdomen indicates spread into the mesentery, or formation of sinuous or fistulous tract.

Crohn (19) doesn't think obstruction symptoms appear as often as thought. Only ten of his cases showed such symptoms and these were partial obstruction associated with borborygini, gurg-

ling and a palpable mass. An inflammatory mass with a long chronic history and signs of obstruction in a young person are highly suggestive of ileitis.

The complications of this disease are several, but fistulae being the most outstanding. Crohn (19), Crohn (17), and Adams (1) have confirmed this. Crohn (19) points out the highly infective and lytic nature of fistulas in this disease. Internal fistulas were observed in eleven cases. They usually originated in the terminal ileum and terminated in some segment of the colon, usually cecum or sigmoid. The bladder, vagina, or even a loop of the ileum or jejunum may be involved. External fistulas were noted in twelve cases. These started in porous ileum and ended on the anterior abdominal wall, usually following a scar of a previous laparatomy. Such fistulas may occur in the inguinal, lateral abdominal wall, right lumbar region without history of operative measures. Peri-anal and rectovaginal fistulas are common.

Clark and Dixon (11) at the Mayo Clinic in a recent article on the clinical features, give a very good summary on forty-four cases. The ages ranged from twelve to fifty-four at the time of onset of symptoms, which is about the same as reported by Koster, Kassman and Sheinfeld (33) in a review by them of sixty-seven cases collected from various reports. Sixty-three per cent of the forty-four cases were less than thirty years of age, and eighty per cent less than forty years of age. The average age

being twenty-seven years. The disturbance had been present about four years before the patients came to the clinic. The shortest duration of symptoms was four days and the longest twenty-five years. Twenty-four of the forty-four were males. More than twenty per cent of the patients were Jews. The disease was not observed in Negros. Their chief complaints were: (1) pain, which was not of a cramp-like nature and usually associated with a diarrhea; (2) diarrhea was seen in eight cases; (3) diarrhea with severe abdominal cramps in thirteen patients; (4) fecal fistula in nine cases. One case had only a palpable mass in the abdomen. Wilensky (50) points out the patient frequently complains of a bloody diarrhea, but this has not been observed in all the literature on the subject. Binney (7), on the other hand, feels that especially where the disease is of the ulcerative type the absence of free blood in the stool is usually seen.

The typical clinical picture of regional enteritis may be encountered in a young adult who usually has had an appendectomy without relief of pain in the right lower quadrant of the abdomen. Subsequently moderate intermittent diarrhea with cramps, a mass in the right lower quadrant, low grade fever, loss of weight and appetite develop and the patient comes to the physician for relief of a chronic, incomplete obstruction.

ROENTGENOLOGIC EXAMINATIONS AND MANIFESTATIONS

Roentgenologic examinations in the diagnosis of regional ileitis are very important.

Crohn (15) in 1932 showed two outstanding facts in roentgenographic observations of this disease which he described. A negative and a positive fact are regularly noted. Since the disease simulates the clinical characteristics of ulcerative colitis, the barium enema is first attempted. The procedure results in a negative report. The reason for this is evident in the light of the pathology of the disease; colon free from ileitis and not from ulcerative colitis. The barium meal is the positive finding. Distended loop of terminal ileum in which fluid level is discernible, and a definite delay in motility of the meal through the distal end of the small intestine is usually present. In the stenotic stage the delayed motility is most striking. The milder degree of stasis is hard to see except by an expert. When the ascending colon is the seat of a fistulous communication with the ileum, stricture deformity of the ascending colon or hepatic flexure may be noted with delayed motility at this point. When the sigmoid is likewise involved, the same is seen and it may simulate carcinoma at that point.

Since Crohn as well as others know now that more than just the ileum may be involved, the roentgen findings are somewhat changed.

Kantor (32) explains the use of barium and fluoroscopic

examinations in showing the early and late phases of the disease. Early changes show loss of segmentation and peristalsis in lower ileum and a rigidity of the intestinal wall. Later stages show filling defects of terminal ileum, often a tapering of the shadow toward the caecum, a fixed and permanent caecal deformity indicates that the disease has spread beyond the ileocaecal valve to the wall of the large bowel. In the third phase the tubular stricture of the ileum shows a thin line of barium passing from a dilated gut above to the ileocaecal angle below. This is the string sign of Kantor. This isn't pathognomonic of Crohn's disease, but with other signs and findings makes the diagnosis a certainty.

Jellen (31) thinks that many cases are misdiagnosed with the x-ray because primarily the examiner focused his attention on the stomach and duodenal bulb and disregarded the rest of the intestinal tract. It is of uttermost importance that special attention be focused on the small bowel, especially the terminal ileum. Pollock (43) feels there are certain conditions that make roentgen studies advisable: (1) Persistent symptoms of colitis in which barium enema, sigmoidoscopy, stool culture and serological examinations are negative; (2) The presence of a mass in the lower right quadrant of the abdomen in a young adult; (3) Cramps in the lower abdomen or an intractable fecal fistula following an appendectomy or the drainage of an appendiceal abscess.

Jellen (31) again points out that particular attention be paid to all six-hour examinations of the ileum where the stomach

and duodenum show negative. In all suspected cases serial films are taken at frequent intervals following the ingestions of a barium meal. These films are usually taken at one, two, four, and six hours after the meal. All films are taken in prone position. A barium meal is contraindicated when there is evidence of obstruction, either partial or complete. All cases that show a delayed motility of the small intestine at the six hour period have films taken then and two hours later. This will usually show the ileum, cecum and ascending colon.

In regional ileitis the essential roentgen finding is the demonstrating of a cicatrized and stenosed terminal ileum. The normal caliber of the ileum is reduced one-half to one-third normal size, and is shown by a stream of barium leading to the cecum. The amount of ileum involved may be shown by this stream of barium, usually eight to ten inches being involved. Usually the narrowing varies in the ileum, some parts more than others. The mucosa is usually obliterated and the four to six-hour examinations usually show the best. In some cases ulceration of the diseased ileum mucosa results in irritability and will not retain the barium, then the involved segment cannot be seen. Dilation of the proximal segment above the diseased area is not always seen because stenosis has to be great in the involved setment to cause dilation of the proximal segment. However, a mass is usually seen.

When cecal deformity is associated with regional ileitis this is usually due to spasm and changes in the cecum because of

adhesions.

Regional ileitis with colitis, Stierlins sign is almost always present. The cecum and proximal colon show marginal irregularity and often contracted. The ulcerative process is shown in the x-ray by spasm, irritability and localized hypermotility of the involved segment of the bowel so that it retains very little barium either by meal or enema. The presence of these findings differentiate this group from the previous one where there is cecal deformity but no ulceration. These findings do resemble ileocecal tuberculosis a good bit.

The roentgen findings in nonspecific jejunio-ileitis the lumen is irregular and narrowed. The mucosa is usually replaced by many oval and round transparent areas which are suggestive of polypoid excrescenses in the mucous membrane. This area of involvement is seldom, however. Jellen (31) reports two such cases, one involving the middle of the ileum; the terminal part showing no evidence of disease. The other case showed involvement in the jejunum, proximal ileum and terminal ileum.

The roentgen findings in fistulae are sometimes difficult. If the tracts lead external, lipiodal injections may show such tracts. Internal fistulae are hard to demonstrate either by meal or enema.

The above findings are characteristic of the disease. However, as pointed out by Kantor (32) the changes are not pathognomonic as they may occur in other stenosing lesions of the

terminal ileum, but those conditions are rare.

In considering the differential diagnosis in regard to roentgen findings two things must be kept in mind the most, namely, primary hyperplastic ileocecal tuberculosis and non-specific ulcerative colitis limited to the proximal colon and terminal ileum.

Weber (49) in his discussion of the roentgenologic distinction of the two forms of enteritis, namely, regional enteritis and tuberculous enteritis, states that any criteria for an unfailing roentgenologic distinction between the two forms of enteritis is frankly lacking, yet there are some evidences which when elicited make at least a good presumptive diagnosis possible. General contraction of the diseased segment, which implies diminished caliber and length, mucosal changes, loss of pliability, and an ileocecocolic distribution of the pathologic process are features which both forms of enteritis have in common. The tuberculous form, however, has been observed to have a different roentgenologic "look" from the nontuberculous form. The contours of the tuberculous intestine have the rougher, more corrugated appearance, corresponding to a more irregular development of the ulcerohyperplastic process. The nontuberculous form of regional enteritis imitates chronic thromboulcerative colitis very closely. The contours are smooth and the narrowing is uniform, corresponding to the diffuse, even development of the underlying pathologic process.

Investigation for extra-enteral foci of tuberculosis, especially in the lungs, should always be made when regional enteritis is discovered. If a focus of active pulmonary tuberculosis is found to be coexisting with a non-neoplastic lesion of the small intestine below the duodenum, it is reasonable to assume that the lesion is also tuberculous. However, in the absence of such a focus, the intestinal lesion is most likely to be nontuberculous. It must be remembered, however, that isolated intestinal tuberculosis does occur and must be thought of.

Other diagnostic clues to help the roentgen diagnosis may be offered by the presence of calcified mesenteric glands, intradermal tuberculin tests and the search for Mycobacterium tuberculosis in the stools.

Jellen (31) believes the hyperplastic type of tuberculosis may occur without other tuberculous infection elsewhere, but this is rare. The string sign described by Kantor (32) may help to differentiate.

Crohn thinks ileocecal tuberculosis as a primary process should be easy to tell, but as Moschcowitz and Wilensky (42), they hold with skepticism the actual occurrence of primary tuberculosis at the ileocecal junction. They feel the latter disease must be rare for only three cases were seen at Mount Sinai Hospital in several years. All the tubercle structures failed to demonstrate the Mycobacterium tuberculosis.

Nonspecific ulcerative colitis and regional enteritis

may make the differential diagnosis hard where the proximal colon and the terminal ileum are involved. Where there is no evidence of terminal stenosis, the diagnosis is made easier. It is important to tell the difference because of the difference in treatment. Crohen (15) points out that sigmoidoscopy and the barium enema suffice for the recognition of colitis in the largest percentage of cases. Where the proximal segments of the colon are involved this may offer confusion. Colitis does not cause fistulas except about the anus and rectum. A mass is rarely palpable or seen in colitis.

The specific granulomas, Hodgkins disease, lymphoblastoma, lymphosarcoma may cause confusion but are usually shown clinically by the examination of excised nodes.

Amebiasis, actinomycosis and malignant disease are discussed elsewhere in this paper.

DIAGNOSIS

The diagnosis of this disease is no small task and Meyer and Rosi (38) point out that the diagnosis of the acute type is usually made at the operation of an appendix or some other trouble which gives about the same symptoms and findings. The association of obstructing symptoms along with the findings and symptoms of an acute appendicitis may be of help in gaining a correct diagnosis before actual operation. Ginzburg and Oppenheimer (27) find that ulcerative enteritis may give confusing findings; for example, diarrhea, loss of flesh, strength, colicky pains and secondary anemia. Felsen (23), however, brings out a very good point in diagnosis. He says any case which lasts for more than three weeks with a diarrhea is considered a suitable one for the development of a nonspecific ulcerative colitis so regional enteritis must be thought of. The chronic type, Meyer and Rosi (38), is diagnosed by roentgen examination and shows a filling defect in the involved segment. The complete roentgen studies and methods have been taken up elsewhere in this paper.

Stafford (46) points out that when any patient has a persistent abdominal fistulae after an appendectomy regional enteritis must be thought of. A palpable mass in the right lower quadrant together with other symptoms and findings already mentioned should make one think of this disease. Bassler (6) claims the diagnosis can be made by x-ray of ileum and colon and rectum by proctoscope.

The differential diagnosis is very important in this disease, especially from the standpoint of treatment and prognosis. The lesion must be differentiated from other well recognized conditions which produce a mass in the lower right quadrant with diarrhea and fever, as nonspecific ulcerative colitis, ileocaecal tuberculosis, mesenteric tuberculosis, Hodgkins disease, lymphosarcoma and more rarely actinomycosis. Lymphogranuloma must be kept in mind as well as malignant diseases.

In making a differential diagnosis from nonspecific colitis the use of the x-ray will help in some cases. It is important to make this differential because of the difference in treatment. The trouble in making a differential diagnosis comes when the terminal ileum and proximal colon are both involved. If there is evidence of terminal stenosis shown by the x-ray, this is of help.

In mesenteric and ileocaecal tuberculosis, Jellen (31), there is usually active tuberculosis elsewhere. X-ray helps along with tuberculosis tests and guinea pig tests.

Hodgkins disease and lymphosarcoma may cause trouble but usually show clinically by examination of excised nodes.

Actinomycosis always must be considered when fistulae are present. The abdominal form usually originates in the cecum. The diagnosis is based on the presence of the characteristic yellow sulphur granules in the discharge.

Stafford (46) in the differential diagnosis from

lymphogranuloma of the large bowel finds the presence of the Frei test helpful in making a diagnosis. In lymphogranuloma the lesions are usually found in the rectum and lower colon but may occur anywhere in the large bowel. Stafford (46) remarks that no cases of lymphogranuloma of the small intestines have been observed in the Johns Hopkins Hospital.

Malignant disease--the age incidence may help. Also malignant disease is found much more than is regional ileitis. Metastatic nodes in the liver and elsewhere are usually seen at operation, which helps in making the diagnosis.

The operative diagnosis made from the gross findings as well as the microscopic findings and diagnoses will not be repeated here since they already appear in other parts of this paper.

PROGNOSIS

Crohn (17) has answered several questions in regard to the prognosis of reginal enteritis. It will be noted however that the prognosis on operative treatment of different types will also appear in the section on treatment.

Crohn (17) points out that A. A. Berg was the first to use the radical resection on regional ileitis and now he has observed thirty-two such procedures with only one death, wide resection of the cecum, ascending colon, and anastomosis between the residual ileum and the proximal transverse colon. The extent of the resection of the ileum depends on the degree of latitude of mesenteric lymphyadenopathy.

Postoperative recovery was good, the shortened gastro-intestinal tract may cause increase gut movements, and increased number of defecations, but cramps and pain were absent. Strength and weight were regained and the blood picture improved. The frequent defecations gradually decreased as time went on. Fistula formation as postoperative complications did not appear. Crohn (17) points out the risk of operation might still be reduced by a two-stage operation doing the anastomosis first and then resection at the second stage.

His observation of the acute cases in regard to prognosis must be guarded. The prognosis is altered by the severity and rapidity of the course of the disease. The question of spontaneously recovery from an acute attack is possible. Several cases

have been reported.

The prognosis of palliative short-circuiting procedure must be kept in mind. Many surgeons have attempted to relieve or cure the disease by anastomosing proximal healthy ileum to healthy colon, thus short-circuiting the lesion. Study of sixteen cases lead to conflicting results. In nine of the sixteen cases this type of procedure failed to cure the disease or alleviate the symptoms. Radical resection was forced in three cases with fatal results. Colp (13), however, reports six cases of ileo-colostomy that are getting along very well after several years with improvement of all symptoms. Koster, Kassman, and Sheinfeld (33), in a review of the short-circuiting operation in fifteen cases, found in thirteen of these cases the short circuiting seemed to alleviate symptoms, but recurrences have not been followed up. Such procedures may for a moment help the patient. It is Crohn's (17) opinion the ultimate prognosis is still in doubt. The risk of palliative short-circuiting is less than resection, but satisfaction is almost assured in resection.

The unoperated cases, seventeen in number, which came under Crohn's (17) observation, in which the diagnosis had been confirmed, either clinically or five by exploratory laparatomy, were still all right after three years. Will stenosis and all the known symptoms come? Medical treatment, if any good, is a strict, nonroughage diet with vegetables and fruits.

Crohn's (17) observation of fatal cases are eight in

number. Three of these had no surgery and five, after surgery had been attempted, usually with resection. In three more unoperated cases death was due to diffuse or localized forms of peritonitis, the formation of a suppurative mass, or as a terminal inanition and exhaustion usually with the formation of multiple fistulae. Had these cases received surgery in time these lives could have been saved.

Postoperative deaths in eleven cases were due to several things. One death was caused by a general practitioner who should have known better than to do an extensive resection of the ileum and much of the jejunum. This case was called nontropical sprue for a long time. Two of the remaining cases were complicated by previous anastomoses and short-circuiting operations. Eight cases were complicated by a violent psychosis and postoperative exhaustion. Probably early operation and direct resection would have saved these lives.

In breaking down the mortality figures Crohn (17) observed a mortality of 17.6 per cent for unoperated cases and 9.8 per cent for operated cases. Therefore, in spite of the risk of surgery the risk seems twice as great when surgery is refused the patient.

TREATMENT

The treatment of this disease entity for which there is no known etiology varies at the present time, but most authorities agree that surgery and excision of the involved segment is the best treatment we have to date.

Crohn (15) in his description of this disease said medical treatment was only palliative and supportive and in general the proper approach was resection for cure. In his first series of cases there was only one recurrence of symptoms and no doubt the original resection was not extensive enough. Harris, Bell and Brann (29) feel the same as Crohn (15) in medical treatment. Surgery may require multiple stage operation and they thought at that time a preliminary short-circuiting operation such as an ileocolostomy should be performed with a later resection of the diseased bowel when the patient had been built up to stand such an operation.

Mixter (39) feels the end result is surgery even if more conservative treatment has been tried. Pallative treatment usually ends up with some complication, for example, abscess or fistula, which then makes resection much more dangerous. Mixter (39) reported he had no cases in which cure was accomplished short of surgery. The danger of surgery and its complications, he feels, must be emphasized. Surgery may activate a latent infection and cause a fatal peritonitis or septicemia. Drainage should be avoided when possible as it frequently leads to fistulae.

Resection of the involved segment in one or multiple stages is the ideal procedure. The operation used is removal of the cecum with the terminal ileum as the ileocecal valve is usually involved. Either an end to side or side to side anastomosis is established with the ascending colon. An ileostomy to relieve the suture line may be of advantage. The operative results presented by Mixter (39) in eleven cases are of interest. Seven cases recovered, 64 per cent, and four cases died, 36 per cent. The one stage ileocecal resection was performed in six cases with five recoveries and one death. Fulminating peritonitis caused the death of one patient forty hours after his operation. The attempted stage resection was tried in five cases which were all complicated by fistulae or abscess. Two of these cases recovered and three died. The completed stage resection was tried in three cases with two recoveries and one death, which was due to multiple pulmonary infarcts and bronchopneumonia three weeks after a Mikulicz resection. Incompleted stage resection he had two cases and both died. One patient had a fecal fistula and died of peritonitis nine days after the operation. The other patient died thirty-six hours after the operation of a general peritonitis. The conclusion that Mixter (39) draws from this group of cases is that a multiple stage operation may be indicated with drainage of an abscess as the first stage followed by an ileocolostomy and finally a resection. His best results have been with the one stage operation, with ileocecal resection and closure with drainage. This

procedure is more applicable in the earlier stage of the disease where complications are minimal.

Brown, Philips, Bargen and Arnold (10) report the following on seventeen cases. At the time of the exploratory operation none died. Three died six months later. Two of these had jejunal lesions and the third had been operated for a fecal fistula and later developed a pulmonary abscess which caused his death.

Ileocolostomy was performed in three cases of terminal ileum involvement and one ileocecal involvement. The reports six months, two, three and five years later showed all in good health, resection not being necessary as long as they were in good health.

Two patients underwent one-stage resections and anastomosis and were all well seven months and three years later.

One patient underwent the one-stage operation where the terminal ileum and cecum were involved. Resection and end-to-end anastomosis were done and nine years later the patient developed an abscess with a fistula.

The remaining six cases were taken care of in this manner; an entero-anastomosis on one patient and ileocolostomy on five, which was followed by a second stage resection. The one patient had a lower ileal involvement and resection was necessary three weeks after the first operation. Several months later the patient was doing well. The other five cases resection was

done three to four months later. The patients had been only moderately relieved during this time. Three of the five were doing well three years after their resection and the other two were not available for check up.

Upham (48) feels that surgery is usually contra-indicated in acute cases of regional enteritis, but more adapted to medical treatment and with the theory of Felsen (25), which has been accepted by many, the use of anti-dysenteric serum is of value. Felsen (24) states that he has used anti-dysenteric serum in the acute phases of distal ileitis, which in his opinion is a manifestation of acute bacillary dysentery. This treatment is no good in the chronic phases, however. Upham (48) feels that surgery depends upon the stage of the disease in a large measure. Many acute phases will retrogress. Never operate with extensive resection in the presence of an abscess.

Kross (34) feels that any disease in which we do not know the etiology the treatment must be empiric. The restitution of the diseased segment is out of the normal so there remains nothing to do but excision of the diseased area. Whether this is performed in one or more stages depends upon the general condition of the patient and the extent of the lesion.

Kross (34) feels that the treatment in early acute stages is entirely different and this must be kept in mind. In this stage there is a diffuse edema of all the intestinal layers, causing a bowel segment to be greatly increased in size. The

color is a dull, lusterless, reddish gray (garden hose). The corresponding part of the mesentery is likewise involved by edema and soft hyperplastic lymph nodes. At this stage the surgeon is confronted with a different problem than in an advanced chronic case. There are two schools of thought in handling at this stage. The first group hold that the early acute form will continue to the chronic form so early surgical removal is the best. The second group think that many early acute stages undergo spontaneous resolution. This group then advocate conservative surgical measures, for example, enterostomy or ileocolostomy, then putting the diseased bowel to rest until it recovers. Barrington, Ward and Norrish (5) and also Koster (33) in his article have seen resolution of cases without surgery, but also cases where surgery had to be used later.

Lekman (35) points out that in early stages of this disease conservative treatment is indicated and that there is no relation to the removal of the appendix and the resolution of the ileitis as thought by some. Bassler (6) believes that medical treatment in early cases is very gratifying and late cases are hopless without the use of surgery. His point is to diagnose early.

Mixter (40) believes the treatment of regional enteritis can best be considered for each of its clinical stages. He believes that surgical intervention in the acute stage is generally unwise as spontaneous resolution may occur. The danger of spread-

ing an acute infection is possible. If a case is diagnosed as appendicitis and at operation a regional enteritis is found the appendix should not be removed. The chance of fistula is great in an operation at this time. A thing of this kind must be forgotten and a medical course must be maintained with rest and a bland diet. If after six to eight months, the patient shows signs of trouble, for example, obstruction, etc., surgery should be considered.

It must be understood there are no clear cut boundaries between the stages. Now in the ulcerative stage where fibrotic changes are at the minimal complete regression is still possible. Late in this stage when infiltrating fibrosis has made the bowel rigid an inelastic and a smaller lumen is being produced causing obstructive symptoms, resolution is hard to imagine. If medical treatment has not helped this far, surgery better be had before obstruction, fistulae and abscess formation occur. At this stage the indications for surgery are a marked fibrotic change in the intestine and extensive mesenteric adenopathy. Wide excision of the bowel and its mesentery in the one stage operation usually gives very good results. The Mikulicz operation is very good.

Treatment of advanced stages is unquestionable surgery. What procedure in surgery to be used must be given some thought, however. If the patient is debilitated, showing nutritional disturbances, for example, edema, neuritis, and anemia together with the most common complications like abscesses and fistulae,

it is usually not safe to do a primary resection.

Obstruction is rarely complete in these cases and a lateral anastomosis will often give relief, at times a preliminary ileostomy is indicated.

As a curative measure short circuiting procedures have never been successful in Mixter's (40) cases, but have been in other cases. However, anastomosis must be considered as merely a step toward the ultimate resection of the involved segment when the condition of the patient is better.

The question of fistula formation is met with at times. They are commonly seen between the terminal ileum, cecum or ascending colon. These can be taken care of at the time of the resection. When fistulae run to the sigmoid usually there is some evidence of large bowel involvement.

Bargen (4) feels medical treatment may be of some value as in combating any serious infection. A high calorie, high protein, high vitamin, and low residue diet is certainly indicated. Repeated small transfusions of blood seem to help. Sun baths and excessive amounts of vitamins help. Bacterins prepared from prevailing bacteria obtained from the lesions have been found to be helpful in some cases. Bargen (4) points out, however, the internist is more concerned with the diagnosis than with the treatment of regional enteritis. This is true for several reasons, but primarily because individuals who have thie condition usually present themselves when the lesion is rather advanced and excision

at this stage seems to be the treatment of choice.

The postoperative treatment of any surgical treatment is more or less the medical treatment outlined by Bargen (4) in the medical treatment of the acute stage. Dixon (22) and Clark and Dixon hold to this idea (11).

PRESENTATION OF TYPICAL AND ATYPICAL CASE REPORTS

The writer wishes to present a few typical and atypical case reports which were of interest in reviewing the literature.

> Terminal ileitis resembling clinically ovarian cyst with twisted pedicle. Reported by Culbertson (20).
>
> A multipara age 48 admitted to Cook County Hospital, complaining of sudden attack of pain eight weeks before in right lower quadrant. A mass had formed which had not been observed before. Patient stated she had nausea and vomiting after meals with dizziness two weeks before her attack. Patient had lost several pounds of weight and complained of night sweats during the eight weeks.
>
> The weight of the patient was 200 pounds. A mass rose to the crest of the ilium on the right side. The mass was firm and tender and not fixed to the abdominal wall. The lower pelvis was empty, but have seen ovarian cysts held out of the pelvis.
>
> A diagnosis of ovarian cyst was made and patient operated.
>
> The mass proved to be two kinks of ileum. Around the gut was omentum which was infiltrated. The mass was twelve to fifteen cm. in diameter. When the ileum was freed it was found to be adhered in two points four inches apart. Part of the omentum was resected, the cecum and appendix removed. The patient made a good recovery.
>
> Case report by Bisgard and Henske (8), University Hospital, Omaha, Nebraska.
>
> J. R., female age entered the University Hospital January 31, 1934. Patient in good health until 31 days before. At that time she had severe headaches and sore throat and general body pain. The patient vomited several times. Five days later patient

had general abdominal pain, mild diarrhea and fever of 102° F., developed blood in vomitus twice.

Ten days she returned to school but complained of generalized abdominal pain and fatigue. Went to school two weeks periodically. Pain gradually shifted to lower half of abdomen. Twenty-four hours before her admission she became acutely ill. Temperature rose to 102° F. and patient vomited several times and a diarrhea developed.

Family and past history negative.

Patient was well developed and nourished but had lost considerable weight.

Head, neck, heart, lungs were normal on examination. The abdomen was tender, some distention, but was acutely tender below and to right of umbilicus where a mass was palpable. The mass was orange size and in midline below umbilicus. It was movable, tender and firm, but not hard. The true pelvis and pelvic organs normal to bimanual examination.

Back and extremities normal. Reflexes normal.

Laboratory: Urine normal, Blood Wasserman negative, Hb. 86%, R. B. C. 4,340,000, W. B. C. 29,600 with staff polymorphonuclear 10%, segmented polymorphonuclear 69%, lymph 21%. The serum did not agglutinate Bacillus typhosus, Bacillus paratyphosus A and B, and Brucella Melitensis. Negative blood cultures. Stools showed no blood, much mucous, no ova, cysts, amebas or abnormal micro-organisms.

X-ray of chest and urinary tract negative, abdomen showed gas filled distended loops of small bowel and in right iliac fossa just mesial to the cecum there was an area of increased density measuring 7 by 5 cm., suggesting a pericecal mass which was movable under the fluoroscope. With a barium sulfate enema the colon filled normally. Proctoscopic examination revealed no abnormality of anal

canal, rectum or lower sigmoid.

Admission temperature 103° F., pulse 120, Resp. 30. These subsided and were normal for seven days, when suddenly they recurred as did the pain in the abdomen and vomiting.

Exploratory operation--Turbid free fluid in abdomen and all but terminal eight inches of small bowel distended. The great omentum was thick and injected. The terminal eight inches of the ileum and cecum was injected, spotted and covered in areas with an exudate. The terminal ileum was rigid and thickened. The lumen did not appear to be decreased. The mesentery of both ileum and cecum felt thick and brawny. The appendix seemed to be normal, but was removed and the peritoneal cavity closed without drainage.

Cultures from mesenteric nodes and peritoneal fluid contained Streptococcus haemolyticus.

Microscopic of appendix normal.

Patient had a stormy postoperative process with infected wound.

A few days postoperatively the urine contained albumin, cast, and many red and white blood cells.

Cystoscopic normal. Done by Dr. Edwin Davis.

The wound healed gradually, the mass slowly disappeared and the patient was discharged, apparently well sixty-six days after operation and has remained well now for two years following operation.

Atypical case of regional ileitis reported by Galambos and Mittelmann (26).

Female age 45 came to me in December, 1934. Her symptoms started eight years ago with pain in the right lower quadrant. Had an appendectomy in 1931 which failed to relieve her suffering. According to patient the

surgeon who opened her was puzzled by unusual adhesions around the small intestines and ascending colon. In the year 1932 she suffered severe heart burns during a period of two months. She was then seized by severe abdominal pains and after a few days terminated with a gastric hemorrhage and melena. The later lasted two months.

The G. I. tract was x-rayed. No peptic ulcer was found and the case undiagnosed. Ulcer diet and Sippys diet was started which made patient feel even worse.

Subsequent condition of patient during last six months until September 24th, 1934, was satisfactory. She then had severe abdominal pains and confined to her bed for a week or so. Patient lost 20 to 25 pounds in last six months. She felt a burning sensation in the throat, bad taste in mouth, anorexia, occasional vomiting, diarrhea, and also mushy stools two or three times per day.

Physical examination negative except for some tenderness in cecal region.

X-ray gall bladder negative.

Gastric analysis revealed complete achylia gastrica.

X-ray of G. I. tract showed a normal stomach, duodenum, jejunum and colon. The pathology found referred only to the ileocecal region. The ileal coils huddled in a mass in the right iliac fossa showing a marked motor delay pointing to an obstructive process. Compression at this area failed to separate the coils. The cecum showed irregularities, kinking and angulation. We made a diagnosis of terminal ileitis.

At operation ten inches of the terminal ileum was involved with infiltration of the mesenteric glands. Adhesions in the form of isolated cord-like bands, constricting but not strangulating some of the terminal ileum.

The mesenteric fat was also involved. Patient made a good recovery in two weeks.

Pathology--Gross specimen revealed 25 cm. of the terminal ileum involved. There were superficial and deep furrows in the mucosa. The mucosa is thickened and indurated, but not hard.

Microscopic study--In places the mucosal epithelium is necrotic and ulcerated. Many plasma and round cells seem in section. There is edema with numerous young fibroblastic and prominent reticulin cells are seen. The cellular infiltration is in the main wall. There is a striking hypertrophy of the smooth muscle.

Why this is an atypical case:

1. The history is an atypical one.

2. Physical examination insufficient to make the diagnosis.

3. X-ray studies were necessary to diagnose the case.

4. Motor power reduction cannot be thought of as only seen in regional ileitis as it may be found in conditions causing stenosis and obstruction of the gut.

Many things could be confused with the correct diagnosis as postoperative adhesions, appendicular abscesses, chronic appendicitis, kinks, angulation with adhesions, tuboovarian tumor, cysts, inflammation, tuberculosis of the ileum, cecum, etc., lipoma, fibroma, myxoma, Hodgkins disease, leukenia, congenital Jackson's membrane, Meckel's diverticular tumor, localized idiopathic dilation of ileum, multiple diverticula of cecum, foreign bodies at last terminal ileitis.

Reasons for our correct diagnosis:

Assumed the presence of adhesive bands because,

1. The cecal angulation as shown in the films.
2. Failure to separate the terminal coils of the ileum.
3. Finding of adhesive bands during previous operation for appendicitis.
4. The well known tendency for regional ileitis to develop adhesions postoperatively.

Regional ileitis with perforation, abscess and peritonitis. Reported by E. E. Arnheim (2).

> Chronic perforation occurs slowly enough to permit walling off by adhesions to a neighboring viscus, the parietal peritoneum or to the omentum. In the following case a striking contrast to the above with a spontaneous perforation into the peritoneal cavity with resulting abscess and peritonitis.
>
> A married woman age 47 admitted to the hospital June 9, 1933. Ten years ago an abscess in the region of the rectum was incised. The past ten years she had occasional periods of diarrhea at which time she would have several brown non-blood stools daily. The last four years she had attacks of abdominal pain, more or less generalized. X-ray at that time showed "growth" in the stomach. Some dietary measures seemed to relieve the diarrhea at that time but would return if diet forgotten. The abdominal pain continued intermittenly and recurred five days before entering the hospital. It was associated with diarrhea, but no nausea or vomiting. Soon the abdomen was distended and the pain became more localized to the left lower quadrant.

Examination--Obese woman age 47, temperature 102.4° F., which looked acutely ill. Moderate abdominal distention, generalized abdominal spasticity and slight tenderness on deep pressure on both sides of the umbilicus. Rectal and pelvic examination negative. W. B. C. 14,300 with 82% polymorphonuclear neutrophils.

Hospital Course--At end of first eight hours temperature to 104.6° F. No increase in pulse rate.

Second day no abdominal pain, abdominal puncture in lower left quadrant revealed milky, purulent fluid which showed no organisms.

Third day, not much improvement, abdomen less distended, tenderness in left side gone, vague mass in right side above the umbilicus.

Fourth day patient developed marked circulatory collapse, temperature to 106° F. The diffuse tenderness and spasticity of the abdomen reappeared.

Fifth day temperature down to 101° F. but circulatory collapse continued in spite of glucose intravenously.

Sixth day pulse improved, temperature 99° F. to 100° F., but patient was icteric. Bile found in urine. The icteric index was 40.

The following six days was marked by a steady decline of patient, the temperature remaining normal. A mass in the right lower quadrant could vaguely be made out and marked tenderness in right lower and left upper quadrants. The urinary output was small, the uterus deepened. The patient became uremic and died on the twelfth day in the hospital.

Necropsy Findings--The significant lesions were found in the abdomen. The peritoneal surfaces were dulled and conjested. There was a fibrino-purulent exudate over all the small intestine. A loop of large and small

> bowel were agglutinated. The appendix was thickened but not inflamed. The sigmoid was pulled to the right side and adherent to the exudate about the cecum. There was an abscess walled off by the posterior wall of the uterus and anterior wall of the rectum. There was an abscess walled off by two loops of ileum and their mesentery. A fistulae ran from this area into the ileum about 18 inches from the ileocecal valve. The terminal three feet of ileum was thickened and indurated. The mucosa presented a granulomatous surface with areas of ulceration. There were superficial fistulous tracts, several of which extended through the serosa and entered the abscess between the loops of the ileum. The surface opposite the mesenteric attachment was relatively free of ulceration. The corresponding mesentery was thickened and indurated. The lumen of the involved segment was narrowed, the ileum proximal to this area was dilated. The ileocecal valve was thickened and indurated. The mucosa of the colon was conjested, but showed no ulcerations.
>
> Microscopis--Ulcerated areas infiltrated with lymphocytes, polymorphonuclear leucocytes, fibroblasts and plasma cells. The muscularis was likewise densely infiltrated with these cells. Some sections showed advanced necrosis of the serosa and muscularis.

The writer wishes to present a case which he observed during the patient's hospitalization at the State Hospital No. 2 Cancer Hospital in St. Joseph, Missouri, during the summer of 1939.

It is of interest to note in the following case history the patient was operated May 18, 1939, for appendicitis. It was at that time the operator saw the enlarged terminal ileum and patient was sent to the cancer hospital with a diagnosis of suggestive undifferentiated lymphocytoma.

An appendectomy was supposed to have been done at this time but later when patient was operated at the Cancer Hospital by Dr. Conrad of St. Joseph, Missouri, it was found that the appendix had not been removed. The writer will add that Dr. Conrad made a preoperative diagnosis of terminal ileitis.

> The patient was a 16 year old white girl who came in complaining of general abdominal distress for a period of eight months, a weight loss of twenty-six pounds, and pain localizing in the appendiceal area. Six months before admission she had had an attack of what was supposed to have been influenza, after which there was pain in toes and legs, and the knees and ankles became swollen. Pain had been present in the right side of the abdomen for some months before. Because of the swollen ankles her family doctor thought that she should have her tonsils removed and that was done on March 4, 1939. Diarrhea appeared sometime in April along with nausea, generalized abdominal pain, and a feeling of weight in the abdomen. An appendectomy was done on May 18, 1939. Postoperatively she was still nauseated after meals and had a continuation of the abdominal pain. She had three to four bowel movements a day, as well as urinary frequency six to seven times a day and nocturia of once to twice. There was some pain and burning on urination. She had occasional headache localized to the frontal region and some dizziness. There was no cough and no dyspnea.
>
> Family history and past history were essentially irrelevant. Menstruation appeared at the age of thirteen and had been regular until May 1939. There had been no periods since the appendectomy.
>
> Operative note at the time of the appendectomy, May 18, 1939: "Upon opening the abdomen we found a growth involving the ileum and the lower one-third of the cecum. Many nodules through the mesentery. Nodes removed for tissue examination." A pathological report--

"Changes in the nodes were not sufficiently advanced for definite diagnosis but are suggestive of an undifferentiated lymphocytoma."

Physical examination essentially negative except for the abdomen which showed extreme tenderness and rigidity in the right lower quadrant. There were no palpable masses. Hypogastrium showed slight tenderness. Extremities showed the ankles swollen and tender. A vaginal examination was not done and a rectal examination was reported as unsatisfactory.

Laboratory Findings--6/24/39. Urine--acid, specific gravity 1.007, albumen--trace, sugar --negative, a microscopic of 4 white cells per high power field. Hemoglobin--58.4, red blood count--3,020,000, leucocytes--7,850. Differential: Lymphocytes, small and large--33%, 63% segmented polymorph, 4% stabs. Blood sugar--119 mg. %, nonprotein nitrogen --29.1 mg. %.

Urine examination--6/27/39 same as before. Wassermann and Kahn negative.

Blood count--7/4/39. Hemoglobin 58.4, red blood count--3,410,000, leucocytes--11,150. Differential: juveniles--3%, stabs--3%, segments--66%, lymphocytes--38%.

On numerous blood examinations through July there was shown an increase in polymorphonuclears to as high as 88% during the postoperative period with a rather rapid return to the original differential.

A sedimentation rate done on 7/17/39 showed 33 mm. in 60 minutes.

Operation--7/22/39. Operative note: "On opening the abdomen we found adhesions of omentum and previous scar. There was a large indurated mass consisting of the terminal ileum about 8 to 10 inches, very hard, infiltrated and indurated almost obstructing the ileo-cecal junction. The medial side of

the cecum, the attachment of the ileum was also indurated and hard. I felt it was necessary to remove the cecum along with the terminal ileum. There were large rather soft glands in the mesentery of the ileum and base of the cecum. About 12 inches of the ileum was removed along with the cecum and about half of the ascending colon. The end of the colon was closed and end-to-side anastamosis done making the anastamosis on the anterior surface of the colon and the ileum. There was very little bleeding, seemed to have good blood supply to remaining colon and ileum. Appendix had not been removed, it was included. One rubber tissue drain was placed in lateral right of the abdomen under the colon."

Pathological report: "Specimen consists of about 18 cm. of ileum, small fragment of cecum and attached appendix. The mucosa of ileum is dark red in appearance, destroyed in many areas and hemorrhagic throughout. Inflammatory granulation tissue has replaced the superficial mucosa in many areas. The gut wall throughout is thickened, indurated and somewhat nodular. In one area there is an annular granulomatous thickening about 3 cm. in thickness. The lumen of the gut was constricted at this point. Hemorrhagic areas are found throughout the wall. The serosa shows a marked chronic inflammatory reaction. No evidence of yellowish granules of actinomycosis or caseation of tuberculosis found. No gross evidence of malignance present. The inflammatory reaction also involves the portion of cecum removed. The appendix is essentially normal in gross appearance."

Microscopic examination: "Much of the mucosa is replaced by hyperplastic follicles and granulomatous tissue containing proliferating fibroblasts endothelial cells and many round cells in places associated with giant cells with typical tubercle arrangement. Eosinophiles are very numerous. The submucosa and muscularis are also involved and in places the latter is thick and fibrotic. Histologically, the picture is that of a proliferative type of tuberculous lesion. However, careful study of

sections stained for the tubercle bacilli failed to reveal this presence. This does not, however, exclude them as the etiological factor. Diagnosis--Tuberculous ileitis." (Examined by Wm. Hunt, M. D. and R. J. Jermstad, M. D., pathologists).

X-ray examination--6/27/39: "X-ray examination of the intestinal tract with barium meal fails to reveal evidence of pathology in the esophagus. The stomach is hypotonic type and within normal limits in size, shape and position. At the 6-hour examination there is about 1 dram of residue in the stomach and the remainder of the meal is distributed throughout the terminal ileum, ascending, transverse and descending portion of the colon. The terminal ileum is markedly thickened and its lumen is more or less fixed. The cecum fails to fill completely but remains deformed and smaller than normal. Examination of the colon by means of barium enema reveals the changes just mentioned and fails to reveal evidence of additional abnormality in this structure. Impression--The condition is probably due to terminal or granulomatour ileitis." (Dr. J. O'Donoghue) Chest X-ray failed to reveal any evidence of pulmonary tuberculosis.

Summary of Case Reports

The case reported by Culbertson (20) of terminal ileitis which resembled an ovarian cyst with twisted pedicle is of interest. This case just reminds one that terminal ileitis may simulate other disease entities besides those effecting the gastro-intestinal tract. Even the age of the patient in the particular case would tend to lead one astray. A woman 48 years of age is out of the age bracket for terminal ileitis as most cases are found in the second and third decade of life. The patient's symptoms and findings were certainly atypical of those

usually found in regional enteritis.

The case reported by Bisgard and Henske (8) is of interest to the writer in the fact no surgery was used except to remove the appendix. From the standpoint that the involved ileum and cecum were not removed and the mass slowly disappeared, with no complications such as fistulae or abscesses certainly agrees with some writers that regional ileitis may regress and the patient again be well.

Galambos and Mittelmann (26) report on an atypical case of regional ileitis again should impress the thought that regional ileitis may be atypical in its symptoms and findings. Their reasons as noted in the case history why the case is an atypical one and their reasons for a correct diagnosis are well worth the time of anyone interested in regional ileitis.

Arnheim's (2) case with spontaneous perforation with resulting abscess formation is rare but must be kept in mind. Perforation in this disease is usually slow enough to permit walling off by adhesions and this prevents peritonitis.

The case presented by the writer is a typical one and as is usually the case the patient is subjected to an appendectomy or an exploratory operation before a correct diagnosis is made.

SELECTED REFERENCES

1. Adams, H. D.: Regional Ileitis, S. Clin. North America, 17: 763-771, June 1937.

2. Arnheim, E. E.: Regional Ileitis with Perforation, Abscess and Peritonitis, J. Mt. Sinae Hosp. 2: 61-63, July-Aug. 1935.

3. Barbour, R. F., Stokes, A. B.: Chronic Cicatrizing Enteritis: Phase of Benign Nonspecific Granuloma of Small Intestine, Lancet, 1: 299-303, Febr. 8, 1936.

4. Bargen, J. A.: Regional Ileitis: Diagnosis, Complications and Medical Suggestions. Proc. Staff. Meet., Mayo Clinic, 13: 550-551, Aug. 31, 1938.

5. Barrington, Ward, and Norrich, R. E.: Crohns Disease or Regional Ileitis. Brit. J. Surg. 25: 530-537, Jan. 1938.

6. Bassler, A.: Medical Treatment of Granulomata (Ileitis) New Y. M. J. 5: 150-154, June 1938.

7. Binney, H.: Nonspecific Granuloma of Ileocecal Region. Ann. Surg. 102: 695-706, Oct. 1935.

8. Bisgard, J. D., and Henske, J. A.: Regional Ileitis, J. A. M. A. 108: 550-551, Febr. 13, 1937.

9. Bockus, H. L., and Lee, W. E.: Regional Ileitis, Ann. Surg. 102: 412, 1935.

10. Brown, Philip N.; Bargen, Arnold J., and Weber, Harry M.: Chronic Inflammatory Lesions of the Small Intestines: Regional Enteritis. Amer. Jour. Dig. Dis. and Nutrition. 1: 426, 1934.

11. Clark, R.; Dixon, Claude F.: Mayo Clinic Regional Enteritis. Surgery, 277-303, Febr. 1939.

12. Coffey, R. J.: Pathalogic Manifestations of Regional Enteritis. Proc. Staff Meet. Mayo Clinic, 13: 541-544, Aug. 24, 1938.

13. Colp, R.: Nonspecific Granuloma of Terminal Ileum and Cecum, S. Clin. North America, 14: 443-449, April 1934.

14. Corr, P.; Boeck, W. C.: Chronic Ulcerative Enteritis (Regional Ileitis) Am. J. Digest Dis. and Nutrition, 1: 161-162, May 1934.

15. Crohn, B. B.; Ginzburg, L.; Oppenheimer, G. D.: Regional Ileitis, J. A. M. A. 99: 1323, 1932.

16. Crohn, B. B.; Ginzburg, L.; Oppenheimer, G. D.: Nonspecific Granulomata of the Small Intestines, Ann. Surg. 98: 1046, Dec. 1933.

17. Crohn, B. B.: Prognosis in Regional Ileitis, Am. J. Dig. Dis. and Nutrition, 3: 736-739, Dec. 1936.

18. Crohn, B. B., and Rosenak, B. D.: Combined Form of Ileitis and Colitis, J. A. M. A. 106: 1-7, Jan. 4, 1936.

19. Crohn, B. B.: Regional Ileitis, Surg., Gyn. and Obs. 68: 314-321, Feb. (No. 2A) 1939.

20. Culbertson, C.: Terminal Ileitis Resembling Clinically Ovarian Cyst with Twisted Pedicle, Am. J. Obs. and Gyn. 28: 456-457, Sept. 1934.

21. Dalziel: Chronic Interstitial Enteritis, Brit. Med. Jour. 2: 1068, 1913.

22. Dixon, C. F.: Surgical Treatment of Regional Enteritis, Proc. Staff Meet. Mayo Clinic, 13: 552, Aug. 31, 1938.

23. Felsen, J.: Nonspecific Ulcerative Colitis, Terminal (Distal) Ileitis and Bacillary Dysentery: Common Pathogenesis, N. Y. State J. Med. 35: 576-578, June 1, 1935.

24. Felsen, J.: Clinical Notes Concerning Distal Ileitis as a Manifestation of Bacillary Dysentary, Am. J. Dig. Dis. and Nutrition, 1: 782, 1935.

25. Felsen, J.: New Clinical Concepts of Bacillary Dysentery: Relationship to Nonspecific Ulcerative Colitis, Distal Ileitis and Nonspecific Granuloma, Am. J. Dig. Dis. and Nutrition, 3: 86-90, April 1936.

26. Galambos, A., Mittelmann: Typical and Atypical Terminal Ileitis, Am. J. Dig. Dis. and Nutrition. 2: 442-447, Sept. 1935.

27. Ginzburg, L., and Oppenheimer, G. D.: Nonspecific Granulomata, Ann. Surg. 98: 1046, 1933.

28. Halligan, E. J. and H. G.: Regional Enteritis: Acute Free Perforation as First Sign, Am. J. Surg. 37: 493-497, Sept. 1937.

29. Harris, F. I.; Bell, G. H., and Brann, H.: Chronic Cicatrizing Enteritis, Surg., Gyn. and Obs. 57: 637-645, Nov. 1933.

30. Homans, John: Regional Ileitis, A Clinical not a Pathological Entity, New Eng. J. Med. 209: 1315, 1933.

31. Jellen, J.: Regional Ileitis: Review 50 Cases, Am. J. Roentgenal. 37: 190-201, Febr. 1937.

32. Kantor, J. L.: Regional (Terminal) Ileitis: Its Roentgen Diagnosis, J. A. M. A. 103: 2016-2021, Dec. 29, 1934.

33. Koster, H.; Kassman, and Sheinfeld: Regional Ileitis, Arch. of Surg. 37: 789, 1936.

34. Korss, I.: Terminal Ileitis: Conservative Surgical Treatment, Am. J. Dig. Dis. 5: 313-314, July 1938.

35. Lekman, E. P.: Regional Ileitis: Acute Phase, Rev. Gastroenteral, 6: 222-233, May-June 1939.

36. Lewisohm, R.: Segmental Enteritis, Surg. Gyn. and Obs. 66: 215-222, Febr. 1938.

37. Lyon, B. B. V.; Swalm, W. A.: Giardiosis, Amer. Jour. Med. Sci. 170: 348, 1925.

38. Meyer, A. K.; and Rosi, P. A.: Regional Enteritis (Non-specific) Surg. Gyn. and Obs. 62: 977-988, June 1936.

39. Mixter, C. G.: Regional Ileitis, Ann. Surg. 102: 674-694, Oct. 1935.

40. Mixter, C. G.: Regional Enteritis, Surg. Gyn. and Obs. 68: 322-326, Feb. (No. 2A) 1939.

41. Mock: Infective Granuloma, Surg. Gyn. and Obs. 52: 672, 1931.

42. Moschowitz and Wilensky: Amer. Jour. Med. Sci. 196: 49, 1923.

43. Pollock, L. H.: Regional Enteritis, J. Missouri M. A. 34: 109-114, April 1937.

44. Sanders, C. B.: Nonspecific Granuloma, Texas State J. Med. 32: 230-233, July 1936.

45. Schapiro, I. S.: Hypertrophic Jejuno-ileitis, J. Mt. Sinai Hosp. 1: 121-124, Sept. 1934.

46. Stafford, E. S.: Regional Ileitis and Ulcerative Colitis, Bull. Johns Hopkins Hosp. 62: 399-407, April 1938.

47. Tietze, Alexander: IV Ueber Entzundlicle Dickdarmgeschwulste Ergebn. d. Chir. u. Orth. 12: 211-273, 1920 (Sighted by 27)

48. Upham, R.: Regional Enteritis. Rev. Gastroenterol. 5: 133-141, June 1938.

49. Weber, H. M.: Regional Enteritis: Roentgenologic Manifestations. Proc. Staff Meet. Mayo Clinic, 13: 545-550, Aug. 31, 1938.

50. Wilensky, A. O.: Essential Nature of Nonspecific Granulomatous Lesions. Surgery 6: 288, Aug.; 552 Sept. 1939.