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NON-SPECIFIC GRANULOMATA OF THE INTESTINAL TRACT.

by

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1937
Introduction.

The insouciant and bellicose manner in which inflammatory lesions may attack the gastro-intestinal tract has long been the bete noire of surgeon, internist, radiologist and pathologist alike. Before 1895 most circumscribed lesions of the intestine appear to have been regarded as neoplastic. However, at that time, Senn (61) distinguished infective granuloma and cancer.

Often times vicariously resembling cancer, tuberculosis and syphilis, these non-specific inflammatory lesions occurring at almost any site in the gastro-intestinal tract have been the source of much consternation among medical men. Patients with the gravest of prognosis have many times rapidly recovered when suffering from this disease. The constantly evanescent clinical picture, along with the apparent wide scope of etiological factors has produced a confusion of loosely classified heterogeneous abdominal pseudo-tumors which are poorly understood by clinician and student alike.

In choosing this subject, I have hoped to clear up in my own mind at least, in part, and to bring together the current medical opinions, on this diversified subject. Modern text-books and medical curricula are surprisingly devoid of information on this subject.
History.

For the past thirty years there have appeared in the American and English surgical literature accounts of tumor like thickenings of the intestinal wall emulating the pathology of the granulomata of tuberculosis, syphilis and commonly resembling carcinoma which were of non-specific inflammatory origin. As early as 1907, Robson (59) described some abdominal tumors simulating malignant disease which he referred to as some of the most puzzling problems with which the profession had to deal. He states: "The cases to which I refer yield some of the most satisfactory though at times unexpected results, for many of the patients have had a grave, perhaps a hopeless prognosis pronounced, and yet as the result of treatment some of them may be restored to perfect health. From a very considerable experience of abdominal tumors that have simulated malignant growths but which arguing from the sequel of events and the ultimate complete recovery of the patient must probably have been inflammatory, I can only conclude that such tumors are much more common than is generally supposed and I feel therefore, that in giving an opinion of an abdominal tumor having the appearance and feel of cancer and even having the clinical signs and symptoms a guarded prognosis should be more frequently given." He further points out the simulation of malignant
disease by chronic inflammatory affections of the sigmoid flexure and presents a series of cases involving sigmoid, colon and ileum (1 case), ascending colon (2 cases), splenic flexure and loops of small intestine with symptoms of obstruction (1 case), and one case with involvement of the cecum alone. He also reports several cases of tumor like thickenings of the stomach with obstruction at the pylorus recovering following short-circuit operations, which were later shown to be the result of chronic inflammation.

In 1909, Braun pointed out the importance and difficulty of differentiating these intestinal granulomata from neoplasms of the intestine, and collected six cases of this type. The granulomata were situated at various places in the large intestine and the majority caused obstructive symptoms. In none of the cases was the etiology apparent.

Dalziel (26) writing in the British Medical Journal, in 1913, on Chronic Interstitial Enteritis describes the following case: "Twelve years ago I saw a professional colleague, suffering from obstruction of the bowels of a fortnight's duration previous to which he had for several weeks numerous attacks of colic, slight attacks of diarrhea with no tenderness over the abdomen, and very slight rise in
temperature, with no appreciable alteration in the pulse rate. When seen by me the abdomen was not distended nor were the muscles rigid, but to the hand gave a sense of putty like resistance. As vomiting was persistent, I concluded that there might be an obstruction high up, and so opened the abdomen, to find the whole of the intestines, large and small alike, contracted, rigidly fixed, so that when a loop was lifted from the abdomen it sprang back into its sulcus. That the wall of the whole intestine was chronically inflamed there was no doubt. In parts the peritoneum seemed edematous, as was also the omentum and mesentery, in which the glands could be felt enlarged. Nothing could be done to restore the function of the canal, and the patient died a few days afterwards. The condition was diagnosed as tuberculosis but disproved by microscopic examination and diagnosed later by the pathologist as a chronic inflammatory condition.

In 1920, Tietze (62) reviewed entire literature on "benign granulomata" of the intestine and reported several cases of his own.

Moschowitz and Wilensky (52), in 1923, reported four cases, in one of which the terminal ileum alone was involved. In 1925, Coffen (17) added a case to the literature and cited previous cases as reported
by Braun, Moschoowitz and Wilensky.

In 1931, Mock (51) described ten cases of granuloma and, in 1932, Golob (39) reported another case, described the subject further, and made some suggestions as to its etiology.

These occasional cases of intestinal tumors encountered in the practice of various surgeons, until this time defied classification, and the etiology, pathology, treatment and prognosis continued to be a source of consternation. These tumor like masses had been reported as occurring in any part or all of both the small and large intestines. They were recognized by most as not being carcinoma, lymphosarcoma, tuberculosis, Hodgkin's or diverticulitis and the multiplicity of the various sites in which they occurred with the varying clinical symptoms produced a confusion of loosely classified heterogenous granuloma with no descriptions of any clear cut clinical entity.

Crohn, Ginzburg and Oppenheimer (24) attempted at this time to isolate from the group a specific entity, both pathologically and clinically, which they termed Regional Ileitis. They encountered and reported fourteen consecutive cases, all with involvement of the terminal ileum, alone, and all with masses in the lower right iliac fossa and they strongly felt at this time that the pathological process would never
traverse the ileo-cecal juncture. Following this work numerous cases of granuloma of the small intestine were reported under various such titles as Crohn's disease, terminal, distal and regional ileitis, nonspecific granulomatous ileitis, ileoceleal pseudotumor of non-specific origin, chronic cicatrizing enteritis and ileocolitis ulcerosa chronica (42, 55, 56, 24, 28, 25, 27, 36). However, many of these case reports showed that the process did involve parts of the intestine other than the terminal ileum and lesions were reported in the jejunum, duodenum and various parts of the colon. This more widespread involvement of the intestine later led Crohn and his co-workers to amend their original concept (19). However, the work of this group tended to awaken roentgenologist, internist and surgeon to more often consider the small bowel when searching for gastrointestinal pathology. Observations previously having been concentrated on the esophagus, stomach and colon for the reasons that pathologist had reported comparatively few organic lesions of the small bowel. Further when exploring abdomens the surgeons had not ordinarily considered the jejunum or ileum as a possible site of pathology and roentgenologists had failed to regard these organs with special attentions because they were not ordinarily considered as possible sites
of disease (12).

Harris, Bell and Brun (40) soon followed with a report of three cases of non-specific granuloma of the small intestine, one involving the jejunum alone and thence offered the term Cicatrizing Enteritis as a more descriptive and inclusive term for this new surgical entity. In the same year Clute (16) reported two cases of the so-called regional ileitis, called attention to the fact that such conditions were often times diagnosed as hyperplastic tuberculosis, actinomycosis and new growth, and divided the condition clinically into inflammatory and obstructive phases.

Colp, in 1934 (18) pointed out that the ileocecal valve does not arbitrarily limit the progress of the disease affecting the ileum aborally any more than it limits the progress of pathology of ulcerative colitis orally. Williams (65) in the same year cited the similarity in personally observed cases to tuberculomata and felt that many cases of the "cured" cancers were actually cured inflammatory lesions. Homan and Hass (41) describe regional ileitis as a clinical but not a pathological entity and call attention to identical pathology occurring at sites other than the terminal ileum.

During 1934, some ten or twelve papers were
written on chronic inflammatory lesions of the bowel without adding much to the concept thus far established as to etiology, diagnosis and treatment. (19, 14, 28, 25, 8, 35). In the following year, Felsen (31, 32, 33, 34) reported some work on the subject with the contention that bacillary dysentery, distal ileitis and non-specific ulcerative colitis are manifestations of the same disease. Musick (54), Galambos (38), Bockus (13), Arnheim (1), Mixter (50) furnished other case histories with inflammatory lesions of the ileocecal region with symptoms resembling appendicitis. An excellent description of the problems arising in differentiating appendicitis in children from regional ileitis was furnished by Erb and Farmer (30) with a report of four cases occurring in children from the age of two to eight. Bacteriological studies performed by them offered possibilities as to etiology in their cases.

In 1936, Rosenblate et al. (58) called attention to the frequency with which parts of colon are involved in association with lesions in the terminal ileum and suggest what they believe to be a more inclusive term, Ileocolitis Ulcerosa Chronica. Further, Dr. Saphir, their associated pathologist, concurs with the opinion of Felsen (31) as to the possibility of bacillary dysentery playing an etiological role in non-specific
infections of the gastro-intestinal tract.

During the last twelve months, there has been an increasing number of case reports (49, 43, 56, 20, 4) from various parts of the country as a manifestation of the growing interest in the subject along with a progressively broadening conception as to the relation of inflammatory lesions existing at various sites in the intestine. Since the original work of Crohn in 1932, he and his associates have observed 60 cases of ileitis, nine with colonic involvement, and they now acknowledge the combined form of the disease the priority of which rests with Colp (18).

Incidence.

Of great interest is the ever increasing number of articles appearing in the American literature on non-specific granulomata of the intestine as contrasted to the relative scarcity of information on the subject a few years ago. It is generally believed that this sudden influx is not the result of an increasing incidence of the disease but rather a trend toward more accurate diagnosis of a previously misunderstood and unclassified entity. Also following the description by Cron et al. many surgeons were able to recall cases encountered previously which were not classified at the time but when reconsidered fit very well into this new clinical description.
At present the large majority of cases have come from metropolitan areas but insufficient information is known thus far to arrive at any idea concerning geographic distribution of the disease. Writers from the Mt. Sinai group and others (22, 41) have called attention to the frequency with which the Jewish race is afflicted. However, this fact is not borne out at other clinics. Bargen, at Mayo's (4) states that patients suffering from this condition come from various parts of the country, a great many of them being farmers from the middle west, and in his experience Jewish peoples are no more prone to have this condition than others. In their work at Rochester they are seeing about twelve cases every year.

The condition seems to be more common in males than in females. Crohn (22), Mixter (50), Musick (54), and Koster (46) state that the ratio is two to one. However, in a personal review of the literature on 128 available cases reported since 1932, it was found that only 50 occurred in woman.

This is predominantly a disease of young adults. However, Erb and Farmer (30) reported a case in a female two and one-half years old and Brown and Barger (14) saw a non-specific granuloma in a male, aged sixty-one. In a series of seventeen cases observed by Koster et al. (46) one occurred in the first decade,
two in the second, eight in the third, five in the fourth and one in the fifth ten years of life. Mixter's (50) series occurred in ages ranging from fourteen to fifty-six. A review of the available literature shows the highest incidence of the disease to be in the third decade. In a series of ninety-two cases, forty-five, almost half, were in people between the ages of twenty and thirty. Six cases have been reported occurring between the ages of one and ten, fourteen in the second decade, seventeen in the fourth decade, nine in the fifth, one in the sixth and one in the seventh.

At present there are no recognized seasonal variations in the incidence of the disease.

A study of the anatomic location of the lesions reveals that they may occur at almost any site in the gastro-intestinal tract. As previously mentioned, as early as 1907, Robson (59) had reported chronic inflammatory lesions simulating cancer existing in the colon, small intestine and even the stomach. At the time Crohn's first article was published in 1932, he and his co-workers felt that the appendix was never involved, that the disease process was limited to the distal 25-35 cm. of the terminal ileum including the ileal side of Bauhin's valve and terminating rather abruptly at this point. This concept was later amended (23) and the so-called Regional Ileitis is now quite
generally accepted as a clear-cut clinical entity but not as a pathological one. One hundred and ten cases were studied from this standpoint as presented in the literature and it was found that the large majority exist in the ileum alone although several involve segments proximal to the ileocecal juncture. Five cases involved the jejunum alone, pathology existing in both ileum and cecum was reported in fifteen cases, and sixteen showed involvement of ileum and colon, two showed lesions in ileum and jejunum, one in cecum and ascending colon without involvement of the ileum, cecum and appendix and ileum in one case, and seventy-four in the ileum alone. It is felt that pathology of this kind existing in the colon is far more frequent than indicated by these figures due to the fact that lesions in the lower colon are more often diagnosed as non-specific idiopathic colitis and are not recognized as granulomata except in far advanced obstructive cases where the true nature of the pathology is evident.

Etiology

Much has been written in retrospect concerning the etiology of these infections. The earliest writers (26) recognized them as part of a chronic inflammation but early attempts at isolating the
organism by culture were unsuccessful. Likewise, intravenous, subcutaneous, intraperitoneal and intracerebellar animal inoculations of suspended material taken from human lesions have failed to produce lesions in rabbits or guinea pigs.

Many cases of granulomata have been found arising from a foreign body (11). One case has been described (65) where the hypertrophic lesions surrounded a chicken bone, some seeds, fecal concretions, and some stiff hairs. Hook (51) believes that they are usually due to a low grade infection. Golob (39) cited a case in which he believed the presence of duodenal ulcer with its "constantly irritating influence over the ileocecal region" might have been a predisposing factor. Musick (54) enumerates bacterial infections, food allergies and nutritional disorders as possible factors.

More recent work by Felsen (33) strongly points to the bacterial factors in the etiology of the disease, and he strongly feels that bacillary dysentery, non-specific ulcerative colitis, terminal distal ileitis and other granulomata have a common pathogenesis, and that they are merely different stages or manifestations of the same disease.

He states: "Recent investigations have shown that bacillary dysentery, notably Sonne-Duval and
atypical Flexner types may manifest themselves clinically in many bizarre forms. Symptomless meningitic and appendicular types of bacillary dysentery have been described (34). Distal ileitis caused by R. dysenteriae unless feces are cultured early in the disease and repeated agglutination studies are made against typical and atypical dysentery strains, the diagnosis will not be proved."

In five cases observed by him in a period of three months, three displayed serological findings of atypical Flexner dysentery and the other two were of the Sonne-Duval type. He feels reasonably certain that in some patients the acute lesions may fail to heal, secondary non-specific infection occurs, B. dysenteriae and the specific agglutination titre having disappeared. He states further: "Within the limits of our recent 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."

Dr. Otto Saphir, pathologist, when examining specimens from the cases of Rosenblat et al. (58) noticed histologically a suggestion of bacillary dysentery. Furthermore, Barbour (3) writing in the Lancet describes a case where the blood serum agglutinated typhoid 1:250, and Bisgard and Henske (10)
report a recent case where cultural studies were positive for dysentery bacilli on urine obtained directly from the right kidney. Probstein (57) was able to isolate B. proteus valerii from the lesions in a personally observed case.

At a recent meeting (23) Felsen in a discussion of a paper by Crohn, states: "Chronic non-specific ulcerative colitis and distal ileitis, either alone or as associated lesions and non-specific ileocecal granuloma are all manifestations of bacillary dysentery. It has been my privilege to describe thirty-eight consecutive cases of chronic ulcerative colitis, eleven of chronic distal ileitis, eleven of acute distal ileitis and two of non-specific granuloma traceable to bacillary dysentery. The longer I work on this problem the more I am convinced that in the Eastern part of the United States at least, the entire pathology is explainable on the basis of bacillary dysentery. Any period beyond three weeks is highly suggestive of secondary non-specific infection. In the latter the ulcerations persist and extend, and usually within a year intramural infection is well established with mural fibrosis, pseudopolyposis, loss of haustration and possibly stenosis. I have seen this develop in the follow-up period in proved cases of acute bacillary dysentery.
The ideal therapy is prevention of bacillary dysentery."

Erb and Farmer (30) took direct smears from mesenteric lymph glands, liver and gall bladder and were able to identify a gram negative bacillus. Cultures from mesentery lymph glands, liver, gall-bladder, spleen, heart, blood vessels, and ulcers in the ileum of an acute case in a 2½ year old girl resulted in the recovery of a bacillus having the following characteristics: gram-, non-motile, fermented dextrose, mannite, maltose, lactose and xylose with formation of acid and gas. It fermented litmus milk, turned Endo's medium red, produced indol, reduced lead acetate, but did not liquefy gelatin. Except, therefore, for its non-motility it possessed the cultural characteristics of B. coli. Blood serum from two other known cases of acute ileitis showed agglutination against the organism recovered in the above case. Seven controls were negative.

The frequent involvement of the ileocecal region is ascribed by Homans (41) to the vascular relations of the appendix being more favorable to ileal than to cecal involvement. Furthermore removal of a diseased appendix frequently precedes the onset of the symptoms of regional ileitis.

It is felt that colonic involvement is probably far more frequent than the present day literature
indicates and that many of the lesions seen in the colon are reported under the heading of idiopathic (non-specific) ulcerative colitis. In discussing etiology, a brief resume of the present status of opinions on chronic ulcerative colitis is included and some arguments offered to the effect that it probably should be included in the scope of this paper.

Chronic Ulcerative Colitis.

The nature of ulcerative colitis is a controversial one. The broadening conception of non-specific granulomata of the intestinal tract in the opinion of certain authors (31, 32, 33, 23) has come to include late phases of the so-called idiopathic non-specific ulcerative colitis. It is quite probable that the disease process is identical with the lesions seen in the terminal ileum, cecum, jejunum and colon in the cases reported under the various terms of regional ileitis, non-specific infections of the intestinal tract, chronic cicatrizizing enteritis, ileo-colitis ulcerosa chronica etc. It is well known that in severe diffuse ulcerative colitis, as well as in localized right sided segmental colitis and oecitis, the ileum may be involved by retrograde extension of the pathological process. Bargen, Buie and Rankin and figures of
Klemperer in Mt. Sinai Hospital laboratory and others (7) all agree in placing an approximate 25% incidence of involvement of the terminal ileum in ulcerative colitis of the more severe type. Radiographers making observations during a Ba sulphate enema recognize at least 10% incidence of ileocecal incontinence and regurgitation. In these commonly fatal instances of colitis wherein the process of destruction extends directly up to and involves the ileocecal valve — retrograde involvement by back-wash into the ileum is easy to understand and at autopsy is susceptible of recognition.

As early as 1888, White (64) reported eight cases of ulcerative colitis and even at the present time it is recognized as the most frequent cause of chronic diarrhea associated with tenesmus and the discharge of mucus, pus and blood from the rectum. Bargen, in 1926, strongly urged the use of a sigmoidoscope in making an accurate diagnosis of the disease. Buie of Mayo's (15) defined further the sigmoidoscopic picture which he has confirmed by examination of over 470 cases. He describes four stages or phases which, as will be described later, fit in rather well with the pathological picture seen in the non-specific infections at higher sites in the
intestinal tract. As described by Crohn (22) one of the chief characteristics is the extreme thickening of the wall of the colon with smoothing out of folds, being due to hyperplasia, edema and infiltration in the mucosa and later to fibrosis in the wall. Later contraction of the fibrous tissue may result in marked narrowing of lumen with symptoms of partial obstruction identical to the stenotic phase of regional ileitis. Here again no constant etiological factor can be discovered.

As early as 1909, Blake and Higge spoke of bacterial etiology and considered B. coli, B. proteus vulgaris, B. pyocaneus, and streptococci. Logan (47) in 1919, reported 117 cases of chronic ulcerative colitis and expressed the belief that the basic etiological factor was a metabolic disturbance. The most exhaustive work on the subject has been done by Bargen who studied 189 cases of chronic ulcerative colitis over a period of several years. He was able to isolate a certain diplostreptococcus in pure culture which when injected into veins of 459 healthy rabbits gave lesions and bloody discharge from colons of 268. In some instances lesions of a similar nature occurred in other parts of the intestinal tract. Bargen has repeatedly described the characteristics of the organism and his claim for specific-
ity of the diplostreptococcus is based upon:
(1) its recovery in 80% of cases; (2) production of ulcerating lesions in the colons of animals following its injection; (3) isolation by blood culture from some patients with severe fulminating ulcerative colitis; (4) isolation from the heart's blood and from sections of the colon after death; (5) isolation of similar organisms from periapical dental abscesses and tonsillar abscess, cultures from which, when injected, produced ulcerative colitis in animals; (6) agglutination of organisms recovered from patients by immune rabbit and horse serums.

Friedenberg, in 1929 (37) working in the Gastro-Intestinal Clinic at the Graduate Hospital attempted to repeat Bargen's work. Nine thoroughly characteristic cases of chronic ulcerative colitis were used. Streptococci were recovered in each case, but their cultural characteristics were variable and different and did not conform to Bargen's criteria for the "diploccocus", although the technique which he recommended was closely followed. A pure diploccocus was finally isolated from strains recovered from five patients. None of the original organisms were agglutinated by Bargen's specific anti-serum. Thirty-nine rabbits were injected with various strengths
of cultured organisms and in only two rabbits were colonic ulcerations produced. These resulted from the injection of mixed cultures. Streptococci were recovered from the heart's blood of animals injected with cultures of organisms recovered from four patients. These organisms were not agglutinated by Bargen's serum. Reinjection of these strains did not produce characteristic lesions in animals.

Three animals were injected with cultures obtained from Bargen without the production of colonic lesions.

Walpor, (3) working in the same clinic the following year, isolated streptococci from cultures obtained through the sigmoidoscope in six of seven patients with ulcerative colitis (85%) and in twenty-eight of fifty-nine patients who did not have ulcerative colitis (49%). He injected 93 rabbits with organisms isolated from the two groups; many of which had the gross characteristic of the diplococcus of Bargen. There was no essential difference in the cultural behavior of the organisms obtained from the two groups of patients. Bargen's antiserum failed to cause agglutination of any of these organisms.

Lesions attributable to the septicemia following injections of the culture in varying strengths were produced in many animals. The most frequent lesions were tracheitis, generalized petechiae, swollen
mesenteric glands and Peyer's Patches, vascular
aborizations and occasional ulcerations in the
ileum and colon. There was no difference in the
type of lesion, whether produced by cultures ob-
tained from the patients with ulcerative colitis
or from patients with normal colons. Organisms
recovered from the heart's blood of 15 injected
animals were not agglutinated by Bargen's serum.

There is also considerable evidence that the
B. Dysenteriae plays an important role in the ini-
tiation of chronic ulcerative colitis. (31, 32, 33,
34). Significant is the fact that culture and sero-
logical investigations are seldom carried out early
in the initial attack and that organisms soon dis-
appear from the stools in epidemic bacillary dys-
entery.

The B. coli, E. Welchii; gonococci and almost
every organism which has been isolated from the
colon, have been given consideration in the etiology
of ulcerative colitis but to date there is insuffi-
cient data to incriminate any specific organism in
its etiology.

The occasional development of an acute ulcerative
colitis in an individual with some common
allergic disorder suggests a state of allergy as
the probable cause of the colitis.
Ulcerative colitis is very rarely seen in association with known deficiency states, such as pellagra, beriberi, xerophthalmia, scurvy or rickets. Nevertheless, evidences of mild deficiency disorders in ulcerative colitis have been noted by many observers.

Vasomotor instability and secretory and motor abnormalities in the gastro-intestinal tract are quite common in patients with ulcerative colitis. These findings suggest the existence of a vegetative imbalance, but it is difficult to decide whether it is cause or effect.

Consideration must be given to the emotional or psychogenic factor in patients with this disease. Emotional upsets and various types of psychic trauma may antedate the onset or precipitate a relapse (2). The outstanding trait in the ulcerative colitis sufferer is fear, although phlegmatic people are by no means exempt.

Summary.

As in segmental lesions of the upper intestinal tract the pathogenesis of idiopathic ulcerative colitis remains a complexity. Thus far, it seems that non-specific granulomata of the intestinal tract are a result of secondary chronic inflammatory changes as a sequel to some primary disorder. Primary conditions may be any of the previously enumerated fac-
tors. Specific bacterial infection may occur at any site in the gastro-intestinal tract, followed by spontaneous remission or secondary non-specific infection may follow which eventually leads to stenosis, fistulae, and obstruction with loss of weight, anemia, etc. Psychogenic disorders may so lower local resistance as to facilitate secondary invasion by normal bacterial inhabitants of the intestinal tract. Vasomotor instability may be manifested early as errors in motility of the gastro-intestinal tract as pain is only a late manifestation of this type of disease. These granulomatous, hyperplastic, obstructive lesions may occur at any site in the gastro-intestinal tract from the stomach to the sigmoid. The so-called linitis plastica so often mistaken for cancer of the stomach is possibly a phase of this disease.
Pathology.

The histologic findings in the chronic hypertrophic types of terminal ileitis with stenosis are those of a chronic non-specific inflammatory reaction involving all the coats of the bowel wall, with a disproportionate connective tissue infiltration. Nodular granulomata composed of hyaline connective tissue with many fibrocytes, leucocytes and occasional giant cells are present. The giant cells are of the foreign body type and in many sections they can be seen engulfing particles of vegetable matter. The presence of giant cells, as noted by Moschowitz and Wilensky (52) undoubtedly led to many mistaken diagnoses of ileocecal tuberculosis that were non-specific granuloma.

The patients with a stenotic phase of regional enteritis of the terminal ileum have symptoms of subacute obstruction and the secondary symptoms of prolonged low grade sepsis. Pain is outstanding complaint. Pain is usually colic. Cramps may be diffuse over entire abdomen, but in most cases localize to lower right quadrant. The pain is often aggravated by food. Vomiting is not a common symptom, probably on account of sub-acute nature of the obstruction. Loss of weight is frequent.

The mucosa of the ileum, when involved, is
edematous and the normal transverse folds are thickened. In the distal portion of the ileum, small inflammatory polyps may be present. In this phase of the disease, the ulceration of the mucosa is limited to the mesenteric attachment of the bowel. The ulcers are usually linear, superficial and run along the longitudinal axis of the bowel. In the distal portion of the bowel the ulcerations can extend through all the coats to the subseros as shown in the roentgenograms. After the ulcerations have penetrated into the mesentery, there is an inflammatory reaction that gives rise to a marked degree of thickening and often to an indurated mass or abscess in the mesentery. It is this type of abscess that is mistaken for an appendiceal abscess and drained. Following drainage there develops a fecal fistula[48]. In late cases one is apt to see fistula formation to surrounding viscera and abdominal wall. Fistulae, either to the abdominal wall or to other viscera should at once arouse the clinician to work cautiously and demand accurate x-rays of the ileum. The gynecologist and obstetrician are brought into the field when they observe vaginal fistulae. The urologist, who through the cystoscope observes an unexplained reddened area or a definite fistulous tract, must at once be alert to the fact
that the terminal ileum may be the underlying cause of the fistula (54).

Upon examination of the resected specimen, the bowel has a hose-like feel, the wall is thickened and miliary abscesses may be found in the mesentery or among the adhesions and folds of peritoneum. Normal bowel may be found among areas of ulceration. The entire mass may be so bound down as to have the appearance of cancer. The wall of the bowel is thickened and the lumen narrowed and irregularly distorted. The proximal segments are usually greatly dilated. The mesentery is thickened and fistulous tracts are found within its walls. The neighboring lymph glands are enlarged, soft and hyperplastic. These fistulous tracts may connect to the bladder, ascending colon, transverse colon, and even the descending colon (54). They may run to the tubes or empty into the small bowel. Some of the tracts may end blindly in a miliary abscess in the peritoneal cavity.

The microscopical picture is a varied one, in the predominance of polymorphonuclear round cell and fibrous ingrowth. Giant cells may be demonstrated in the presence of foreign body, vegetable cells. The pathological specimens have been mistaken for tuberculosis because of the foreign body giant cell
found in the tissues, but the research work done in the Mt. Sinai Hospital, New York City, has failed to demonstrate the presence of tubercle bacilli on cut section or on guinea pig inoculation. Two of the cases studied were in young adults with negative tuberculin tests.

Symptomatology.

Symptoms of non-specific granulomata depend on the site of the lesion and the phase of the disease. There may be present a picture of acute, subacute, or chronic inflammation depending on the stage of the process.

Crohn has divided the clinical course of the disease into four distinct types. (1) acute intra-abdominal disease with peritoneal irritation, (2) symptoms of ulcerative enteritis, (3) symptoms of chronic obstruction of the small intestine and (4) persistent and intractable fistulae. Although this classification originally applied only to involvement of the terminal ileum, it may very well be applied to lesions existing elsewhere.

1. Signs of Acute Intra-Abdominal Inflammation.

These cases almost invariably simulate acute appendicitis. There are generalized colic, pain and tenderness in the right lower quadrant and
fever up to 101 or 102°F. The white blood count is elevated but the development of symptoms seems to be somewhat slower than in appendicitis. The presence of a mass without actual abscess formation is a fairly constant feature. The picture encountered at operation is that of a greatly thickened, red or blotchy terminal ileum, jejunum, cecum or colon with marked edema of the surrounding tissues and slight exudate of the intestinal wall. The mesentery is thickened and edematous, and contains numerous large glands. There is usually clear fluid present in the abdomen. Some undergo spontaneous resolution and others pass into one of the more chronic phases of the disease. Cases with abscesses which are drained may develop intractable fistulas.

2. Symptoms of Ulcerative Enteritis.

These patients complain of colicky periumbilical or lower abdominal pain. There is a tendency towards looseness of the bowels. The stool is usually liquid or mushy and contains pus, mucus and occult or visible blood. A constant fever is present but the temperature is rarely above 100°F. With the progress of the disease a marked secondary anemia may develop reaching as low as 35% hemoglobin. Considerable loss of weight and
strength may occur. In some instances disturbances of general nutrition are slight. This course may continue for as long as a year until exhaustion sets in or more commonly the cases pass gradually into the stenotic phase of the disease.

3. Symptoms of Chronic Obstruction.

This is the most common type encountered. The symptoms in this stage are those of a subacute or small intestinal obstruction of varying severity. The obstruction as in most obturating lesions of the small bowel is not complete. Violent cramps, borborygmus, occasional attacks of vomiting and constipation are present. Visible peristalsis and intestinal erection are common. A palpable mass is practically always present in the lower right quadrant. In this phase of the disease fistulous communication with the colon or sigmoid may lead to the signs and symptoms of colitis, and mask the true nature of the disease. Occasionally the stenotic phase occurs as a primary manifestation of the disease; again, the symptoms may have been present for years.

4. Persistent Fistulae

Many of the persistent and intractable fistulae which follow the drainage of a supposedly appendiceal abscess are in reality due to non-
specific inflammatory disease. Also numerous fistulae may ramify in the mesentery of the small intestine, connect with loops of small intestine or to any part of the colon.

The following information is supplied by Koster (46) gathered from a study of seventeen cases.

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 days or less</td>
<td>6</td>
</tr>
<tr>
<td>4-6 months</td>
<td>5</td>
</tr>
<tr>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>2-4½ years</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>13</td>
</tr>
<tr>
<td>Localized, LRQ</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Generalized</td>
<td>1</td>
</tr>
<tr>
<td>Localized, LRQ</td>
<td>11</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nausea</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>11</td>
</tr>
<tr>
<td>Localized, LRQ</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vomiting</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>13</td>
</tr>
<tr>
<td>Localized, LRQ</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous Attacks</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>10</td>
</tr>
<tr>
<td>Localized, LRQ</td>
<td>3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Loss of weight</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>3</td>
</tr>
<tr>
<td>Localized, LRQ</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 99</td>
<td>1</td>
</tr>
<tr>
<td>99-100</td>
<td>13</td>
</tr>
<tr>
<td>100-</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 99</td>
<td>1</td>
</tr>
<tr>
<td>99-100</td>
<td>13</td>
</tr>
<tr>
<td>100-</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Rate</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
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<table>
<thead>
<tr>
<th>WBC</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>8000 or less</td>
<td>2</td>
</tr>
<tr>
<td>8-10,000</td>
<td>1</td>
</tr>
<tr>
<td>10-12,000</td>
<td>2</td>
</tr>
<tr>
<td>12-14,000</td>
<td>2</td>
</tr>
<tr>
<td>14-16,000</td>
<td>2</td>
</tr>
<tr>
<td>16-18,000</td>
<td>3</td>
</tr>
<tr>
<td>18-20,000</td>
<td>3</td>
</tr>
<tr>
<td>20-</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simple Appendectomy</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>One Stage Resection</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Two Stage Resection</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3</td>
</tr>
</tbody>
</table>

Spasticity and rebound tenderness in 13 and distension in 10.
Physical Examination

Certain physical findings characterize this disease, the most constant ones being (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 (22).

1. A moderate sized mass is usually felt in the lower right iliac region or in the lower mid-abdomen. The mass is usually the size of a small orange, tender, firm, irregular, and only slightly movable. This mass is composed of tremendously hyperplastic ileum, the stenotic inflamed portion of intestine which may and often does assume a size of from two to five times that of a normal portion, and frequently an adherent section of the colon or sigmoid to which a fistulous tract has been created. When the sigmoid is adherent and involved, the mass may lie more to the left; when the cecum or ascending colon or hepatic flexure constituted 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 the mass. The tumor is usually palpable
per rectum, though felt only very high with the examining finger.

2. Fistula formation is a constant feature of the disease process. The most common site of adherence is the sigmoid; next in frequency is the cecum and the ascending colon and occasionally the hepatic flexure. As the necrotizing process of the mucosa of the ileum progresses through its several coats, the serosa becomes involved. Any hollow viscus, usually the colon, now becomes adherent to the point of threatened perforation. A slowly progressive perforation is thus walled off, but results in a fistulous tract being formed between the two visera.

3. Loss of weight and anemia may be marked. Hemoglobin may be as low as 35% and weight loss may be as great as fifty pounds.

4. In about half of the cases the appendix has been removed at some previous operation. This appendectomy usually antedated by several months or years the present symptoms. In many cases the appendix has been removed several months or years previous, at which time thickening and tumor-like massive inflammation of the small intestine and mesentery had been noted, though nothing beyond the appendectomy had been attempted.

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 through the emaciated abdominal wall, and pudding is frequently observed in the flat 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 distension and ballooning of the whole abdomen are unusual.

Any appendectomy scar, with a retention of the original pain, should receive much consideration, for 50% of the reported cases have had an appendectomy.

Laboratory findings are fairly constant, with occult blood in the stool, secondary anemia and leucoeytosis. The x-ray study is a pathognomonic feature. The usual oral opaque meal is employed as well as a barium sulphate enema. Serial observations are made at hourly intervals from the period just before the oecum fills to the normal period of emptying. This is about 3 to 9 hours after ingestion of the opaque meal. The patient is then permitted to partake of an ordinary meal as soon as the stomach is empty. The abnormalities as revealed by the roentgenologic studies, may be
in either the ileum or colon, or both. The changes in the latter may be reflex in nature—that of a secondary spasm—or may show actual progress of the disease from the ileum. Principal changes in the ileum are:

a) Filling defect just proximal to the cecum.

b) Abnormality in contour of the terminal loop of ileum.

c) Dilatation of ileal loops just proximal to the lesion. (stenotic phase).

Kantor (45) describes a roentgenologic sign which, though not pathognomonic alone of the disease, is strikingly suggestive and characteristic. He called this the "string-sign" within a slightly irregular linear shadow suggesting a cotton string in appearance and extending from the region of the last visualized loop of ileum through the entire extent of the filling defect, and ending at the ileocecal valve. It represents the attenuated barium filling of the greatly contracted intestinal lumen. Weber (14) has recently offered the term "twisted cord appearance" as an alternative for string-sign.

Differential Diagnosis.

Granulomatous lesions of a non-specific nature have probably most often been called tuberculosis or cancer. The diagnosis of tuberculosis has even
been substantiated by pathologists who wrongly mis-interpreted the giant cells so often seen in these lesions which are the result of foreign body vegetable cells which enter through openings in the mucosa (22). In fact, Schiaparelli (50) has reported in the Journal of Mt. Sinai Hospital a case of jejuno-ileitis with a hypertrophic non-specific enteritis in the intestinal wall, while the lymph nodes in the involved region revealed a tuberculosis process. Two views were taken on the character of the pathology. One view is that the condition in the intestines and nodes are both due to tuberculosis, the other that the intestinal lesion is of non-specific character and that the diminished resistance of the diseased gut due to infection and ulceration has allowed the passage of tubercle bacilli through the intestinal wall and so accidentally involved regional lymph nodes. "The lymph nodes in this case were so rich in typical anatomical tubercles that it would be difficult to ascribe the lesion to anything but tuberculous infection." However, the general feeling is that tuberculosis has nothing to do with these granulomata.

As pointed out earlier, it is quite probable that many of the so-called cured cancers are in reality cured inflammatory lesions. As early as
1907, Robson (59) described several lesions resembling cancer and which could not be differentiated clinically. He felt at this time that in giving an opinion of any abdominal tumor having the appearance and feel of cancer, a guarded prognosis should be more frequently given.

Further, mucous colitis, ulcerative colitis, acute and chronic appendicitis should be considered and proctoscopic examination should be done. If the lesion of ulcerative colitis is located low in the bowel, it is easily seen through the proctoscope, but if the lesion is in the transverse or ascending colon, then only by means of the x-ray are we able to differentiate it from terminal ileitis. Usually colitis has more tenesmus at stool, more blood and pus in stool examination, and in many instances more bowel movements. Ulcerative colitis cases are usually more ill and have lost more weight than those of ileitis. Mucous colitis has more mucous, as a rule, even to the point of passing great casts which seem to conform to the shape and contour of the bowel. Slight blood may occur in mucous colitis and low grade fever. The x-ray examination is always necessary in every mucous colitis case to rule out terminal ileitis.

The fulminating attack of acute appendicitis cannot be differentiated from terminal ileitis only
at operation. In chronic appendicitis, in those cases in which the barium fills the appendix, one may find that the appendix on fluoroscopy is bound down to surrounding structures, but never is the lumen of the terminal ileum narrowed as displayed on x-ray.

In tuberculosis of the ileocecal region there is an increased motility of barium as shown on x-ray, while in terminal ileitis there is a decreased motility together with the typical string sign as described by Kantor (45). The Von Pirquet test may be negative in terminal ileitis, especially in younger individuals and guinea pig inoculation is always negative. In tuberculosis of the intestine, one nearly always finds evidence of tuberculosis in other parts of the body and a definite distortion of the cecal shadow, because the cecum as well as the ileum and the valve are involved.

Galambos (38) offers the following as a differential diagnosis: Postoperative adhesions; appendicular and peri-appendicular abscesses; chronic appendicitis with adhesions, kink, angulation; tubo-ovarian tumor, cyst inflammation, abscess; tb of ileum, cecum or peritoneum; lues; gummata or glands; actinomycosis; ca, primary or secondary; sarcoma, lymphosarcoma; benign tumor; lipoma, fibroma, myxoma;
lymph gland enlargements; Hodgkin's disease, leukemia, or rarely, lymphogranulomatosis, reticulois, foreign body granuloma, carcinooid, mucocele or lymphoma of the appendix, congenital Jackson's membrane, Meckel's diverticulum, tumor cyst, inflammation, or strangulation through its rudimentary ligamentous band, localized idiopathic dilation of the ileum, multiple diverticula of the cecum with concretion, accumulated foreign bodies swallowed by the insane and at last terminal ileitis.

Treatment.

It is an impasse to outline any universal panacea per se in the treatment of these non-specific infections encountered at different sites in the gastro-intestinal tract. There is, of course, the medical and surgical treatment. It is quite obvious that in those cases where serological studies when taken early prove to be positive, different types of sera should be employed. Among them may be used intravenous dysentery serum, Bargen's diple-strep-tococic serum, autogenous vaccines, etc., according to the identified etiological agent. Thus far these cases are recognized early only rarely and the great burden of the treatment rests with the surgeon who sees the cases late with symptoms of intestinal obstruction. Following operation most cases do
An operative mortality of 5% is encountered (54).

The method of surgical attack is not universally agreed, however Homans and Hass (41) are advocates of side-tracking operations rather than attempting to remove portions of diseased intestine. Homans states: "It seems to me that in any other part of the body if we were dealing with a recognizable infection, or even anything that appeared to be an infection we would not try to cut it out. If we did, we would expect to spread the disease. Here we are dealing with what looks like an infection and yet we attempt to excise it. This does not seem right." He further advises graded surgery as being safer and more likely to be effective than the immediate resection. In two personally encountered cases where resection was done the results were not altogether satisfactory and he feels that it would be much better to begin with a simple side-tracking operation, joining the ileum proximal to the lesion, to the ascending colon. Should this operation prove curative no more will be required. In the event that it should fail, or incompletely relieve the patient, the diseased bowel at a second stage can be removed.

Brown, Bargen and Weber (14) state that enterocanastomosis alone has proved sufficient to relieve some of their patients but resection of the diseased
segment has also usually been necessary, later.

Probststein and Gruenfeld (57) substantiate the above by reporting a case where a simple ileostomy was done in which they later went in to restore continuity and found the formerly diseased ileum to be perfectly normal. This fact alone shows that the condition may subside and it is quite probable that many cases of unoperated enteritis or in those cases where simple appendectomy is done, with subsidence of symptoms, spontaneous recovery is quite apt to occur.

Crohn (23) has frequently observed attempts at palliative surgery in which diseased ileum was anastomosed or short circuited to segments of the colon in the form of ileo-transverse colostomy, ileo-ascending colostomy, or ileo-sigmoidostomy. In all these operations in which the diseased ileum was not resected, the anastomotic operation failed to heal the disease but the symptoms continued. For instance, in one case the diseased ileum was inadvertently cut across, the terminal segment left in situ and the proximal inflamed portion anastomosed to the ascending colon. Sixteen years later a corrective second stage and radical resection was performed. He observed that, though a markedly diseased ileum had been anastomosed directly to a healthy ascending colon.
and had lain in that continuous relationship so that the contents of the pathological ileum were continuously washed into the ascending colon, no disease of the latter organ had transpired, the mucosa of the resected colon being intact and of normal texture. He further feels that in those cases where there is an associated colitis, removal of the diseased ileum will cure up the condition. He states: "Obviously, the ileum is the controlling seat of the disease process, the colitis being itself of less importance. Remove the focus of infection here as everywhere else. Colitis is the stumbling block of both physician and surgeon. The union of colitis, essentially a disease requiring medical therapy with ileitis, a surgical problem, constitutes a paradoxical combination."

"The plan of a two-stage resection which is a more conservative procedure is associated with a lower risk and has the advantage that the second stage is frequently unnecessary." (49).

Obviously opinions at different clinics are exceedingly controversial. In view of the case of Probst and Gruenfeld where the disease process in the ileum spontaneously subsided and because of the many people who are apparently cured by a simple appendectomy, it would seem wise to treat the acute cases with peritoneal irritation medically, for a
time at least. In those chronic cases with signs of obstruction, simple side-tracking operations may be performed or resection done with anastomosis. Avoidance of drains is urged by most operators because of the many persistent fistulae encountered following attempts at drainage. Young people are more apt to exhibit the acute phases of the disease and are more apt to get well spontaneously or following simple appendectomy. The chronic phases are seen in the older people with obstructions of long duration. The treatment of choice, as described by most operators (50) is a one-stage ileocolostomy with resection of diseased segment of bowel. Dr. A. A. Berg of New York reports a cure in 13 out of 14 cases treated at the Mt. Sinai Hospital in this manner. It is further believed (50) that a higher mortality is encountered with two-stage operations such as the Mikulicz. Mixter (50) reports 50% mortality with this operation while Binney (9) in reviewing 26 cases reports a mortality of 4% with other methods. He also favors the one-stage ileocecal resection and closure without drainage. Obviously treatment here as in anything else should be individualized and different methods are of greater value in the hands of different people.
Summary.

Non-specific inflammatory lesions of a segmental nature may occur at almost any site in the gastro-intestinal tract, developing secondarily as a sequel to a wide variety of primary factors. Primary factors may include foreign bodies, parasites, local allergic conditions, neurosis, deficiency states, and bacterial infection. (E. coli, "diplococci," bacillary dysentery, etc.)

Significant is the fact that cultural and serological investigations are seldom carried out early in the disease and organisms soon disappear from the stools.

Oftentimes simulating appendicitis, cancer and tuberculosis, this subject has long been misunderstood and only recently has attention been called to the true nature of the disease. The great increase in available medical literature in recent years is undoubtedly the result of more accurate diagnosis rather than an increasing incidence of the disease.

Any appendectomy scar with retention of original pain should receive much consideration, for 50% of reported cases have had appendectomy.

Acute cases are probably better handled
medically. Chronic cases are treated surgically. One-stage ileocolostomy with resection of diseased segment of bowel and closure without drainage in most cases is the treatment of choice.
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