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Regional enteritis

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REGIONAL ENTERITIS

BY

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INTRODUCTION

Non-specific inflammatory tumors of the gastro-intestinal tract have been known for a long time and have been reported at various times in the medical literature. These tumors were considered as medical curiosities rather than well established clinical entities until Crohn, Ginzburg, and Oppenheimer (1932) separated from this group an inflammatory lesion of the terminal ileum which they believed to be a clinical and pathological entity.

Benign granulomas is a loose term covering a multiplicity of lesions in the stomach and small and large intestines. It includes all chronic inflammatory lesions of the gastro-intestinal tract of unknown etiology or due to unusual physical agents. It represents all benign inflammatory tumors which are neither neoplastic nor due to a specific agent, A few of these tumors are due to the presence of foreign bodies or to trauma, but most are of unknown etiology.

Terminal ileitis was originally defined as:

"a disease of the terminal ileum, affecting mainly young adults characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with multiple fistulas."

No other author has defined this disease satisfactorily, but if the words "intestinal tract" are substituted for "terminal ileum",

the original definition defines the disease as it is now known.

Clute (1953) found that the disease may spread beyond the ileocecal valve and since then many others have reported similar lesions elsewhere. Brown, Bargen, and Weber (1934) state that inflammatory tumors not distinguishable from "terminal ileitis" are also found in the jejunum, ileocecal coil and colon.

Because of the multiplicity of sites of possible involvement, Harris, Bell, and Brunn (1933) suggested the term "chronic cicatrizing enteritis" as a more descriptive and inclusive name. Some still do not attempt to differentiate the disease from benign granulomas while others call it sarcoid of the intestine, regional ileitis, regional enteritis, Crohn's disease, chronic ulcerative enteritis, chronic hypertrophic enteritis, or ulcerous ileitis; of these various terms, regional enteritis is the most generally used.

Although found in all parts of the intestinal tract, this disease is most commonly encountered in the ileum, particularly the terminal portion. The next most frequent point is the cecum and ascenting colon. Most authorities agree that the jejunum is rarely affected. No authenticated cases have ever been reported in the stomach. Benign granulomas, as a group, are most frequently encountered in the large bowel, then ileum, jejunum, duodenum, and stomach in order of frequency but is rarely encountered in

these last three locations.

The earliest known reported case of regional enteritis was presented before the Royal College of Physicians of London on July 4, 1806 by Charles Combe and William Saunders. The title was A singular case of Stricture and Thickening of the Ileum. The account of this case was first published in 1813.

"The patient was William Payne Georges, Esq., of a very nervous and delicate habit ... at necropsy (Monday, Feb. 10, 1806) ... it was found that the stomach, duodenum, and the upper part of the ileum, liver, pancreas, spleen, and kidneys were in a natural and sound state. The lower part of the ileum as far as the colon, was contracted, for the space of three feet, to the size of a turkey's quill...

The next known case was reported by John Abercrombie (1828). He tells of -

"a girl, aged 13, about a year before her death, began to be affected with pain of the abdomen and frequent vomiting ..." The lower end of the ileum, to the extent of about eighteen inches, was "distended, thickened in its coats, externally of a reddish color, and internally covered by numerous well-defined ulcers, varying in size from the diameter of a split pea to that of a sixpence." The lungs and all other viscera were healthy.

Tietze (1920) made an exhaustive review of benign intestinal granuloma as reported in the literature up to that time but failed to describe a single case resembling regional enteritis. Moschcowitz and Wilensky (1923) described four cases of benign intestinal granuloma, one of which closely resembles regional enteritis. No cases were described by Mock (1931).

Freeman (1922) first focused the attention of the medical

world on what was then considered a rare and musterious entity, mesenteric lymphadenitis, which closely resembles regional enteritis. Since then, however, no one has successfully linked these two diseases, although some apparently confuse these two conditions. Mackson (1937a) feels that these two conditions are closely related, both possibly being due to low grade infections of the lymphatic system.

Regional enteritis is frequently confused with appendicitis, in both the acute and chronic forms and has lead to numerous appendectomies which not only have failed to relieve the symptoms but in some instances have resulted in the formation of intractable fecal fistulas. This fact had lead Jackson (1937a) to make the following statement:

> "Even now, undoubtedly many innocent appendices are being removed while the real source of the discomfort is overlooked. If more need be said as to the inadequacy of the former popular button hole incision, it might be urged that even the remote possibility of ileitis demands an adequate abdominal exploration when conditions permit it. Regional enteritis, mesenteric lymphadenitis, a diseased Meckel's diverticulum, and lesions of the gall bladder and pelvis are but a few of the pathological entities which, through inadequate exposure may escape the surgeon's eye."

In their original report, Crohn, Ginzburg, and Oppenheimer (1932) found that one-half of their patients had been subjected to previous appendectomy without relief and were later found to have regional enteritis.

Homans and Hass (1933), although agreeing that terminal il-

eitis presented a rather characteristic picture, were the first to dispute the statement that this disease is a pathologic entity. They felt that because of the numerous possible sites of involvement and because of its unknown etiology, the disease should be considered as a granulamatous process of unknown etiology which should be carefully sought for at any point along the entire length of the intestinal tract.

The original description of the disease as given by Crohn, Ginzburg, and Oppenheimer (1932) was presented in such acurate detail that subsequent investigators have been able to add but little to the picture; for this reason the author of this paper has found it necessary to refer to these authors far more frequently than to any others.

INCIDENCE AND DISTRIBUTION

This disease was first described by Crohn, Ginzburg, and Oppenheimer (1932) as being essentially a disease of young adults, a feature generally upheld by American investigators. Jellen (1936) found the ages of fifty patients to range between fourteen and fifty-four years with an average of twenty- four years. It originally was also considered to be about twice as common in males as in females, but a survey of more recent literature indicates that while it is still slightly more common in males, there is practically no difference between the sexes as to incidence. Fenster (1936) reviewed the cases reported in German literature and found the disease to be too common among women in individuals between the ages of fifty and eighty years to warrant considering the disease predominating any sex or age group.

Case reports also tend to indicate that regional ileitis more common in the Jewish than in other races. Mixter (1935) reported eleven cases of which eight were in Jewish patients. Several others have reported a high percenage of Jewish patients, but so few case reports give the race of the patients that accurate conclusions as to the racial characteristics of the disease can not be drawn.

Although the largest number of case reports have come from America, there are enough reported from other countries to indi-

cate that the disease has a word wide distribution. A few of those reporting this disease in other countries are Fisher and Lurmann (1933), Ropke (1934), von Haberer (1934), and Fenster (1936) all reporting cases in Germany; Jackman (1934) and Hodgson (1937) in Great Britain; Ross (1936) and Kinsella (1937) in Australia; Serafini (1936) in Italy; and Hansson (1937) in Sweden.

ETIOLOGY

Wilensky (1932) in discussing nonspecific granulomas of the intestine, thinks the etiologic factor to be a low grade infection, a theory that has proven quite popular, but no one has yet been able to demonstrate the specific agent. Erdmann and Burt (1933), in their paper on the same subject, think there to be first an interruption in the continuity of the mucosa as a reaction to the presence of an infectious or toxic agent or an indefinite foreign body resulting in ulceration of the mucosa. Active infection follows and extends up into the wall of the intestine setting up a low grade inflammatory process which manifests itself in the cellular infiltration and connective tissue formation.

Clute (1933) states that the appendix is not primarily involved hence chronic or subacute infection of the appendix cannot be considered as an etiologic factor. He states that the disease process may begin in the mesenteric lymph nodes and that the edema and thickening of the intestinal wall is secondary.

Crohn (1934) reported finding the condition in brother and sister, suggesting the possibility of a transmissable causative agent or a congenital predisposition. No other such case has been reported and in all probability this was purely accidental

Dunchess and Warren (1934) were able to demonstrate streptococci in the lymphatics in some patients but did not attach any

any etiologic significance to this discovery. Several others have made similar findings since then and some believe the disease to be on a streptococcic basis.

Felsen, Rundlett, Sullivan and Gorenberg (1934) and Felsen and Gorenberg (1936) made a study of two hundred and one cases of bacillary dysentery (Flexner) and found that ten per cent developed a chronic dysentery resembling regional enteritis. Felsen (1935a) definitely stated that regional enteritis was due to B. dysenteriae. At this time he reported five cases, three with clinical, operative, cultural, and serological findings of Flexner dysentery and two of the Somne-Duval type. Repeated cultures and serological studies were necessary to establish these findings. Later in the disease, Felsen claims that there may be a secondary nonspecific infection and that the B. dysenteriae and specific titre disappear. This same year (1935 b, and c) he made further investigations tending to uphold this theory. In 1936 he reported eleven cases with serological findings of bacillary dysentery; six of the Flexner type and five of the Somne-Duval type. Five of these patients gave positive stool cultures. Paulson (1936) believes the disease to be due to B. dysenteriae and says:

"Its seemingly relative propensity for the distal ileum may be due to stagnation at the ileocecal valve and the greater abundance of lymphatic tissue there than at any other bowel segment, factor favoring bacterial absorption."

Crohn's experience has covered sixty reported cases to date and in but one of these has he found evidence of B. dysenteriae.

Erb and Farmer (1935) describe a condition closely related to, and what they believe to represent the acute phase of, regional enteritis. They reported six cases all of whom gave positive agglutination tests for Bacillus coli and four of whom gave a positive agglutination test for Bacillus W.

Reichert and Mathes (1936), experimenting with dogs, injected the subserosal lymphatics with irritating and sclerosing solutions. In some cases they added appendiceal contents to the solution before injection and in others preceded the injection by one to three hours with the intravenous injection of a suspension of a twenty-four hour broth culture of B. coli. This produced a chronic lymphedema and, in some cases, a picture similar to that seen in regional enteritis. The thickening of the bowel wall was most marked in the instances in which the lymphatic injection was preceded by the intravenous injection of B. coli. These experiments led them to believe regional enteritis to be due to lymphatic sclerosis and obstruction along with blood vascular thrombosis. They attribute the marked hypertrophic changes of the later stages of the disease to a chronic low grade bacterial infection.

Ross (1936) had one case in which he was able to isolate a coliform bacillus from the stool. This bacillus was non-motile

and gave the following cultural reactions: fermented lactose, saccharose and adonite with the formation of acid and gas; it did not ferment dulcite, inulin, or inosite; gave a two plus indol reaction; formed acid and clot in milk and did not liquefy gelatin. An emulsion of these organisms was agglutinated by the patient's serum at 1:320. He was unable to isolate this same organism or obtain any serological reaction with the original culture three weeks after the patient's recovery.

Many of the references included in the bibliography are not referred to in this text as their authors have contributed no original observations concerning regional enteritis. They are of value, however, in that they give the reader an idea of the large number of investigators who have been unable to find any etiologic factors.

PATHOLOGY

When Crohn, Ginzburg, and Oppenheimer (1932) gave the first detailed description of this disease, they considered it to be limited to the terminal ileum, but, though it has subsequently been shown that the disease can exist elsewhere. The pathological changes are essentially the same regardless of the location of the lesion. The terminal ileum is by far the most common site of the lesion, but it may occur at any point in the intestinal tract. Knapper (1936) states that the disease almost always occurs in the last loop of the ileum and the cecum is seldom involved.

The acute stage can be described only as to the view presented at operation, for as yet, resection has never been performed at this stage of the disease because of the possibility of spontaneous resolution. At this stage the involved area of bowel is greatly thickened and soggy and edematous. The serosa is red or blotchy and the mesentery is thickened and edematous and contains hyperplastic glands. There is a small amount of exudate on the bowel wall and a small amount of serous fluid in the abdominal cavity. The appendix usually shows evidence of a periappendicitis without mucosal involvement and there may be abcess formation; the pus in this type of abcess is not as foul smelling as that in an appendiceal abcess. The acute stage has never been described except in involvement of the terminal ileum, but it is

assumed that the same changes would be present in the case of a lesion elsewhere in the intestinal tract.

Crohn, Ginzburg, and Oppenheimer (1932) state that the disease is not a static one nor is the entire diseased segment affected at one time. In "terminal ileitis" the oldest lesions begin at or just oral to the ileocecal valve and the more recent ones are situated proximally. No other investigators have made any observations as to the direction in which the disease progresses along the intestinal tract.

The chronic stage is more frequently seen at operation than the acute. The disease is generally limited to the terminal twenty-five to thirty-five centimeters (ten to fourteen inches) of the terminal ileum, including the ileal side of Bauhin's valve and terminating rather abruptly at that point. The severity of the process gradually abates proximally, gradually shading off into normal bowel. When the disease extends beyond the ileocecal valve or when it involves some region other than the terminal ileum, it usually gradually shades off into normal bowel distally as well as proximally.

Meyer and Rosi (1936) found that in the chronic stage the mesentery of the involved bowel may be as much as two centimeters thick. Fistulas are often found between the ileum and large bowel, usually the sigmoid, and may be found between the bowel and

bladder as reported by Forbes and Duncan (1937). The intestine proximal to the involved area is frequently but not always greatly dilated. Felsen (1935) noted marked congestion of the mesenteric vascular loops and arborizations. Sproull (1936), in describing the type involving the terminal ileum, found that there was a varicose condition of the blood supply and an overgrowth of mesenteric fat to extend upon and almost encircle the bowel: normally the mesenteric fat does not extend beyond the mesenteric border of the small intestine. Crohn, Ginzburg, and Oppenheimer (1932) describe the involved segment as a "soggy hose-like mass".

On opening the resected specimen, the intestinal wall is found to be greatly thickened, in some instances reaching two to three times its normal thickness. The lumen is irregular and distorted and broken up by the destructive ulcerative process and rounded and blunted by edema, giving a bullous structure to the mucosal aspect of the intestine, or frequently a cobblestone appearance of the surface of the mucosa may result.

A series of small linear ulcerations lying in a groove on the mesenteric side of the bowel is almost always present: Crohn, Ginzburg, and Oppenheimer (1932) think that these might be mechanical erosions due to the formation of darmstrasse by the shortening of the fibrotic mesentery. Sproull (1936) described these ulcerations as serpiginous, and found them to possess greyish diph-

theritic-like membranes. Homans and Hass (1933) found that in some instances the mucosal ulcerations were uniformly distributed instead of being restricted almost entirely to the mucosa adjacent to the mesentery. The dilated portion of intestine proximal to the diseased segment frequently shows superficial irregularly placed tension ulcers.

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

There is a marked tendency toward chronic perforation during the later stages of the disease. The perforation is usually slow enough to permit walling off by adhesions to a neighboring viscus, to the parietal peritoneum or to the omentum. This walling off process, however, does not always take place as is shown by the case reported by Halligan and Halligan (1937) in which peritonitis was the first symptom to manifest itself. Internal fistulas frequently form, usually to the large intestine, but occasionally to the bladder as reported by Forbes and Duncan (1937). Indirect perforation of the cecum may result from perforation of

the ileum into the terminal mesentery with secondary termination of the fistulous tract. Harris, Bell, and Brunn (1933) found that fistulous communication is most commonly established with the sigmoid, and then with cecum, ascending colon, and even transverse colon. They found that fistulas of the anterior abdominal wall which appear to communicate with the cecum are really communications between necrotic terminal ileum and anterior abdominal wall.

Stained histologic sections reveal various degrees of acute, subacute, and chronic inflammation with variations in predominance of polymorphonuclear, round cell, plasma cell, and fibroblastic elements. In the early stages the lesion is diffuse, involving chiefly the mucosa and submucosa with some inflammatory mucosal reaction. There are areas of marked destruction of the mucous membrane in which at times even the glandular structure is almost completely gone, leaving a layer of atrophic epithelium. The inflammatory reaction becomes more focal in character later in the disease, and focal areas of inflammation of the serosa give the gross appearance of tubercles.

Although not an essential feature of the disease, the presence of giant cells is quite striking in some cases and are occasionally surrounded by large pale cells or groups of cells which Crohn, Ginzburg, and Oppenheimer (1932) believe to be veg-

etable in nature. They think that small particles of vegetables became entrapped in ulcers and are encapsulated in the process of healing, thus acting as foreign bodies causing the formation of giant cells.

Homans and Hass (1933) describe a case with numerous focal, miliary, tubercle-like lesions in the ileum and regional lymph nodes. These lesions more closely resemble the so-called Boeck's sarcoid than those of tuberculosis. They believe the giant cell reaction and tubercle formation to be a response to a foreign body, which, in all probability, in the majority of instances is a lipoid. This lipoid may gain access to the tissues either directly from the lumen of the bowel or by obstruction of lacteals. Reichert and Mathes (1936) found the lymphatic vessels and lacteals to be engorged and thrombosed in some instances, a finding which lends strength to the theory of Homans and Hass (1933) as to the mode of entrance of the foreign body lipoid into the tissue.

No investigator has ever been able to demonstrate any evidence of tuberculosis, syphilis, actinomycosis, Hodgkin's disease, or lymphosarcoma in a proven case of regional enteritis.

SYMPTOMS

Crohn, Ginzburg, and Oppenheimer (1932) were the first to describe the symptoms in any detail, and since then, very little has been added to their findings. As the original disease was described as one involving the terminal ileum alone, it is natural that a few symptoms have since been added to the list: namely those seen when the process involves some portion of the intestinal tract other than the terminal ileum.

The general symptoms which persist throughout the course of the disease are weakness, progressive loss of weight, poor appetite and fever. The temperature is unusually intermittent with long periods of apyrexia being interspersed with shorter and irregular cycles of moderate temperature. Occasionally, though rarely, the temperature rises above 103 F. It is during these febrile bouts that the appetite is poorest. Some cases run the complete course without fever. Pemberton and Brown (1937) point out that there is usually a history of early exacerbations and remissions.

The original authors divided the disease into four clinical phases, each of which presents its own symptoms.

The acute stage presents signs of acute intra-abdominal inflammation and is impossible to distinguish clinically from acute appendicitis. The most constant symptoms here are generalized

colic, pain and tenderness in the right lower quadrant, and fever to 101 or 102 F. In addition there may be nausea or vomiting or both and diarrhea or constipation. These symptoms develop somewhat slower than in acute appendicitis, an observation which has been substantiated by many investigators in more recent years.

The second phase, that with symptoms of ulcerative enteritis, is characterized by colicky periumbilical or lower abdominal pain, tendency toward loosness of the bowels, constant fever, and loss of weight. This stage may be the first to manifest itself.

Pain, one of the most constant features of the disease may be located in any part of the abdomen but is usually periumbilical or right sided and is colicky in nature. Brown, Bargen, and Weber (1934) found that most patients described it as "cramp-like", while others described it as "colicky", "knife-like", "gripping", "obstructive", "sickening", or "to-and-fro colic". Sproull (1936) found that while the severity of the pain usually varies with the degree of involvement of the intestine, some patients present few or mild symptoms even though there is severe intestinal involvement. Jellen (1936) in reviewing fifty cases seen at the Mount Sinai Hospital of New York City, found that 66% complained of pain as the first symptom while the remaining 34% complained of diarrhea.

Diarrhea is usually an outstanding feature of the disease.

The number of movements and intensity of the actions never approach those of a true colitis. The average patient has two to four loose or semi-solid defecations daily. The stools are rarely mushy or liquid and generally contain free pus, coagulated lumps of mucus, and occult blood or streaks of free blood. There is no gross melena and tenesmus is always lacking. Forbes and Duncan (1937) describe a case with painful defecation as a symptom, but as this patient had recently had an abcess anterior to the rectum drained, this symptom can be eliminated as being a symptom of regional enteritis. Although diarrhea is usually constant throughout this stage, Brown, Bargen, and Weber (1934) found that it is occasionally intermittent and may even alternate with short periods of constipation. Regional enteritis does not show the common complications of true colitis: perianal fistulas, condylomas, a perianal abcesses.

The fever in this stage rarely rises above 100 F. but has been known to go as high as 104 F. (Brown, Bargen, and Weber, 1934) In most instances the fever is constant but may be intermittent.

Loss of weight and strength is a fairly constant symptom and shows a wide variation in degree. Even with marked loss of weight, disturbances in general nutrition may be slight. This may continue over a year or more until exhaustion sets in as in the case

reported by Abercrombie (1828), but this stage more commonly passes on into the stenotic phase before this can happen.

Anemia is another feature often encountered in this stage as well as the following one. This is secondary to the loss of blood in the stool and varies greatly in intensity: many cases being so mild as to pass unobserved while other cases are very severe.

The third or stenotic phase is the one most commonly encountered and occasionally occurs as a primary manifestation. The symptoms of this stage are those of subacute or small intestinal obstruction of varying severity. It is characterized by violent cramps which are most severe when there is visible peristalsis, borborygmus, and occasional attacks of vomiting and constipation. The vomiting is never marked or persistent and is usually accompanied by abdominal pain and visible peristalsis. The pain often accompanies or is followed and relieved by defecation. It is most commonly seen in the right lower quadrant, but may be referred across the entire lower abdomen. Visible peristalsis and intestinal erection are common. An abdominal mass may also be noticed by the patient as is brought out by Ravdin and Rhodes (1937). Brown, Bargen, and Weber (1934) found the pain to be localized about the unbilicus in cases of jejunal involvement. The pain is often increased by the ingestion of food and is frequently relieved by

vomiting or bowel movement, either normal or by means of enema. They also found that the vomiting is not that of complete obstruction, but only part of the food and drink taken is lost.

The fourth stage, that of fistula formation, is closely connected with the preceding phase and the two are usually present at the same time. Fistulas usually lead to the colon or sigmoid and such cases frequently give rise to symptoms of colitis, thus masking the true nature of the disease. With fistula formation between the ileum and sigmoid, the pain is mainly localized in the left lower quadrant. Pollock, (1937) observed that with internal fistula, the pain frequently radiates to the point of the fistula. Forbes and Duncan (1937) report two cases with enterovesicle fistula in which symptoms of cystitis developed and gas and fecal material was passed by urethra.

External fistula are frequently encountered and are the result of previous drainage operations or appendectomies. They may persist from the time of the original operation or may not develop for several months, the wound meanwhile having healed and having remained healed for a few months. Harris, Bell, and Brunn (1933) state that the appearance of a persistent fistula in the abdominal wall following the removal of a supposedly acute appendix which turns out to be innocent is practically diagnostic of regional enteritis. These authors also state that these fistulae

not only resist simple surgical closure, but never close spontaneously and therefore are different from simple appendiceal fistulae. Pollock, (1937), found that debility is most marked in the presence of a chronic fecal fistulae.

Halligan and Halligan (1937) report a case in which acute free perforation was the first symptom to appear.

PHYSICAL FINDINGS

Crohn, Ginzburg, and Oppenheimer (1932) found but few physical findings of value in making diagnosis in regional enteritis, and Brown, Bargen, and Weber (1934) bring out this fact again and state that the physical examination is practically negative during the quiscent phases of the disease.

During the acute stage there is usually fever up to 101 or 102 F. and even higher in rare instances, rapid pulse, abdominal tenderness, usually in the right lower quadrant, occasionally abdominal rigidity, and frequently a palpable mass in the lower abdomen, usually on the right.

As the disease passes into the chronic phase, the temperature becomes remittent, seldom going above 100 or 101 F. The presence of an abdominal mass is more constant than in the acute stage. It is usually felt in the right iliac region, but may be more to the left when the sigmoid is adherent and involved, or more to the right and higher when the cecum, ascending colon, or hepatic flexure constitutes the distal end of a fistulas tract. It is usually about the size of a small orange, tender, firm, and slightly movable. The tumor is usually palpable per rectum where it is felt very high. Knapper (1936) describes the tumor as being sausage shaped. Pollock (1937) states that in 58% of the cases there is a palpable mass which is usually ovoid, measuring about two by three inches, somewhat tender, smooth or slightly nodular,

and often not movable. This tumor can sometimes be felt only by rectal or vaginal examination because of deep pelvic location. With involvement of the jejunum or sigmoid the mass might be felt on the left. Other common findings of the chronic stage are evidences of loss of weight and secondary anemia.

Fecal fistulas are often encountered in cases in which there has been previous appendectomy or drainage of an abcess, a condition which Bissell (1934) stresses as a valuable diagnostic point. Many cases, however, show evidence of previous appendectomy without any fistula formation.

Sigmoidoscopic examination reveals nothing unusual except in an occasional case with secondary involvement of the terminal bowel.

In the late stage when there is partial obstruction, there is, in addition to the other findings of the chronic stage, abdominal distension of varying degrees and frequently by visible peristalsis.

LABORATORY FINDINGS

There are few constant laboratory findings in this disease. There is usually but not always a mild leukocytosis which is never extremely high except in the case of perforation with peritonitis. There is a mild to moderate secondary anemia which is progressive throughout the disease. Brown, Bargen, and Weber (1934) report one case in which the hemoglobin dropped to 20% and the red cell count to 2,700,000 but this is quite unusual.

Felsen and his associates found the serum to give positive agglutination tests with B. dysenteriae in the earlier stages of the disease and at the same time they were able to culture the organisms from the stool. Erb and Farmer (1935) obtained positive agglutination reaction to Bacillus W. and Bacillus coli while Ross (1936) obtained a positive reaction to coliform bacillus isolated from the patient's stool.

In most instances, however, examination of the stool reveals only pus, mucus, and fresh or occult blood and is negative for parasites, ova, and bacteria not normally found in the intestinal tract.

There are no unusual urinary findings except in case of entero vesicle fistula as reported by Forbes and Duncan (1937).

ROENTGENOLOGIC FINDINGS

Croh, Ginzburg, and Oppenheimer (1932) observed the colon to be uniformly free of changes even though the ileocecal valve is the seat of greatest intensity of the process. There are distended loops of terminal ileum in which a fluid level is discernible and there is a definite delay in the motility of the barium meal through the distal end of the small intestine. This delay is most striking in the late or stenotic phase. There is a stasis or puddling in the ileal loops which may be overlooked in milder cases. With fistula formation between the ileum and ascending colon or hepatic flexure with delayed motility at this point. When the sigmoid is similarly involved, a true narrowing and delay at this point may simulate carcinoma.

Clute (1933) advised the exposure of plates every hour in making x-ray examination with the barium meal because of the danger of the barium passing entirely through the area before the plates are made in following the ordinary routine.

Harris, Bell, and Brunn (1933) found the barium enema to be negative, but Meyer and Rosi (1935) found that in some instances the barium may regurgitate into the ileum and aid in making diagnosis.

Kantor (1934) was the first to make a detailed study of the roentgenologic findings in "terminal ileitis". He found changes

in both colon and ileum. Changes in the colon are inconstant and are due to reflex spasm. They may involve the entire colon but are usually limited to the cecum alone. Fixed deformity results with actual involvement of the colon by adhesion or fistula. The most important changes occur in the ileum when there is a constant irregular filling defect with a peculiar taper at its proximal end. The most striking finding is a thin, slightly irregular linear shadow extending from the last visualized loop through the entire extent of the filling defect. This shadow has become known as the "string sign".

Bell (1934) advocated the injection of the barium through a duodenal tube inserted beyond the pylorus, especially in making examination for lesions high in the small bowel.

Sproull (1936) noted "mucosal relief pattern of finger-print-depression type resembling that produced by polyposis." He also stresses the value of the barium enema in cases with involvement of the colon.

Connell (1936) states that if examination is not made from various angles, some abnormalities of the small bowel might be overlooked.

DIFFERENTIAL DIAGNOSIS

Although preoperative diagnosis of regional enteritis is very difficult to make, it is being made more and more frequently, particularly by those who encounter the condition relatively often.

The disease must be differentiated from conditions which produce a mass in the right iliac region with fever and diarrhea. The acute stage closely simulates acute appendicitis, and although Crohn, Ginzburg, and Oppenheimer (1932) observed that the symptoms usually come on more gradually than in appendicitis, differentiation is practically impossible except at the operating table. Brown, Bargen, and Weber (1934) found this stage to resemble intussusception or diseased Meckel's diverticulum in some cases; heretoo diagnosis can be made only by exploration.

Nonspecific ulcerative colitis is another condition frequently confused with regional enteritis. Here differentiation can usually be made by sigmoidoscopy and the barium enema. Jellen (1936) found differentiation to be difficult only when there is an ulcerative colitis involving the proximal colon and terminal ileum, a condition in which accurate preoperative diagnosis is sometimes impossible. If the terminal ileum shows evidence of ulceration without stenosis, differentiation can be made with some degree of assurance, because whenever regional ileitis is asso-

ciated with colitis, the process in the terminal ileum is usually far advanced and shows evidence of considerable stenosis. The converse of this, however, does not always hold, and roentgen evidence of what appears to be a stenotic ileum does not exclude proximal colitis with involvement of the terminal ileum. Crohn, Ginzburg, and Oppenheimer (1932) stated that colitis is never associated with fistula formation except about the rectum and anus and that there is seldom a palpable mass with this condition. Bissell (1934) pointed out that regional enteritis is never associated with the common complication of colitis: namely perirectal abcesses, condylomas, or perianal fistulas.

Intestinal tuberculosis is another condition frequently confused with regional enteritis. Jellen (1936) made a review of the literature on intestinal tuberculosis and was able to find several points of value in making differential diagnosis. Ulcerative intestinal tuberculosis is usually secondary to pulmonary tuberculosis and is relatively common. The hyperplastic type may be found in the absence of pulmonary lesions and is very rare, Rockey (1933) states that there were only nine cases of hyperplastic tuberculosis of the terminal ileum reported in the literature up to 1933.

Moschcowitz and Wilensky (1933) pointed out the similarity in pathology between nonspecific granulomas and of the intestine

and primary hyperplastic intestinal tuberculosis and stated that "many if not the majority of the cases of so-called hyperplastic tuberculosis of the colon are really simple granulomata." The demonstration of tubercle bacilli in the lesion is the only way to make positive diagnosis of tuberculous enteritis.

Stierlin (1911) first pointed out the absence of normal barium shadow in the proximal colon in ileocecal tuberculosis. This sign is of value in making diagnosis, but it must be kept in mind that this sign may appear with any ulcerating lesion of the ileocecal region.

One of the most valuable diagnostic points between intestinal tuberculosis and regional enteritis is the roentgenologic demonstration of evidence of spasm as commonly seen in tuberculosis.

Fibroplastic appendicitis and typhlitis must also be considered, and can not be accurately differentiated except at operation.

Lymphosarcoma and Hodgkin's disease also simulate regional enteritis and are seldom differentiated before operation. Lymphosarcoma of the intestine is usually multiple and causes dilatation at various levels. Hodgkin's disease may give rise to a characteristic monocytic blood picture or enlargement of the regional lymph nodes may reveal the true nature of the disease.

Mesenteric tuberculosis is differentiated only at operation.

Actinomycosis should be considered in every case with persis-

tent abdominal fistula. Diagnosis of this condition is made on demonstration of sulphur granules in the discharge.

Amebiasis rarely involves the small intestine but may simulate regional enteritis of the large bowel. The diagnosis of amebiasis rests on the demonstration of amebae or cysts in the stool.

Carcinoma can not be preoperatively diagnosed from regional enteritis, and in some instances can be differentiated only by microscopic examination. Sproull (1937) describes a case in which an operative diagnosis of inoperable carcinoma was made, thus illustrating the difficulty sometimes encountered in making diagnosis.

TREATMENT

Crohn, Ginzburg, and Oppenheimer (1932) state that medical treatment is futile, being purely palliative and supportive. They advocate leaving the acute stage alone because of the possibility of spontaneous resolution. In other than the acute stage, however, the resection of the diseased segment is the treatment of choice. They feel that shortcircuiting operations are of value, but with this method of treatment there is possibility of recurrence or persistence of symptoms.

Meyer and Rosi (1936) advise wide resection into normal bowel to avoid leaving behind any small focus which might lead to recurrence of the disease.

Ravdin and Rhoads (1937) bring out the danger of the process extending along the ileum to the site of anastamosis if the ileum is not divided and to contiguous structures if divided but not resected. They feel that ileocolostomy with division of the ileum between the anastamosis and involved portion is the best procedure when resection is not possible.

Experiments conducted by Holm (1933) showed that the sidetracked ileal loop of a lateral ileo-ileostomy or ileocolostomy for obstruction of the terminal ileum is likely to become greatly elongated, dilated, and ulcerated. An enterocolitis with mucosal ulceration and degenerative lesions of the liver and kidneys.

If resection is inadvisable because of the condition of the patient, the lateral anastamosis should be done as near to the obstruction as possible and be regarded only as a first stage operation to be followed by resection. As an alternative procedure they suggest that the intestine be divided as close to the obstruction as possible and be followed by an end to side anastamosis which eliminates a blind pouch.

Clute (1934) feels that fistula formation and obstruction are the only indications for resection, and in all other cases ileotransverse colostomy is the treatment of choice. This may be followed by resection if the symptoms persist. Extensive resection is contraindicated in the presence of an abcess unless there is marked obstruction. In case of abcess formation without obstruction, drainage of the abcess and rest of the affected area by a shortcircuiting procedure may well result in complete recovery.

Mixter (1935) advocates a multiple stage procedure with drainage of the abcess, if one is present, as the first stage, and to follow this with ileocolostomy and finally resection.

Pollock (1937) does not feel that drainage should be done following resection as this procedure increases the possibility of fistula formation. In treating fistula, the diseased portion of the bowel must be resected along with the tract.

SUMMARY

Although no age, sex or race is immune to this disease, regional enteritis is essentially a disease of young adults, is slightly more common in males than in females, and is somewhat more common in the Jewish than in other races.

This disease, like mesenteric lymphadenitis, is probably due to a low grade infection of the lymphatic system. Its etiology is unknown.

The symptoms depend on the stage, location and severity of the disease; the most important are pain, diarrhea, vomiting, fever and loss of weight.

The most valuable physical findings are evidences of fistula formation and a palpable abdominal mass: many cases never present either of these findings.

There are no laboratory procedures of value in making diagnosis.

This disease presents a fairly characteristic roentgenologic picture: the demonstration of Kantor's "string sign" is almost diagnostic.

Regional enteritis must be differentiated from appendicitis, intussusception, diseased Meckel's diverticulum, nonspecific ulcerative colitis, tuberculous enteritis, fibroplastic appendicitis, typhlitis, lymphosarcoma, Hodgkin's disease, mesenteric tu-

berculosis, actinomycosis, amebiasis, and carcinoma.

The only known treatment of this disease is surgical and consists of resection of the diseased segment or a shortcircuiting procedure. The acute stage is left alone because of the possibility of spontaneous resolution.

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