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Regional enteritis : current concepts of pathogenesis and medical management

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REGIONAL ENTERITIS: CURRENT CONCEPTS OF PATHOGENESIS AND MEDICAL MANAGEMENT

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Regional enteritis, or Crohn's disease, is defined in Stedman's Medical Dictionary[6] as a "chronic cicatrizing enteritis of unknown etiology, perhaps a low grade infection." Because of recent changes in concepts of etiology and accordingly treatment, a review of the literature was performed to compile this information into one source reference.

HISTORY

The first description of a non-specific granuloma of the bowel was attributed to Morgagni (1761), who recorded a case of inflammatory thickening of the terminal ileum.[70] Combe and Saunder (1813) and Abercrombie (1828) described patients with ileitis who showed skip lesions in the small bowel and a localized segmental colitis.[23, 1] These skip lesions were areas of recognizable thickening separated by normal appearing bowel. Subsequently two cases involving the colon (1907) and nine cases (1913) of non-specific jejunitis, ileitis and colitis were described.[75, 32] Six of the latter group might now be considered regional enteritis. Moschwowithz and Wilensky (1923) described four cases of non-specific granulomata of the ileo-cecal region and colon.[73]

In 1932, Crohn, Ginzburg and Oppenheimer presented the now classical "Regional Ileitis--A Pathologic and Clinical Entity," a report that brought about recognition of regional enteritis as a distinct disease process by the medical world.[28] Crohn's description was based on a study of fourteen cases and because of the disease's constant and well defined characteristics proposed the name "regional ileitis."

The disease was described as one involving the terminal ileum, affecting mainly young adults and characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa was accompanied by a disproportionate connective tissue reaction of the adjacent walls of the involved intestine, a process frequently leading to stenosis and formation of multiple fistulas.

Crohn originally reported that the terminal ileum alone was involved. His work aroused widespread interest and many cases were reported. It was soon realized that lesions with similar histology could affect any part of the alimentary tract.

Harris et al (1933) noted a jejunal enteritis; the following year Colp described colonic involvement.[22] The broader term of "regional enteritis"

was suggested by Brown et al in 1934.[16] Similar changes were recorded in the duodenum by Shapiro (1939) and the stomach by Ross (1949).[90, 86]

Hadfield recognized lymphatic obstruction aspects of the condition and distinguished between primary and secondary pathologic processes. He also described the structures which resemble tubercles, designating them as giant cell systems and suggested their pathogenesis.[48] Warren and Sommers (1948) related the focal lymphatic endothelial proliferation to lymphatic obstruction.[105]

TERMINOLOGY

As it became recognized that the disease affected more than the terminal ileum, confusion developed concerning terminology. These variations in the site of location, as well as the inadequacy of understanding the cause of this disease process, have lead to many descriptive terms including Crohn's disease, terminal ileitis, regional ileitis, regional colitis, regional jejunitis, regional duodenitis, regional gastritis, segmental enteritis, nonspecific granulomatous enteritis, cicatrizing (sclerosing) enteritis, cicatrizing ulcerative enteritis, and cicatrizing entercolitis.[19]

Morphological terms included segmental enteritis, which emphasizes the tendency of the disease to involve portions or segments of the intestine with abrupt transitions from abnormal to normal; cicatrizing enteritis and cicatrizing ulcerative enteritis call less attention to pathognomonic features of the disease but again describe characteristics often seen; cicatrizing entercolitis is a term introduced to indicate dual involvement of the small and large intestine; regional jejunitis, regional duodenitis, etc., simply describe the portion of bowel involved. Non-specific granulomatous enteritis refers to the unknown etiology and that the inflammatory reaction is granulomatous in nature. It is considered a more precise term by many authors. Regional enteritis is the term most widely used at the present time. In view of the effort to discourage the use of eponyms, the popular term Crohn's disease has little value other than to refer to the historian. It is likely that when the etiology of this disease is better understood a more acceptable term will be generated.

EPIDEMIOLOGY

It is generally agreed that regional enteritis occurs with equal frequency among males and females and is not limited geographically (some authors have noted a slight male predominance).[21] It is more prevalent in individuals of Jewish extraction according to statistics of the US Army in World War II and the Veterans Administration Hospitals of the United States.[3] The disease afflicts all ages but most commonly the 15 to 30 years stage of life. Daffner reports 55 percent of his 100 patients were less than 31 years of age; however, 15 percent were more than 50.[31] In Van Patter's series of 600 patients the onset occurred between 11 to 35 years in 76.6 percent of the patients.[103] While the pediatric literature contains many reports, this condition is very rare under the age of four years.

Although responsible for much invalidism because of its tendency toward recurrences, complications and chronicity the death rate in the United States is only 0.08 per 100,000; Canada, 0.09; and England and Wales, 0.11. Davis gives a probable incidence rate of 1 per 100,000.[33] Both the

incidence and the mortality are usually quoted as being approximately one-fifth that of ulcerative colitis.

The disease is apt to occur in families and the family members are always of a close blood relationship.[29] Schofield states he has seen three examples of familial regional enteritis: one brother and sister; two cousins; and a family in which seven members had the disease.[57]

PATHOLOGY

Gross Observations: Upon opening the abdomen, free peritoneal fluid is often present. The initial process preceding inflammation and deposition of fibrous tissue appears to consist of submucosal edema and lymphangiectasia, as determined by examination of tissue proximal to ulcergranulomatous areas.[4, 67]

During the so-called acute phase, the involved intestine appears red or dusky blue, with the serosal surface granular and marked by venous and capillary engorgement. Adjacent loops of bowel may be adherant and covered with a fibrinous exudate.[67]

In the chronic stage the involved intestine presents a nearly normal color with many adhesions resulting from organization of inflammatory exudates.

The most characteristic gross finding is a tremendous thickening and stiffening of the bowel due to inflammatory edema and fibrous proliferation. The appearance has often been likened to a garden hose.[87]

The mesentery is markedly thickened owing to edema and/or fibrous tissue proliferation. Gross enlargement of the lymph nodes extending deep into the root of the mesentery is also a regular feature. It is this thickening of the bowel wall and surrounding structures that causes the marked narrowing of the lumen and partial or complete intestinal obstruction that so often develops.[103]

The mucosal surface of the intestine appears red, swollen, and at times "cobblestoned," because of granulomatous changes in the submucosal layers. Ulcerations of irregular shape leave isolated islands of intact epithelium. These ulcers are usually grouped longitudinally along the mesenteric border and are covered with shaggy grayish-white exudate.[105, 106]

In advanced cases fistulous channels form internal shunts between involved loops of bowel or burrow into contiguous viscera. Table I lists the most common locations of these internal fistulas.

These tracts may give rise to abscesses between involved bowel and neighboring organs or end in large chronic inflammatory masses. Free perforation is rare and usually occurs in acute cases.[63]

TABLE I Locations of 113 internal fistulas in 81 patients with regional enteritis.[103]

Locations	Percentage
Ileo-ileal	23.0
Ileocecal	24.0
Ileosigmoidal	19.5
Ileovesical	9.0
blind fistula	8.0
Ileo-transverse colon	4.4
Ileo-ascending colon	2.6
others	9.5

Histologic Observations: Using the technique of Van Patter, the histologic features of regional enteritis are considered under two headings: the primary pathologic process supposedly related to the etiologic agent, and the secondary inflammatory changes. The primary process includes microscopic features by which a diagnosis of regional enteritis can be predicated even though individually they are non-specific.[103]

Distortion of the mucosal pattern by submucosal edema results in necrosis of the epithelium, abnormal mucosal regeneration, and often branching tubular

glands of the goblet cell type. In the vicinity of the lesions, the number of goblet cells has been observed to be increased--frequently leading to complete replacement of other epithelial elements.[55] Mucigenous glands of this type appear in other ulcerative and inflammatory diseases of the bowel, perhaps as an adaptive mechanism.

Cellular response usually consists mainly of plasma cells, which with polymorphonuclear neutrophils, line the walls and floors of ulcerations. Marked lymphocytic infiltration also occurs in these areas. Fibroblastic activity seems to be dependent upon the age of the lesions and occurs through and about the entire process.[48]

The muscularis mucosa is found to be markedly thickened, especially around areas of involvement. This is due in part to the obligatory shortening caused by the concentric narrowing of the intestinal lumen and in part to focal areas of leiomyomatous proliferation.[103]

It is in the submucosa that the most characteristic changes are seen. Here is observed interstitial edema, lymphoid hyperplasia, and dilation and tortuosity of the lymphatics. The intense edema is not accompanied by a commensurate inflammatory reaction when there is no adjacent ulceration and infection.[21, 43]

Partial or complete focal occlusion of the lymphatic vessels is produced by proliferating cells projecting into the lumens of the channels and forming granulomatous structures resembling tubercles. These "granulomas" are composed predominantly of epitheloid cells and contribute to the sclerosing lymphangitis that is found in all layers of the bowel wall, the mesentery, and the lymph nodes.[9]

Distinct from the granulomas, giant cells are observed of a foreign body type and often contain lipids, talc, or unidentified foreign material. The widespread hyperplasia extends to the serosa where aggregations are sometimes mistaken for tubercles.[103]

The secondary inflammatory changes are somewhat arbitrarily ascribed to being the result of ulceration, secondary infection, and tissue destruction with its resultant repair. As a result of these secondary changes the granulomas often merge with surrounding tissue reactions and lose their circumscribed borders. Fibrosis and, occasionally, hyaline substances replace the submucosal edema. These inflammatory lesions tend to be especially pronounced around the deeper ulcers

or fistulous tracts. Stercoraceous mucosal ulcers now appear on the side of the bowel opposite the mesentery, unlike the primary ulcerations which occur on the mesenteric side of the bowel.[21]

PATHOGENESIS

A comprehensive concept of pathogenesis of regional enteritis has been lacking because the etiology of the disease process has been unknown and the initial histopathologic lesions have not been well understood.[16] There is no general agreement on the nature of the primary lesion or whether it represents a response to a specific inciting agent or merely a common reaction to many possible causative factors.[4] Some of the theories of pathogenesis that have been proposed are based on advanced secondary histologic changes that are of non-specific character.

Methods of obtaining pathologic materials have been the cause of some of the confusion concerning the lesions. Little is known concerning the acute forms of the disease. Because of the likelihood of inducing a complication as a fistula or abscess, surgeons are reluctant to perform a biopsy in an acutely involved area. Pathologic specimens are usually obtained in advanced stages of the disease.

Thus identification of the fundamental disease process is difficult due to the long-standing secondary infections and tissue repair. Often peripheral lesions with lesser involvement are examined and identified as the primary lesion.[4, 67] Such an assumption must be viewed cautiously.

Lymphedema is generally considered the hallmark of regional enteritis even though it is observed in other diseases of the intestine. There have been various explanations of the production of the lymphedema. Hadfield directed attention to the lymphoid hyperplasia.[48] Later Warren and Sommers ascribed it to focal areas of lymphatic endothelial proliferation with progressive granulomatous lymphangitis and sclerosis of the lacteals in the intestinal lamina propria immediately beneath the epithelium of the intestinal glands.[82, 105] A recent theory suggests that incoordination of the circular and longitudinal muscle coats of the intestine interfers with proper emptying of the extensive lymphatic plexus between them.[91]

Hadfield considered the formation of the structures resembling tubercles the products of the germinal centers of lympoid follicles and by numerical increase were able to replace lymphoid

follicles.[48] Warren and Sommers explained them as being foci of lymphatic endothelial proliferation which fill the entire lymphatic channel and are capped by a mantle of lymphocytes.[105] These endothelial cells acquire an epithelioid nature and some coalesce to form giant cells. Van Patter suggests that some of the formations resembling tubercles arise from mononuclear phagocytes of the blood and tissue and may develop apart from any lymph channel or lymphoid structure.[103]

The diffuse cellular infiltration of plasma cells and lymphocytes is generally considered to be a primary process. It has been suggested that they develop, in part, as a response to the secondary changes resulting from mucosal infections.

Secondary changes observed may be envisioned as occurring in the following pathologic sequence: submucosal lymphangiectasia leads to submucosal edema and lymphoid hypertrophy, with eventual flattening of the mucosal folds overlying the area; further edema and hypertrophy of the muscularia mucosae then causes small rents in the mucosa as well as further edema; aided by diminished blood flow, shaggy ulcerations develop; further penetration of the ulcers leads to fistula formation,

abscesses, and to the complications of advanced regional enteritis. The primary process also causes partial obstruction of the bowel permitting a numerical increase in bacteria. The significance of this increase in bacteria will be discussed shortly.[4]

The occurrence of fibrosis seems to be dependent upon the fluid of edema and its high protein content, the infection of considerable duration, and the cellular transition of lymphocytes and histiocytes into fibroblasts.[103]

ETIOLOGY

Current etiologic concepts are quite varied as is often true of diseases of unknown cause. Many causative factors have been considered and several important possibilities appear to have been excluded. The suggested causes include infectious agents (bacteria, viruses, and protozoa), allergic reactions, familial tendency, response to emotional stress, reaction to foreign bodies, toxic substance reactions, and irritative lipid substances absorbed because of faulty fat metabolism.

Many attempts have been carefully made to consistently isolate a bacterial agent. No specific infectious agent (bacterial, fungal,

viral, or protozoal) has been identified, nor has it been possible to transmit the disease to man or animal.[29] While both the clinical and pathologic features suggest that an infectious process is responsible, it has been noted that the cellular inflammatory reaction does not parallel the edema in intensity, location, or time.[4] The lymphedema occurs early and is diffuse whereas the inflammatory changes are most prominent near deep fissures, abscesses and fistulae, and appear late in the evolution of the disease.

An occasional instance of regional enteritis has been confused with hyperplastic ileo-cecal tuberculosis, but the failure to demonstrate or isolate tubercle bacillus and the absence of the characteristic caseous necrosis make it exceedingly unlikely that the two diseases have a common etiology.[16] Other granulomatous lesions such as sarcoidosis have been suspected, but the granulomas of regional enteritis are confined to the intestine, its mesentery, and the surrounding lymph nodes. These rarely are involved in sarcoidosis. An attempt to devise a skin test analogous to the Kveim test for sarcoidosis, by intradermal injection of an extract of a lymph node from a patient with regional enteritis, failed.[91]

In patients with acute bacillary dysentery, especially of the Shigella type, a late incidence of ileitis in 10 percent of the cases has been reported. Such epidemiologic observations have not been widely confirmed and the correlation is not evident in the majority of the cases.[38, 103]

In view of these extensive studies and attempts at isolation it appears that a bacterial etiology may be excluded. However, the likelihood of an inflammatory mechanism in the pathogenesis of the disease, investigation of the possible role of so-called L-forms of bacteria may be desirable. It is generally admitted that much remains to be learned of the microflora of the gut, its relationship to health and disease, as well as the role of bacterial endotoxins in the pathogenesis of inflammatory diseases of the bowel.[8]

The viral etiology of regional enteritis has been suggested frequently but viruses have not been consistently isolated from diseased intestine. Schneierson reported that no single viral group or species were consistently isolated from either diseased bowel or lymph nodes. His studies were conducted on 75 patients with regional enteritis. Schneierson further points out that viral infections

are usually accompanied by the production of a specific immune antibody in the blood of the infected host which is capable of reae ing with the causa-tive agent. In no instance were specific antibodies against any of the viruses recovered demonstrable in the Blood of any of the patients. Further, no experimental lesions simulating those of regional enteritis were producible with any of the recovered viruses.[88]

A Positive Frei test for lymphogran.uloma venerum in seven patients w1th regional enteritis caused some interest in this viral agent.[102] However, the extensive involvement of the small intestine in regional enteritis differs from. the circumscribed stricture of lymphopathia venerum. Also the frequency of the disease among children not 1n contact with this virus and the failure of isolation of the virus make th1.s a doubtful etiologic agent.[8]

The occasional finding of a markedly thickened and edematous terminal ileum with enlarged mesenteric lymph nodes in patients with known food allergy has suggested a casual relationship.[92] Although the gross appearance simulates regional enteritis, microseopic examination reveals extensive eosinophilic

infiltration of the entire intestinal wall and none of the ulcerations and giant-cell systems that are usually so prominent in regional enteritis. Symptomatic relief of enteritis with the elimination of specific foods (most often milk) and an alleged predilection for recurrences during the high pollen seasons have been advanced in favor of an allergic etiology.

The theory of an autoimmune reaction in a hypersensitive bowel has been proposed, and while not inconsistent with some of the clinical and pathologic features, it awaits confirmation. Shnitka suggests a local autoimmune reaction, corresponding to the Arthus phenomenon, might initiate local interstitial edema that in turn leads to obstructive lymphedema and fibrosis.[91] All attempts to establish an immunologic basis for regional enteritis thus far have failed,[59] although this concept remains appealing.

The theory that absorption of a foreign body as the percipitating factor of the disease has recently been more strongly suggested by several authors. The microscopic finding of tubercles and giant-cell systems, some actually containing foreign material such as talc or sand, lends

support to this theory.[19] A pathologic picture resembling regional enteritis has been induced in dogs by the intravenous injections of Escherichia Coli in combination with serial injections of silica into the mesenteric and subserosal lymphatics.[76, 83] This resulted in lymphatic hyperplasia in the terminal ileum, associated with submucosal thickening and lymph node hyperplasia, but the findings do not duplicate those of regional enteritis.

Further support to the foreign body theory is suggested by the pathology observed. The microscopic appearance of massive edema of the intestinal wall, mesentery, and mesenteric glands is suggestive of the elephantiasis seen in chronic lymphatic obstruction of the lower extremities from a variety of causes. The lymphatic blockage and fibrosis by foreign bodies in other viscera, as in silicosis or asbestosis of the lung, suggest a possible similar mechanism in the lymphatics of the bowel.[91, 103] The question as to the extraneous agent, if any, which initiates the primary lesion remains unanswered and further work in this field may prove rewarding.

Trauma has been implicated as a possible etiologic agent from clinical observations.[50, 51] Crohn states that trauma plays a role in the initiation of the disease, especially the modern types of abdominal trauma (auto accidents).[26] These clinical observations stimulated efforts to produce disease in dogs by temporarily constricting their small intestine with steel clamps. The lesions produced did not resemble regional enteritis.[95] Nonpenetrating trauma of a degree that is clinically recognizable and remembered by the patient does not appear to statistically constitute an important factor, though it may sometimes precipitate progression in an otherwise inactive or unrecognized case of enteritis.[107]

No new evidence has appeared in support of a psychogenic or neurogenic cause of regional enteritis. Of interest, however, is an apparent increase in the number of neural elements in the intestinal wall.[103] The common clinical observation that psychologic stress has preceded a recurrence of regional enteritis throws little light on the etiology of the initial attack. Emotional tension influences function of the small intestine, and theoretically the repeated impact of such

disturbances may culminate in structural changes, but the weight of evidence does not warrant considering regional enteritis as primarily a "stress disease." EmotionaJ. stress may well trigger an exacerbation of symptoms, however. At the present time the results of psychiatric inter-views have been conflicting and subject to challenge far lack *ot* adequate controls.46, [68]

A familial pred1spos1t1on has been pointed out earlier 1n this paper.* A comprehensive family and genetic study 1s lacking at this time, however. Social and racial observations are pointed out but these are subJecx to the limitation of possible differences in the uniformity of diagnostic apprasials by the various observers. The frequency of regional enteritis among children, teen.agers, and young adults 1s striking. There may well be a significant patholog1c :factor 1n this but. the nature of the relationship has yet to be described.

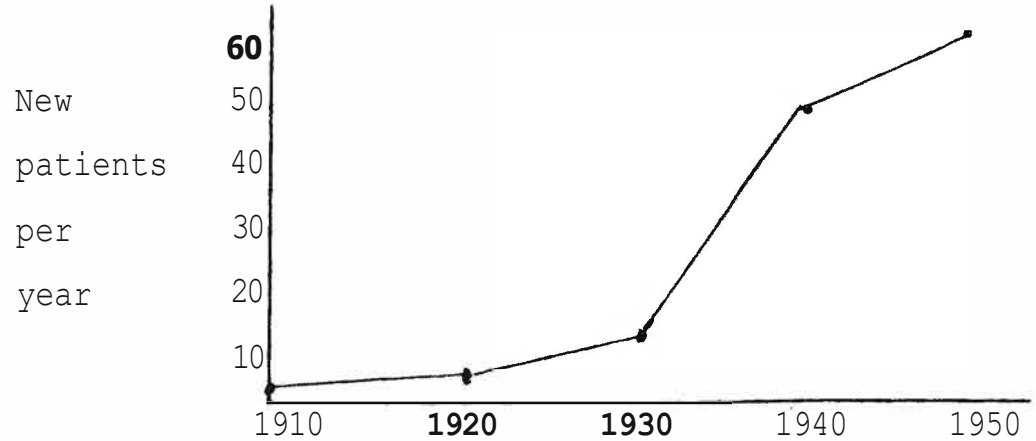
The findings of lipid deposits in giant-cell systems have suggested to some authors that the histopathology of regional enteritis could be a reaction to irritative lipid substances. They suggest that this may represent a by-product of some biochemical abnormatity of lipid absorption in the

*See page 5

bowel.[105] It would appear that the rapid 1 provement that appears in a by-passed loop of diseased bowel after a by-passing operation supports this theory. Perhaps the reappearance of the disease after resection or ileocolostomy represents new areas of small or large bowel absorbing a noxious substance where such had not occurred before.[107]

Alth,ough difficult to acess, it is usually agreed that the incidence of regional. enteritis has increased in the past 30 years (See Graph I). That this trend reflects greater awareness and improved dignosis is evident, but several authors feel this is a true rise in 1ncidence.[103, 101] If this assumption is valid, speculation into the role of agents to which man is exposed today more extensively than in the past can prove interesting. These would include such th1ngs as food additives, pasteurization of milk, drugs (including antibiotics) and numerous other possibilities.

GRAPH I Admission rates of new patients per year103 at Mayo Clinic (Adapted from Van Patter)



If obstructive edema is indeed a common pathogenetic factor, it is possible that a variety of etiologic agents may produce the same type of histopathologic reaction by different mechanisms.[91] At present, there is no conclusive evidence for any specific etiological agent. In fact, Pugh's suggestion in 1945 still holds true--that in order to make the diagnosis of regional enteritis, the etiology must be unknown.[103]

DIAGNOSIS

Crohn states that regional enteritis should not be regarded as a disease difficult to diagnose. He feels the clinical manifestations are clearly marked and the radiographic demonstration of the disease is obvious.[26] Chronic regional enteritis is usually characterized by a gradual onset of cramping abdominal pain, diarrhea, weight loss, anemia and fever. Acute disease may mimic acute appendicitis so closely that the diagnosis is made only at time of operation. Appendectomy under these circumstances is claimed to be safe,[65] but resection or biopsy is not recommended because of danger of fistula formation.

In other instances, most often reported in children, gastrointestinal symptoms may be absent

or minimal.[74] Systemic symptoms of fever,[104] tachycardia, weight loss and growth retardation[94] may be the prominent features. It is because of these varied clinical manifestations that it is necessary to consider regional enteritis in the evaluation of obscure conditions, especially when accompanied by an unexplained fever and weight loss.[62]

Physical examination may show evidence of infection, undernutrition and abdominal tenderness. There may also be a mass in the right lower quadrant composed of inflamed loops of bowel, adherent thickened mesentery and perhaps an abscess.[28, 31] Rectal and perianal examination can be very enlightening since the findings of a perirectal abscess or fistula is frequently the initial clue to the presence of regional enteritis. Proctoscopy may demonstrate a granular slightly friable mucosa, punctate ulcerations surrounded by erythema, or the mucosa may appear normal. Biopsy of the minimally inflamed rectum may demonstrate granulomatous lesions which directs the attention to the possible presence of regional enteritis.[72]

Laboratory findings often include leukocytosis, an elevation of the sedimentation rate, and the presence of occult blood in the stools. Melena is not a usual feature of this disease.[45]

Ancillary laboratory information such as alteration in serum electrolytes,[99] decreased plasma proteins,[111] and evidence of malabsorption may help show the severity of the illness but are not diagnostic of regional enteritis. Occasionally extensive disease of the ileum will be reflected by decreased vitamin B_{12} absorption as well as other indications of malabsorption. It has also been demonstrated there is a diminution of the net water and sodium absorption among patients with regional enteritis.[7] Elevation in the percentage of alpha-2 and beta globulins has been reported during active phases of the disease and diminishing with the remission of symptoms.[111] Similar trends have been noted in other diseases however, and it is likely that this finding only indicates a secondary response.

Roentgen findings may, and often do, establish the diagnosis when used in conjunction with the clinical observations. The barium enema is important and should be performed first, but examination of the small bowel with special emphasis on the terminal ileum often is necessary and always indicated if this area has not been clearly visualized in the colon study. Helpful signs include the "string sign" indicative of narrowing, dilation proximal to an

area of stricture, fixation of bowel loops, cobblestoning of mucosa, ulceration, and the presence of skip areas of involvement.[64] Obliteration or distortion of the fine parallel line running longitudinally in the terminal ileum may suggest early regional enteritis.[74] In spite of the importance of the roentgen examination, a negative study in a patient with the appropriate symptoms and signs does not exclude the diagnosis of this disease and repeat x-rays are sometimes indicated.

Regional enteritis has been misdiagnosed initially as anorexia nervosa and as depressive disorders.[68] Occasionally the clinical distinction between lymphosarcoma of the small bowel and regional enteritis is difficult. Adenocarcinoma and carcinoid tumors of the bowel have sometimes caused confusion.[13,71,97] Inflamed bowel, adhering to pelvic organs, may suggest pelvic inflammatory disease as the primary diagnosis.[81] Adherence to the urinary bladder occasionally may present urinary symptoms. Acute appendicitis, diverticulitis, specific granulomas, vascular disease (thrombosis or embolism), lymphogranuloma venerum, and others must also be considered in the differential diagnosis of regional enteritis.[37]

In addition to the findings mentioned above, the patient may present symptoms or signs of any of the many complications of the disease. These complications will be discussed shortly.*

TREATMENT

In Crohn's original article in 1932 he thought that the proper therapeutic approach to regional enteritis to accomplish a complete cure was surgical resection of the diseased segment of intestine. Medical treatment was statedly "purely palliative and supportive" but the results by operation "speak vehemently in favor of surgical methods as the logical successful therapeutic procedure."[28]

Later Crohn (1956) stated that while most cases of localized regional enteritis were admirably adaptable to surgical intervention, he points out his disappointment with the recurrence rates in the surgically treated regional enteritis patient. He then advised that until the lesion in the small intestine was localized, until it was well defined, or until it showed scarring and healing, to delay operation until the acute symptoms subside. Crohn further points out that in diffuse ileojejunitis, no surgical procedure is possible and the patient

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* See page 39

should be treated by "general measures and steroid therapy."[26] At this time he described medical management in some detail. It was noted in this diffuse disease that a high percentage of spontaneous recovery occurred and was among the most satisfactory form of the disease to be cured by conservative management.

Since Crohn's original article, the recognition of very high recurrence rates after resection of the diseased bowel has caused considerable conservatism concerning the surgical approach to regional enteritis. While there is still considerable disagreement among authors regarding the surgical versus medical management, many investigators now agree that the treatment of regional enteritis is primarily medical and that surgery should be reserved mainly for the complications of the disease.[8,11,29,33,43,103,110] Even those supporting the surgical approach recognize that non-surgical management is necessary both to help prevent recurrences and aid the extensively involved patient.[9,21,42]

The success of medical management varies greatly from author to author. Davis reports a failure rate of 94 percent by nonoperative management[33] while Daffner has had a 65 percent success![31]

A conclusion as to the proper choice of treatment is not possible in view of these varied reports.

The basis for non-surgical management is most difficult to determine. Although several etiological mechanisms have been suggested,* no single agent or agents have yet been indentified. Non-surgical treatment is, therefore, primarily supportive and symptomatic and supposedly specific measures are used only on theoretical or empirical grounds. Patients generally agreed as being best suited for medical treatment are those found to have acute ileitis, uncomplicated chronic enteritis, diffuse jejunoileitis, and selected cases of recurring enteritis after surgical management.[11,26,31,43]

Supportive Measures: Nutritional rehabilitation requires a sufficient caloric intake to supply energy needs of a frequently febrile catabolic state, to compensate for the intraluminal losses of protein,[99] blood and electrolytes,[49] and to provide sufficient excess to accomplish cellular repair and restoration of tissue. To accomplish this a low-residue diet high in protein content and adequate in palpable fats to meet caloric requirements is generally recommended.[26, 110]

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*See ETIOLOGY pages 14-23

A high caloric, 100 gram or more protein diet of low residue content and devoid of irritating agents is commonly utilized. Because of the diarrhea and malabsorption problems, 1000 to 2000 calories more than the usual intake, as calculated for age, sex and activity should be administered. It has been noted that a well constructed diet is especially important after surgical resection of diseased small bowel or by-pass procedures which not only reduce total absorptive area but become complicated by unexpected malabsorption defects.[8]

It has been recommended that four well-spaced meals a day are preferable to repeated small feedings which seem to initiate a sequence of abdominal pain, rectal tenesmus and diarrhea. Since symptomatic discomfort is usually greatest in the afternoon or evening, a large percentage of the day's calories have been recommended in the first two meals of the day.[107]

A careful dietary history should be taken to determine any food which might cause a symptomatic aggravation of the disease. Milk and milk products are especially important in this regard and if any are noted by history, they should be eliminated from the diet. However, rigid restrictions which

ignore the patients tastes and habits may be self-defeating.[110]

Vitamin supplements, particularly of the B-complex are indicated. In mild cases, twice the daily minimal requirements are recommended and may be administered orally. Following extensive resections this dosage may be much higher. Careful watch should be kept of the tongue, corners of the mouth, and skin for evidence of deficiency.[16]

Bleeding and anemia are considered rare by some authors[107] and common by others.[11] Oral iron preparations have been noted to increase abdominal discomfort and diarrhea.[8] Anemia in the post-operative patient may be macrocytic in nature and will respond well to folic acid and B_{12} supplement. Microcytic anemia should be given a trial of intramuscular iron preparation (Imferon). Blood transfusions are often necessary and prove of great value.[11]

During the acute phases of regional enteritis electrolyte disturbances often occur and may require appropriate intravenous replacements. Of interest is the observation that chronic potassium loss from diarrhea can weaken the power of contraction in the bowel wall and cause obstruction. This acute obstruction can be easily overcome by electrolyte restoration.[16]

It is recommended that physical activities be restricted during exacerbation of the disease in order to reduce caloric requirements as well as being a potential nonspecific benefit to the disease itself.[26] In view of the possible psychogenic factors influencing this disease, psychologic needs should be considered and help given in this area when possible.[46] The chronicity of regional enteritis as well as its sometimes debilitating effects requires a considerable emotional adjustment on the part of the patient. Simple sedatives may prove helpful in this connection. Physican understanding may prove adequate however. In difficult cases psychiatric consultation may prove beneficial.[68]

Medications: Sedatives such as phenobarbitol may be used to control crampy abdominal pain. The tranquilizing drugs such as meprobamate can also be useful if there is an aggravating emotional disturbance. Antispasmodic medication of the atropine-belladonna group are usually of little value in giving sustained symptomatic relief. The narcotics are generally not recommended because of the chronicity of the disease and the resulting danger of addiction.[8,67]

Sulfonamides are among the most useful drugs for the long term treatment of regional enteritis. They seem to suppress the inflammation and may be reasonably safely employed over long periods of time. Their function seems to curb secondary bacterial infection.[8]

The poorly absorbed preparations such as sulfasuxidine and sulfathalidine are often preferred because they rarely produce a toxic reaction. However Asulfidine is frequently more effective in subduing a flare-up and is likewise useful in resistant cases. Unfortunately it has many side-effects such as nausea, vomiting, skin rash, fever, lymphadenopathy, headaches, malaise, paresthesias, granulocytopenia, hemolytic anemia, hepatitis, and renal calculus formation. Such difficulties have been reported as high as 30-45 percent of the cases with Asulfidine.[37] Nevertheless, a number of patients can tolerate small doses more or less indefinitely and are greatly benefited by this drug.

Its dosage varies from 2 tablets every 3 to 4 hours during the acute stage to 1 to 3 tablets daily as a continuous maintenance. An average course is about three months. Immediate results do not usually occur, but within 3-7 days some encouraging improvements become apparent.

Antibiotics are recommended in treating purulent complications such as impending perforation but are not recommended routinely. The use of antibiotics carries the risk of staphylococcus enteritis and should not be used indiscriminately.

Steroids: No sound rationale can be given for the use of ACTH and corticosteroids in regional enteritis other than the emperical observation that they produce a clinical remission better than any other agent currently at hand. There is no definite evidence whether these agents inhibit the primary pathologic process or simply modify the secondary inflammatory reaction.[67] Supression usually occurs but relapses can be expected after the reduction of dosage or its discontinuance. Eisenstadt reports about 70 percent of the patients may expect a rather prompt, favorable effect within 48-72 hours after the iniation of steroid therapy.[37]

In mild cases steroid treatment often results in an elevation of mood, appetite increase, and a decrease in diarrhea. In fulminating disease, fever and toxemia decrease and often obviates premature surgical intervention. Steroids have been very useful in patients with extensive disease and in patients with recurrent disease after definitive operative treatment.

The employment of steroids in these latter conditions usually commits the patient to long-term therapy and requires special precautions to avoid adrenal failure should subsequent surgery be necessary. Since the patient is already prone to electrolyte inbalance, steroid treatment requires extra care to avoid potassium depletion.[16]

Recommended steroid dosages vary somewhat and their long-range use must be clinically titrated so as to give the smallest daily dose that affords an effective control of symptoms. Dosages are generally quite high:[110] intially ACTH gel 40 units parenterally every 12 hours followed in 7 to 10 days with prednisone orally at a level of 20 to 30 mg. per day in divided doses.[8, 26] Unfortunately a great number of undesirable side effects appear sooner or later with steroid treatment. These are well known and will not be listed in detail. Among them, the most feared complication is the development of permanent hypoadrenalism. In addition, steroid treatment of the regional enteritis patient have occasionally been noted an increased tendency towards hemorrhage and perforation.[26, 37]

Indocin (Indomethocin) a nonsteroid anti-inflammatory agent is under investigation at this time. The drug has been reported to be well tolerated in low dosage but numerous side-effects have been noted with large doses. More complete evaluation of this drug must await further investigation.[37]

Radiation: Radiation therapy, with its anti-inflammatory and fibrosing action as well as its effect on lymphoid hyperplasia and lymphocytic infiltration, has been recommended with enthusiasm by Bargen.[11] Clinical evaluation at this time is difficult. Some patients experienced a favorable result but long-term results have not been encouraging, nor has irradiation received general acceptance. It is possible that radiation therapy will be useful in managing the patient with extensive involvement and who is in poor physical condition, and the recurrent case after multiple resections. Evidence remains to be gathered as the advisability of this treatment and the potential hazards.

The indications for operation in regional enteritis may be absolute or relative. Absolute indications include acute or chronic obstruction, fistulae, abscess, perforation and massive hemorrhage.

The relative indications involve a clinical judgement concerning deteriorating health despite adequate medical management, abdominal mass, acute lower abdominal disease when the diagnosis is in doubt, and multiple perirectal fistulae with anal incontinence. See Table II. Other complications, local and multi-systemic, will be outlined shortly. These also influence the choice of management for the individual patient.

TABLE II Indications for Operations in 304 patients (Adapted from Colcock)[20]

Finding	Percentage
Obstruction	83.6
Internal Fistula	18.1
External Fistula	17.1
Abdominal Mass	16.8
G. I. Bleeding	8.9
Acute Perforation	2.9
Acute Abdominal Pain	2.6

PROGNOSIS

In most patients regional enteritis, is relatively benign, despite periodic exacerbations and remissions. The death rate of 0.08 per 100,000 population in this country is much lower than that of ulcerative colitis.[3] The age of the patient at the onset of the disease and the site of occurrence of the inflammatory process are important factors in

determining the severity of the disease. The disease seems to be more severe when the patient is young or when more than the terminal ileum is involved. Early observations noted that the occurrence of metaplastic pyloric-type glands in areas of involved small bowel correlated with a high recurrence rate.[55] More recent studies have not confirmed this association, however.[5] Although the lesions may remain stable, occasionally the inflammation will progress until the entire colon is involved.[52]

Not more than 10% of the patients remain cured after the initial attack. The rest suffer periodic exacerbations. One third of these can be maintained in satisfactory health with a well supervised medical program. The other two thirds will require an operation of some sort.[8] Careful medical management can maintain half or more of this latter group in good health without requiring further surgical procedures.[20]

Regional enteritis during pregnancy does not usually threaten the mother or child. This is in contrast to ulcerative colitis in which pregnancy is an alarming complication. In most cases the pregnancy is uneventful and neither the fetus nor mother is seriously affected by the disease.[26]

The relationship between acute and chronic regional enteritis is ill-defined.[69] Acute disease is often present in children.[101] Presumably chronic regional enteritis begins as an acute process, but in many instances an initial mild reaction may progress to the chronic state with no overt transition through the acute stage. It has been estimated by some observers that one-fourth of the acute patients progress to chronic enteritis, while some of the remaining have no further symptoms.[62, 47] However, in prolonged observation of the patients, recurrences have been noted after twenty years of quiescence.[103]

Regional enteritis may be associated with numerous intestinal and rectal complications including partial to complete obstruction of the bowel, fistula, and perianal abscesses. Intra-abdominal abscesses are not uncommon and may involve the presacral space[54] or present in the region of the thigh by extension along tissue planes.[35] Perforation of the small intestine in regional enteritis necessitates consideration of this problem in the differential diagnosis of the acute abdomen.[30,76,85] Bright red rectal bleeding or melena occasionally occurs as a result of ulcer penetration into larger blood vessels.[45] There has been noted an increased incidence of

nephrolithiasis[34] and urinary obstruction due to involvement of the ureter by inflamed bowel and mesentry.[84] Hepatic complications such as biliary cirrhosis[79] and multiple suppurative liver abscesses occur. Adenocarcinoma of the small bowel, originally thought not to be associated, has been reported in regional enteritis with increasing frequency.[108,112]

Systemic complications include malabsorption, arthritis,[41] rheumatoid spondylitis,[2,66] erythema nodosum,[53] retardation of growth and clubbing of the fingers. Secondary amyloidosis may complicate regional enteritis and ultimately result in renal failure due to kidney involvement.[109] Rheumatoid spondylitis has been reported twenty times higher in regional enteritis than in the general population.[2]

SUMMARY

In the thirty-five years that will soon have elapsed since regional enteritis was introduced to the medical scene, progress has been made in establishing its physical and clinical features. Although the etiology remains unknown, genetic, immunologic, and "toxic" agents in the intestinal content are receiving strong consideration.

The earliest pathologic abnormalities seen include submucosal edema and lymphangiectasia. These changes are apparently implicated in the development of the characteristic tissue reactions of regional enteritis. Inflammation of the lymphatics appears to be a significant component of the disease.

The symptoms and signs of cramping abdominal pain, fever, diarrhea, weight loss, and anemia in young persons are strongly suggestive of regional enteritis. The diagnosis may be obscure, however, presenting as unexplained growth retardation or fever. X-ray examination of the small intestine is often very helpful in establishing the diagnosis.

The clinical course of regional enteritis is often characterized by many complications, especially involving the small intestine and perirectal region. Systemic complications are recognized with increasing frequency.

Many authors now agree that the treatment of regional enteritis is primarily medical and that surgery should be reserved for the complications of the disease. Medical management 1s complex requiring a broad approach of adequate nutrition, physical and emotional rest, and chemotherapeutic agents. Adrenal corticosteroids and cort1cotroph1n have been useful adjuncts 1n treatment, but their ultimate value in this disease are not clear. Roentgenotherapy, recently recommended, is a doubtful aid in the management of lesional enteritis.

Surg1cal intervention is frequently required tor management of the complications *ot* reg1cnal enteritis, but its usefulness is limited Wythe frequent recurrences, and, at times, by relentless progression of the disease. In any instances, despite exacerbations and remissions, the course of the disease appears relatively mild or controllable. Though "spontaneous" cures are infrequent, they have been observed. An important recent concept 1s the realization that any portion of the gastrointestinal tract is vulnerable to regional enteritis.

CONCLUSIONS

At the present time, lymphedema is considered the hallmark feature in the pathogenesis of regional enteritis. The etiology of this disease remains unknown. Genetic, immunologic and toxic agents--alone or in combination--appear to be important considerations.

Careful medical management is the treatment of choice in regional enteritis. There have been no major advances in therapy in recent years, nor are any likely until the etiologic mechanisms are better understood. Surgical treatment should be reserved for the complications of regional enteritis.

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