# ULCERATIVE COLITIS AND ITS COMPLICATIONS

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Ulcerative colitis is a disease of unknown etiology that essentially involves the large intestine exclusively. There are crypt abscesses and superficial ulcerations of the colonic mucosa. Patients commonly present with rectal bleeding or with bloody diarrhea. The disease involves many other organ systems including the skin, musculoskeletal system, eyes, liver, etc. There is a much higher incidence of carcinoma of the colon than in the population at large. The clinical course varies widely but the majority of patients have recurrent episodes over many years with significant morbidity and increased mortality. Since the availability of steroids and nonabsorbable sulfa drugs, more effective therapy for both acute and chronic symptoms is available.

## *Prevalence and Incidence*

The incidence of new cases diagnosed as ulcerative colitis is relatively uniform in the populations of Western European derivation. As shown in Table 1

TABLE 1.
PREVALENCE AND INCIDENCE VALUES FOR ULCERATIVE COLITIS FROM THE LITERATURE

| Authors | Period | Area | Prevalence per 100,000 inhabitants | Incidence per 100,000 inhabitants per year |
|---|---|---|---|---|
| Evans & Acheson 1965 | 1951-1960 | Oxford | 79.9 | 6.5 |
| Gjone & Myren 1964 | 1956-1960 | Norway | | 2.06 |
| Lindenberg & Aagaard 1964 | 1940-1961 | Denmark | | 1.6 |
| Monk et al. 1967 | 1960-1963 | Baltimore | | 4.5 |
| Wigley & MacLaurin 1962 | 1954-1958 | New Zealand | | 5.6 |
| Bonnevie & Anthonisen | 1961-1967 | Copenhagen County | 44.1 | 7.3 |
| Mean | | | 62.0 | 4.6 |

the incidence varies from 1.6 in an early Danish study to 7.3 per 100,000 inhabitants per year in a more recent study from the immediate Copenhagen area. The mean incidence is approximately 5 cases per 100,000 inhabitants per year. The incidence is lower in Black and Oriental populations and is more common in White Jews than in non-Jews. Despite these differences in apparent incidence, it should be emphasized that ulcerative colitis may occur in patients of any racial or ethnic background. As also shown in Table 1 the prevalence of this disease per 100,000 inhabitants varies from approximately 40 to 80 cases, at least in Denmark and England, the two countries from which these data are derived.

Patients affected with this disease clearly have an excessive mortality rate when compared with age-matched controls. As shown in Table 2 the mortality rates per 100,000 inhabitants per year are remarkably similar in the western

TABLE 2.
MORTALITY VALUES FOR ULCERATIVE COLITIS FROM THE LITERATURE

| Authors | Period | Area | Mortality per 100,000 inhabitants per year |
|---|---|---|---|
| Acheson 1959 | 1952-1956 | USA | 0.47 |
| | 1952-1957 | Canada | 0.49 |
| | 1953-1955 | England/Wales | 0.85 |
| Evans & Acheson 1965 | 1951-1960 | Oxford | 0.7 |
| Mosbech 1960 | 1951-1959 | Denmark | 0.5 |
| Wigley & MacLaurin 1952 | 1954-1958 | Wellington, New Zealand | 0.9 |
| Bonnevie, Riis, Anthonisen | 1961-1967 | Copenhagen County | 0.6 |
| Mean | | | 0.64 |

countries from which data are available. These values range from .47 to .9 deaths per 100,000 inhabitants per year and average .64.

The vast majority of cases of ulcerative colitis occur sporadically yet, as shown in Table 3 there is a higher incidence in ulcerative colitis of having similarly affected family members than would be expected by chance alone. Thus, in over 3,000 cases there was a history of 1 or more relatives with the same disease in approximately 3% of the cases. In a few reported families there has been a remarkable clustering of the disease. These cases are outlined in detail in the accompanying references.

TABLE 3.
FREQUENCY OF FAMILY HISTORY IN U.C. AND CROHN'S DISEASE

| | No. Cases | Percent |
|---|---|---|
| U.C. | 3084 | 3% |
| Crohn's Disease | 985 | 4% |

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*Pathology*

In almost all cases of ulcerative colitis the rectal mucosa is involved in the pathologic process and, in various patients, the disease process extends proximally for variable distances. In the common form of moderately severe ulcerative colitis the disease usually extends at least to the mid-transverse colon and commonly involves the entire colon. The disease does not involve the small bowel, however. The earliest histologic lesion is the appearance of scattered PMN leukocytes about the base of the crypts. These cells can be seen moving outward between mucosal columnar cells into the crypt lumen. At a slightly more advanced stage there is dissolution of the basement membrane and destruction of the villus epithelium with formation of a crypt abscess. At this stage it is common to see streamers of pus cells and mucus pouring out into the colonic lumen. With fusion of adjacent crypt abscesses there is microscopic and gross ulceration of the surface epithelium and bleeding from markedly distended superficial vessels. The abscesses commonly burrow beneath the mucosa to form mucosal bridges. Despite this marked inflammatory reaction in the superficial mucosal layers of the colonic mucosa, there usually is relatively little involvement beneath the muscularis mucosa so that adhesion of the colon to adjacent organs is minimal and there seldom is fistula formation except in the perianal area.

This histopathology is in sharp contrast to that seen with Crohn's disease. In Crohn's disease there is marked thickening of the submucosal tissue with a profuse infiltrate of chronic inflammatory cells and plasma cells. This infiltrative process also invades the muscularlayer and extends to the serosal surface. In at least half the cases, in addition, there are collections of cells in the submucosal tissue and on the serosal surface that resemble epithelioid granulomas. Because of marked involvement of the serosal surface there characteristically is adherence of the involved bowel to surrounding structures such as the peritoneal surface, bladder dome, vagina, adjacent bowel loops and other intra-abdominal structures. Deep, penetrating clefts form from the ulcerated superficial mucosa through the submucosa and muscular layers into adjacent organs or to the outside of the body. Crohn's disease may involve any area of the gastrointestinal tract

from the esophagus to the anus but most commonly is seen in the terminal small intestine.

While in many instances the histopathology of these two diseases is indistinct in that both may present with diffuse inflammation and superficial mucosal ulceration, there characteristically are differences in the behavior and in pathology that should be emphasized: 1) ulcerative colitis is seen exclusively in the colon while Crohn's disease may occur at any level of the bowel, 2) granulomas, when present, are characteristic of Crohn's disease and are not seen in ulcerative colitis, 3) ulcerative colitis is classically a superficial ulcerative mucosal disease while Crohn's disease is an infiltrative transmural disease, 4) serosal reaction with adherence to adjacent structures and fistula formation is characteristic of Crohn's disease but is very uncommon in ulcerative colitis, 5) free perforation into the peritoneal cavity, however, is rare in Crohn's disease but may occur in the acute fulminating forms of ulcerative colitis.

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## *Clinical Course*

Characteristically the initial symptom of ulcerative colitis is rectal bleeding. At first, such bleeding may occur as blood streaking on the outside of the well formed stool. Invariably, however, the symptoms progress to a bloody diarrhea in which significant amounts of mucus and pus also may be evident. The onset of the disease may be insidious or the illness may begin with an acute fulminating attack of bloody diarrhea. Occasionally, the disease begins with what appears to be an attack of acute shigellosis or amoebiasis that fails to respond to appropriate therapy. Prior to the use of steroids there was approximately a 10-12% mortality with the first attack. With the advent of steroid therapy this mortality has dropped to only 4-5%. Approximately 10% of

TABLE 4.
CLINICAL COURSE AFTER FIRST ATTACK
(250 Patients)

| | | |
|---|---|---|
| Death During First Attack | | 2-4.5% |
| Chronic Intermittent | | 64% |
| Chronic Continuous | | 8-10% |
| No Subsequent Attacks | 5 yrs. | 13% |
| | 10 yrs. | 14% |
| | 15 yrs. | 9% |

patients experience only a single attack and remain essentially asymptomatic for many years thereafter. The vast majority of patients, however, follow the more classic pattern of either chronic intermittent or chronic continuous colitis. These patients usually have low grade rectal bleeding and diarrhea interspersed with acute attacks during which they become acutely worse and have fever, white blood cell count elevations, accentuation of the bloody diarrhea, fluid and potassium loss and, commonly, extracolonic complications. There is a significant mortality with each acute attack of the disease.

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## *The Diagnosis of Ulcerative Colitis*

Since there are no specific serologic, chemical or histologic methods of diagnosing the syndrome of ulcerative colitis, this diagnosis depends upon the demonstration of a characteristic group of clinical findings and the specific exclusion of diseases that may mimic ulcerative colitis. While lymphoma, metastatic carcinoma, lymphogranuloma venereum and vascular insufficiency at times may be confused with ulcerative colitis, more commonly it is important to rule out amoebiasis and Crohn's disease of the colon. As outlined in Table 5 a patient presenting with the onset of rectal bleeding or bloody diarrhea should

TABLE 5.
DIAGNOSIS OF U.C.

| | Reason | Conditions |
|---|---|---|
| 1) Sigmoidoscopy | 1) Mucosal Appearance<br>2) Mucosal Smear<br>3) Parasites | 1) Don't Biopsy<br>2) Don't Prep |
| 2) Barium Enema with Ileal Spill | 1) Delineate Extent Disease<br>2) Look for Ileal Involvement | 1) Don't Do In Seriously Ill Patient |
| 3) Small Bowel Series | 1) Look for SB Lesions | 1) Don't Do In Seriously Ill Patient |
| 4) Biopsy of Rectum | 1) Look for Compatible Pathology<br>2) Look for Granuloma<br>3) Look for Amoeba | |

first be sigmoidoscoped with no prior colonic preparation. Administration of any kind of enema, barium or a variety of mediactions will make the search for amoeba fruitless. At this sigmoidoscopic examination the appearance of a mucosa should be observed for the presence of friability, bleeding and ulceration and preparations should be made for ova and parasites. Most important, a portion of clean mucosa should be firmly wiped with a dampened cotton applicator. This applicator should then be smeared on a dry slide and stained for blood cells. The presence of many PMN leukocytes is diagnostic of inflammatory bowel disease and these cellular elements may be present even when the bowel mucosa grossly appears normal. No biopsy should be taken at this time since this procedure would preclude a barium enema. After sigmoidoscopic examination a barium enema should be done with an effort to obtain ileal spill. This allows one to evaluate the extent of the colonic disease as well as to determine if there is inflammatory disease of the terminal ileum. In most cases a small bowel series should be undertaken next in order to determine if inflammatory bowel disease is present in more proximal portions of the small intestine. Finally, if the diagnosis is still equivocal repeat sigmoidoscopy may be done with rectal biopsy. Such a biopsy may reveal histopathology typical of and compatible with ulcerative colitis but it may also reveal the presence of granuloma or amoebic forms. In extremely ill patients during very acute attacks barium enemas should be done only with extreme caution since this may lead to further exacerbation of the disease or even perforation of the colon.

The presence of amoeba either in rectal smears or in rectal biopsies obviously demands appropriate anti-amoebic therapy. In addition, any case of apparent ulcerative colitis in which there is a reasonable suspicion of amoebiasis should be treated appropriately. The presence of ileal disease, predominantly right-sided colitis, segmental colitis, sparing of the rectal mucosa, fistula or sinus tracts or granuloma in the rectal biopsy all strongly suggest that the inflammatory colon disease is Crohn's disease and not ulcerative colitis. The diagnosis of ulcerative colitis, then, depends upon the demonstration of an inflammatory, ulcerative mucosal disease that is present in the rectum and

that extends proximally for variable distances, the absence of amoeba and the absence of findings characteristic of Crohn's disease.

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## *Clinical Course in Specific Subsyndromes*

*Ulcerative Colitis in the Elderly*. While ulcerative colitis most commonly has its onset in the younger age groups, approximately 10-15% of patients will have their first symptoms after the age of 50. Such patients may present with watery diarrhea without blood, massive lower bowel hemorrhage, typical bloody diarrhea, nonspecific abdominal cramps and pain, intestinal obstruction or acute fulminating colitis. The major point to be emphasized is that ulcerative colitis may begin abruptly in this age group, otherwise the same general considerations outlined above apply. In addition to the differential considerations outlined for younger patients, the possibility of colonic carcinoma and mesenteric vascular occlusion with mucosal ischemia should be more strongly considered in the work-up of these patients.

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*Ulcerative Colitis in Childhood.* Ulcerative colitis may have its onset at any age during childhood including infancy. Again there is significant morbidity and mortality; there is approximately a 40% mortality in this group by the age of 20 as compared to an expected mortality of only 2%. In approximately 10-15% of these children death occurs because of complications of progressive disease, secondary to operative intervention, infection, liver disease, perforation and intestinal hemorrhage. Approximately 10% die of carcinoma of the colon and rectum. Since these children have had the onset of their disease at early age, it is not uncommon to develop carcinoma in the late-teens or early-twenties. However, it should be pointed out that this 10-15 year delay in the onset of malignancy is seen in adults and even elderly patients at the same time interval after the onset of their symptoms. That is, the average interval between the onset of the disease and the development of carcinoma is approximately 15 years in children and 17 years in adults. Thus, with respect to the complication of development of carcinoma there is no difference between children and adults. One of the most unique features of ulcerative colitis in childhood is the accompanying cessation of growth evident in children with serious diffuse ulcerative colitis. While steroids theoretically may contribute to growth failure, it should be emphasized that in many instances successful control of active colon disease by steroid administration is accompanied by a return to normal or near normal growth patterns.

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*Ulcerative Colitis in Pregnancy.* Occasionally ulcerative colitis may manifest its first symptoms during pregnancy. In such cases there is the impression that the disease may be particularly severe. In patients with well established disease who become pregnant the disease generally becomes worse during the first trimester and in the postpartum period while remissions are common during the second and third trimesters. In one series of 80 pregnancies, for example, there were 11 acute attacks during the first trimester and 19 acute attacks in the postpartum period; only 7 acute attacks occurred during the second and third trimesters, however. The outcome of the pregnancy is generally good, and in approximately 80% of the cases a normal full-term delivery will occur.

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*Ulcerative Proctitis*. This represents a special subsyndrome of generalized ulcerative colitis in which the ulcerative disease is localized to the most distal portions of the colon, principally the rectum. Sigmoidoscopically the mucosa is characteristic of ulcerative colitis and a mucosal smear will demonstrate abundant PMN leukocytes. It may be possible in many cases to reach normal mucosa above the involved area with the sigmoidoscope. Characteristically, the barium enema is perfectly normal or, at most, shows minimal ulcerative changes in the rectal segment. In general, this is a relatively benign syndrome which is associated with a much lower incidence of local and distal complications and which usually responds well to local topical steroid therapy. This form of disease must be distinguished from Crohn's disease involving the rectum, localized amoebiasis, local carcinoma or lymphoma, radiation proctitis, lymphogranuloma inguinale, gonorrhea, syphilis and proctitis due to chemical or mechanical irritation.

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## *General Complications of Ulcerative Colitis*

Ulcerative colitis is associated with complicating lesions throughout the body. In general, these may be divided into those which result from local extension of the colonic disease and those that involve remote organ systems. As listed in Table 6 there are a variety of complications in and around the colon. These are all relatively infrequent and many are of relatively minor consequence. However, such lesions as ischio-rectal abscess, recto-vaginal fistula, bowel perforation, acute toxic dilatation of the colon, massive

TABLE 6.
LOCAL COMPLICATIONS OF U.C. IN 624 PATIENTS

| | |
|---|---|
| Ischio-rectal abscess | 4.0% |
| Fistula-in-ano | 4.2% |
| Recto-vaginal fistula | 3.8% |
| Entero-colic fistula | 0.5% |
| Rectal prolapse | 1.3% |
| Hemorrhoids | 20.7% |
| Fibrous stricture | 6.3% |
| Pseudo-polyposis | 14.9% |
| Perforation | 3.2% |
| Acute dilatation of the colon | 1.6% |
| Massive Hemorrhage | 3.4% |
| Carcinoma of the colon | 3.5% |

hemorrhage and carcinoma of the colon are, by-and-large, indications for immediate surgical intervention and are discussed later in this protocol. As shown in Table 7 there are a variety of more distant complications many of which presumably arise from complex and poorly understood auto-immune phenomena. These complications include a variety of skin lesions, arthritis, eye lesions, transient or progressive hepatic disease and mucosal membrane lesions such as ulceration or moniliasis. In addition, during acute severe episodes a majority of patients demonstrate protein-losing enteropathy and significant anemia. There is commonly extracellular fluid volume loss and, in particular, significant potassium secretion.

TABLE 7.
SYSTEMIC COMPLICATIONS OF U.C. IN 624 PATIENTS

| | |
|---|---|
| Erythema nodosum | 2.2% |
| Pyodermia gangrenosum | 0.6% |
| Other skin eruptions | 15.9% |
| Arthritis | 5.6% |
| Ankylosing spondylitis | 1.8% |
| Eye lesions | 7.5% |
| Transient hepatitis | 4.8% |
| Chronic hepatitis | 2.6% |
| Renal disease | 4.6% |
| Pulmonary embolism | 1.6% |
| Venous thrombosis | 6.4% |
| Oral aphthous ulceration | 8.2% |
| Oral moniliasis | 1.8% |
| Extensive moniliasis | 0.5% |
| Osteoporosis | 1.4% |
| Anemia due to ulcerative colitis | 20.4% |
| Other disorders of the blood | 2.9% |

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## *Specific Complications: Skin Lesions*

The skin and mucus membrane commonly are involved as a distal, major extracolonic complication of active ulcerative colitis. Table 8 reports the incidence in various series from a total of 3297 cases of chronic ulcerative colitis. The incidence varies from 2.4% to 34%. The latter series, by Siamitz and Greenberg is probably one of the more reliable since it was undertaken by both a dermatologist and a gastroenterologist. As illustrated by the data in Table 9 the skin lesions can be broken down into four major groups of lesions: aphtha ulcers and other lesions of the mucus membrane of the mouth and esophagus, ulcerating lesions of the skin, urticaria and erythema nodosum-like lesions. Aphthous ulcers of the mouth are among the most common mucocutaneous lesions. Ocassionally there is an accompanying mucocutaneous syndrome involving the esophagus. It is not uncommon for the aphtha lesions to precede or to become manifest within 24-48 hours of an acute attack of ulcerative colitis. Other lesions of the mouth include glossitis, stomatitis and gingivitis. Pyoderma gangrenosum is one of the most severe and significant dermatologic complications of ulcerative colitis. It usually begins as a subepithelial bulla which becomes milky and frankly purulent, but it is usually sterile. When the bulla bursts, it leaves a raw, oozing crusted area which may become secondarily infected. The lesions may spread resulting in massive loss of skin over large areas of the extremities

TABLE 8.
INCIDENCE OF SKIN LESIONS IN 3297 CASES OF U.C.

| | |
|---|---|
| Bargen | 2.4% |
| Ricketts and Palmer | 11.0% |
| Warren and Sommers | 9.0% |
| Collected Series | 3.8% |
| Siamitz and Greenberg | 34.0% |
| Average | 12.0% |

TABLE 9.
TYPES OF SKIN LESIONS SEEN IN U.C.

| | | |
|---|---|---|
| Aphthae and other Mouth Lesions | (30%) | - Aphthous ulcers<br>Glossitis<br>Stomatitis<br>Gingivitis |
| Ulcerations and Pyodermas | (24%) | - Pyoderma Gangrenosum<br>Decubiti |
| Urticaria (including palmar erythema) | (17%) | - Urticaria<br>Petechia<br>Palmar Erythema<br>Pigment Changes |
| Erythema Nodosum-like | (12%) | Erythema Nodosum |

and trunk. It is clear from the literature that more than half the cases of pyoderma gangrenosum occur in individuals with chronic bowel disease. In those cases reported to occur in the absence of ulcerative colitis or Crohn's disease, the patients often report some sort of bowel dysfunction and few of these cases have been worked-up to evaluate the possibility of occult ulcerative colitis. The third major group of skin lesions include erythema nodosum and erythema marginatum. These lesions may precede acute attacks of ulcerative colitis or, in well established chronic recurrent cases, may appear in crops with each acute attack. In general, most mucocutaneous lesions relate to the degree of activity of the bowel disease. When the active ulcerative colitis is controlled either by steroid therapy or by colectomy there is usually rapid and spontaneous resolution of the skin lesion. However, it should be emphasized,that the appearance of aphtha ulcers, pyoderma gangrenosum or erythema nodosum-like lesions in otherwise asymptomatic patients should be an indication for careful GI history and for proctoscopic examination including a careful mucosal smear.

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### *Specific Complications: Eye Lesions*

Eye lesions, usually inflammation of the uveal tract, are another relatively common manifestation of ulcerative colitis. As shown in Table 10, in one series of 465 patients the overall incidence was approximately 4%. In general, the highest incidence of ocular complications occurs with the most severe attacks of colitis in patients with the greatest extent of colonic involvement. In contrast to other extracolonic complications, however, eye lesions are more common during the first several years of symptomatic colitis and become relatively uncommon after very prolonged chronic ulcerative colitis. The ocular complications usually respond to local steroid therapy and do not dictate a

TABLE 10.
FREQUENCY OF EYE LESIONS IN 465 PATIENTS WITH U.C.

| | |
|---|---|
| Episcleritis | 7 |
| Iritis | 5 |
| Blepharo-keratitis | 2 |
| Choroiditis | 1 |
| Dacryostenosis | 1 |
| Interstitial keratitis | 1 |
| Overall Incidence | 3.6% |

need for colectomy. However, in patients whose colitis is controlled by colectomy or by systemic steroid therapy there is spontaneous resolution of the ocular manifestations in a majority of the cases. While in most cases there is a general parallelism between the severity of the colitis and attacks of non-granulomatous uveitis or episcleritis, there are case reports in which dissociation of the two clinical syndromes occurs. Most important there are cases in which the uveitis preceded the onset of symtoms referable to the GI tract. This again points up the importance of looking for occult ulcerative colitis particularly in young individuals who present with idiopathic anterior uveitis. Finally, several cases of the mucocutaneous-ocular syndrome have been reported in patients apparently having ulcerative colitis.

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### *Specific Complications: Arthritis*

Arthritic complications occasionally appear simultaneously with the onset of ulcerative colitis, more commonly appear after the appearance of GI symptoms and, rarely, may precede symptoms of bowel dysfunction. As shown in Table 11, the incidence of arthritis in various large series of ulcerative colitis varies from less than 1% to as high as 22%. However, in most recent series where attention has been paid to the extracolonic complications the incidence of arthritic involvement has averaged approximately 20%. Generally speaking, the severity of the arthritic manifestations parallels the severity of the disease in the colon. Arthritis is more common in individuals with more extensive colonic involvement and the incidence of arthritic attacks is highest in patients with a more prolonged symptomatic bowel syndrome.

As shown in Table 12, musculoskeletal involvement in patients with ulcerative colitis can be broken down into three specific groups. The first of these which involves arthralgias and arthritis accounts for about 60% of the cases and is commonly referred to as "colitic arthritis". As summarized in Table 13 this type of arthritis usually affects large joints (knees, ankles and elbows) in an asymmetrical fashion. The severity of the arthritic attacks parallels closely the degree of colonic involvement (Table 14) and tends to be more severe and more common in ulcerative colitis of long duration. The arthritis usually does not produce joint destruction and spontaneously subsides with control of colitis

TABLE 11.
INCIDENCE OF ARTHRITIS IN ULCERATIVE COLITIS

| Date | Total No. of Patients with Colitis | Percentage with Arthritis |
|---|---|---|
| 1930 | 693 | 4.3 |
| 1935 | 40 | 2.5 |
| 1935 | 50 | 4.0 |
| 1938 | 871 | 6.3 |
| 1938 | 88 | 0.8 |
| 1938 | 66 | 7.5 |
| 1942 | 145 | 8.3 |
| 1946 | 206 | 5.8 |
| 1948 | 100 | 8.0 |
| 1949 | 85 | 22.0 |
| 1950 | 112 | 9.0 |
| 1950 | 129 | 5.4 |
| 1950 | 2,000 | 7.7 |
| 1951 | 147 | 7.5 |
| 1952 | 267 | 7.1 |
| 1956 | 148 | 0 |
| 1956 | 131 | 13.0 |
| 1956 | 182 | 22.0 |
| 1957 | 138 | 2.2 |
| 1957 | 180 | 22.0 |
| 1958 | 109 | 21.0 |
| 1958 | 108 | 15.7 |
| Total | 5,995 | 9.1 |

TABLE 12.
MUSCULOSKELETAL INVOLVEMENT
IN ULCERATIVE COLITIS

| | |
|---|---|
| Overall Incidence in Patients with U.C. | 20% |
| Arthralgias and Arthritis ("Colitic arthritis") | 60% |
| Ankylosing Spondylitis | 25% |
| Miscellaneous forms, unrelated to U.C. | 15% |

TABLE 13.
SUMMARY OF CHARACTERISTICS OF COLITIS ARTHRITIS

| | |
|---|---|
| Joints Involved | Commonly large joints (knees, ankles and elbows) involved asymmetrically |
| Relationship to Colitis | More common in U.C. of long duration and extensive colon involvement. Rarely precedes U.C. |
| Prognosis | That of colitis, rarely does arthritis produce permanent deformity |
| Sex Incidence | Equal to incidence of U.C. |
| Relationship to Other Extracolonic Diseases | Associated with eye, mouth and skin lesions |
| Laboratory Findings | ↑ WBC<br>Anemia<br>↑ ESR<br>Rheumatoid factor absent<br>Antinuclear factors may be present<br>X rays of joints minimal to no change |
| Synovial Fluid | Turbid but sterile<br>5000-7000 WBC/$cm^3$ mostly PMN<br>Fair mucin clot<br>Reduced viscosity<br>Normal sugar or slightly decreased |

TABLE 14.

Relationship of Arthritis to Extent of Colon Involvement

| | Entire Colon | Transverse and Descending | Descending | Rectum |
|---|---|---|---|---|
| % Arthritis | 22% | 22% | 12% | 5% |

by medical or surgical means. Typically, synovial fluid from an affected joint is turbid but sterile, contains 5000-7000 WBC's per $cm^3$ and has reduced viscosity. Typically rheumatoid factor is absent but antinuclear factors may be present in the blood.

The second major category of arthritic involvement in ulcerative colitis is ankylosing spondylitis. This accounts for approximately one-fourth the cases of chronic bowel disease complicated by arthritic complaints. Depending upon whether the diagnosis was based upon radiographic or clinical grounds the incidence, as shown in the lower portion of Table 16, in many series of patients with ulcerative colitis is commonly quoted to 3-5%. Another critical question, however, is given a group of patients who present with ankylosing spondylitis, what percent have underlying chronic bowel disease? As shown in the upper portion of Table 16 such statistics commonly are based upon a history of diarrhea and weight loss; in this series of 560 patients with established ankylosing spondylitis 3% were said to have ulcerative colitis. However, it is quite clear that such series represent gross underestimations. For example, in Table 15 Brown and Doll reported only a 0.2% incidence of ulcerative colitis in 13,352 cases of ankylosing spondylitis. These and other series in the literature are largely based upon a very imprecise and uncritical evaluation of patients for chronic inflammatory bowel disease. In the series by Jayson and Bouchier, 33 patients with ankylosing spondylitis and minimum or no gastrointestinal complaints were subjected to sigmoidoscopic examination and barium enema. Six of these patients (18%) were found to have occult ulcerative colitis. Again, it should be emphasized that in patients with rheumatoid factor-negative arthritis or ankylosing spondylitis there should be a diligent search for chronic inflammatory bowel disease regardless of whether the patient is asymptomatic or not.

TABLE 15.
INCIDENCE OF U.C. IN PATIENTS
PRIMARILY DIAGNOSED AS HAVING ANKYLOSING SPONDYLITIS

| | |
|---|---|
| Brown and Doll (1957) | - 22 of 13,352 A.S. died of U.C. (0.2%) |
| Jayson and Bouchier (1968) | - 33 patients with A.S. subjected to B.E. and sigmoidoscopy → 6 found to have U.C. (18%) |

TABLE 16.

560 patients with established ankylosing spondylitis ⟶ 20 gave history of diarrhea and weight loss; 14 diagnosed as U.C. (3%)

5 patients had x ray evidence of ankylosing spondylitis (3%) ⟵ 170 patients with established U.C. or Crohn's Disease

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Finally, it should also be recognized that there is commonly an association between the presence of arthritis and the presence of other complicating skin, oral and uveal lesions. Erythema nodosum, in particular, appears to occur with a high frequency in ulcerative colitis associated with various arthritic complaints.

TABLE 17.
ASSOCIATION OF SKIN LESIONS, ORAL ULCERS AND UVEITIS WITH ARTHRITIS IN U.C.

(Total of 108 patients, 17 had U.C. arthritis)

| | | |
|---|---|---|
| % Total with Skin Lesions | - 11% | (50% Arthritis) |
| % Total with Oral Ulcers | - 24% | (31% Arthritis) |
| % Total with Uveitis | - 8% | (44% Arthritis) |

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## *Specific Complications: Liver Disease*

It is now well recognized that chronic inflammatory bowel disease, both ulcerative colitis and Crohn's disease, cause significant liver abnormalities. Pathologically this dysfunction is manifest by fat infiltration and by a "triaditis", i.e., an infiltration of the portal triads by inflammatory cells and plasma cells. Clinically such hepatic involvement is manifest by three

specific syndromes. First, the patient may have no overt liver dysfunction other than liver functional abnormalities such as an elevated alkaline phosphatase or BSP. Second, some patients with chronic inflammatory bowel disease manifest a cholestatic syndrome with jaundice, severe itching, elevated bilirubin levels, elevated phosphatase and normal SGOT values. A third, less common syndrome is that of recurrent cholangitis with fever, elevated white count, an enlarged tender liver, elevated bilirubin, elevated alkaline phosphatase and SGOT. At surgical exploration or autopsy there is no evidence of obstructive biliary tract disease. Both of these clinical syndromes tend to recur and tend to be independent of the severity of the underlying ulcerative colitis. Again, it should be emphasized that the bowel symptoms may be minimal or none existent and the patient may present with the symptoms of either the cholestatic or cholangitic syndrome. Any patient who has such symptoms without apparent cause or in whom a liver biopsy has demonstrated a triaditis should be investigated for occult colitis.

TABLE 18.
LIVER DISEASE IN U.C.

| | |
|---|---|
| Pathology | 1) Fatty Change<br>2) Triaditis |
| Clinically | 1) Liver Function Abnormalities<br>↑ Alk. Phosphatase, ↑ BSP<br>2) Cholestatic Syndrome<br>↑ BR, ↑ Alk. Phosphatase<br>3) Cholangitic Syndrome<br>Fever, ↑ WBC, tender liver,<br>↑ BR, ↑ Alk. Phosphatase,<br>↑ SGOT |

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## *Specific Complications: Cancer*

Carcinoma of the colon is one of the most serious complications of chronic ulcerative colitis. There clearly is a relationship between the incidence of carcinoma and the amount of colon involved, the duration of the illness, and the severity of the illness. In many series, the incidence of carcinoma of the colon in patients with ulcerative colitis is in the range of 20-40%. Clearly such series are slanted in favor of the most seriously ill patients with particularly severe disease. When a group of 250 cases was followed from the first referred attack, the cumulative percentage risk of developing carcinoma was approximately 0.5% after 5 years of active disease, 2% after 10 years, 5% after 15 years and 12% after 20 years. Within such a group of patients, however, it is evident that there are those with a much higher or much lower incidence of potential carcinoma. For example, the overall incidence of carcinoma developing in patients with only distal proctitis is very low, less than 1%; in those patients with total colonic involvement, in contrast, the incidence of carcinoma may approach 20%. Similarly, there is a relationship to the activity of the disease. For any amount of colonic involvement those patients with chronic continuous symptoms have at least a 2-fold higher incidence of development of carcinoma than patients with chronic intermittent symptoms. The duration of active colitis is also of critical importance in determining the development of carcinoma. By-and-large, carcinoma usually develops 10-15 years after the onset of the initial symptoms. This appears to be the case regardless of the age at which initial symptoms began. For example, in one series the average time between the onset of colitis in childhood and the development of carcinoma was approximately 14-15 years. In a similar group of older patients the median period between the onset of symptoms and the development of carcinoma was nearly identical. Thus, patients who have the onset of ulcerative colitis in childhood commonly development carcinoma of the colon as young adults whereas adults having the onset of chronic bowel disease at an older age will develop carcinoma later in life. In summary, the clinical features that favor a high incidence of carcinoma are a very severe first attack, chronic continuous disease, extensive involvement of the colon and a long duration of illness. In the group of patients with continuous symptoms and involvement of the whole colon, the incidence of carcinoma is approximately 18%. With less severe disease and less extensive involvement, the incidence of carcinoma is much lower; nevertheless, it should be emphasized that the incidence of carcinoma even in these milder cases is

FACTORS ASSOCIATED WITH HIGHEST INCIDENCE Ca IN U.C.

1) Very Severe First Attack
2) Chronic Continuous Form
3) Extensive Involvement
4) Long Duration

higher than the risk of developing colonic carcinoma in a group of patients without ulcerative colitis.

Once carcinoma develops, the prognosis is grave. This may primarily derive from the fact that it is often difficult to make a diagnosis of carcinoma of the colon in patients who are having chronic or intermittend bloody diarrhea. Nevertheless, it is apparent that carcinoma of colon behaves differently in patients with ulcerative colitis. First, on the average carcinoma in these patients develops at a younger age than idiopathic carcinoma of the colon. Second, there is a change in the sex ratio so that both males and females may be affected nearly equally. Third, in contrast to idiopathic carcinoma where nearly two-thirds of the lesions are in the rectosigmoid area, carcinoma superimposed upon ulcerative colitis is more or less evenly distributed throughout all levels of the colon. Fourth, at the time the diagnosis of carcinoma of colon is made in patients with ulcerative colitis it is not unusual to have several primary lesions. Such multicentric disease is uncommon in idiopathic carcinoma. Finally, at the time of diagnosis carcinoma in patients with chronic bowel disease commonly already is invasive; hence, the five years survival is very poor and is at least one-half of that found in idiopathic carcinoma. In one British series, for example, just under 20% of the patients survived for five years.

CHARACTERISTICS OF Ca IN U.C.

| | With U.C. |
|---|---|
| Median Age | In Younger Patients |
| Distribution | Whole Colon |
| Sex Ratio | Equals that of U.C. |
| Multicentric | Common |
| Prognosis | Very Poor |

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## *Therapy*

In general, the object of therapy in the treatment of ulcerative colitis is: 1) to bring under control as rapidly as possible acute attacks and 2) to decrease the frequency of such acute attacks. There are a number of excellent controlled therapeutic trials in the British literature, outlined below, indicating that the administration of nonabsorbable sulfa drugs such as azulfidine are relatively uneffective for treating acute episodes of ulcerative colitis but are very valuable in reducing the number of attacks per year. Similarly, there are good data indicating that relatively large doses of steroids are an effective means of terminating acute attacks and, indeed, since the advent of steroid therapy the mortality associated with such acute attacks has been reduced by at least half.

Specific therapy must be tailored to the severity of the disease. In patients with very mild symptoms and, in particular, in those with only distal colitis or ulcerative proctitis local topical steroid therapy commonly is all that is required. Thus, acute symptoms may be treated with either steroid suppositories or steroid enemas each night until the symptoms are brought under control. The steroids may then be decreased in frequency over a period of time. These patients probably also should receive maintenance doses of azulfidine, 2-4 gm/day, and the administration of opiates such as lomotil or deodorized opium may be useful in controlling abdominal discomfort.

In the more acute and serious attack characterized by massive bloody diarrhea, fever, elevated white count, volume depletion, etc. hospitalization is usually indicated. There must be prompt replacement of fluid volume with particular attention to acid-base balance and potassium repletion. If there has been significant blood loss, blood replacement may be required. Such patients

| | |
|---|---|
| Mild | 1) Steroid suppostories<br>steroid enema<br>2) Azulfidine<br>3) Lomotil, DTO |
| Acute Episode | 1) Hospitalization<br>2) High dose oral steroids<br>steroid enema<br>3) Azulfidine<br>4) Lomotil, opiates<br>5) Fluids, blood, $K^+$ prn |
| Interval Therapy | 1) Azulfidine<br>2) Steroids to lowest maintenance |

should be promptly placed on high doses of oral steroids or, if nausea and vomiting is prominent, parenteral steroids. If the disease is predominantly distal, steroid enemas also may be utilized. Azulfidine should be started or continued. Lomotil or other opiates may be useful in the control of abdominal pain and diarrhea. However, in the very seriously ill patient, opiates and anticholinergics should be used with considerable caution since there is a clinical impression that excessive amounts of such medications may induce ileus and possibly lead to the development of the toxic megacolon syndrome. After resolution of the acute episode the steroid dose should be reduced to the lowest possible level necessary to maintain the patient essentially free of symptoms. In many instances it may be possible to eliminate steroids entirely. However, all patients with chronic continuous or chronic intermittent ulcerative colitis should be maintained on azulfidine. As outlined in the table there are specific instances where direct, immediate surgical intervention is indicated. If, during an acute attack a

INDICATIONS FOR SURGERY

1) Progressive Deterioration In Face Of Adequate Therapy

2) Massive Bleeding

3) Evidence of Free Perforation

4) Chronic Recurrent Disease Of Long Duration

patient fails to respond promptly to adequate fluid replacement, potassium repletion, high dose steroids, etc. and, in particular, if there is evidence of progressive abdominal distention and dilatation of the colon, then the decision should be made to do an emergency colectomy (or proximal diverting procedure) immediately. Any delay under these circumstances may lead to development of a full-blow "toxic megacolon" syndrome in which the colon becomes grossly distended and necrotic, and free perforation occurs. If surgery is delayed too long under these circumstances, the operative mortality is formidable. Other indications for immediate surgery include massive exsanguinating bleeding from the colon or evidence of free perforation for any reason. Occasionally, local complications such as ischio-rectal abscess or recto-vaginal fistula also may be indication for surgery. In the past, colectomy was occasionally also undertaken because of serious extracolonic manifestations of disease; for example, progressive destructive arthritis, uncontrollable eye

lesions, progressive pyoderma gangrenosa, etc. In the present era of steroid therapy such extracolonic complications seldom if ever dictate a need for surgical colectomy.

Finally, elective colectomy must be considered in any patient who has chronic intermittent or chronic continuous disease with a gradual downhill course over a prolonged period of time. In such patients there is significant morbidity from the colonic and extracolonic complications, there is significant mortality associated with each acute attack and, after 8-10 years there is a significant potential for the development of fatal carcinoma. In each such patient the risk of colectomy and the psychological problems of a permanent ileostomy must be weighed against the continuing morbidity and potential mortality of the underlying disease.

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