# Long-Term Corticosteroid Therapy for Regional Enteritis: An Analysis of 58 Courses in 54 Patients

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CURRENT TREATMENT of regional enteritis is far from satisfactory. Abdominal pain, diarrhea, fever, and weight loss, the most common symptoms of regional enteritis, often are not severe enough to warrant operation, yet are distressing problems. "Standard" medical therapy, including a bland diet, sedation, antispasm and antidiarrhea medication, and antibacterial drugs, suffices in some patients; but many are not relieved continuously by these measures. Operation is required in many patients, particularly for the complications of obstruction, fistula formation, and localized perforations of the bowel, with abscess formation. Extensive involvement of the small bowel (jejunoileitis) prevents complete removal of the disease. After multiple resections, recurrent regional enteritis may be no longer treatable surgically because of the limited extent of residual functioning intestine.

The prolonged use of corticotrophin (ACTH) and corticosteroids is an important therapeutic adjunct in ulcerative colitis.[1, 2] These agents were utilized in the treatment of regional enteritis shortly after their introduction, with encouraging results initially.[3–7] Therapeutic failures often appeared attributable to insufficient quantities of steroids.[8] Information regarding prolonged therapy with corticosteroids is unavailable, although their use is mentioned.[9, 10] The purpose of this report, therefore, is to present the results of long-term corticosteroid treatment in a series of patients with chronic regional enteritis.

## MATERIALS AND METHODS

The records were reviewed of 217 patients with typical symptoms and roentgenographically identifiable regional enteritis involving the small bowel. Regional enteritis involving the large bowel (ileocolitis, granulomatous colitis, or Crohn's disease of the colon) is excluded from this analysis. Corticosteroids or corticotrophin were administered to 83 patients (38%), for

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variable periods of time. Long-term corticosteroid therapy, defined as at least 6 months of continual treatment, was employed in 54 patients (25%): 32 males and 22 females. Fifty-one individuals required 1 such course; 2 patients required 2 courses, and 1 patient required 3 courses, for a total of 58 among the 54 patients. In this report, each treatment program is considered as a separate event.

Corticotrophin was administered initially in many instances, but subsequently was replaced by an oral corticosteroid. Prednisone was prescribed in most cases, with prednisolone, hydrocortisone, and cortisone less frequently. Methylprednisone, betamethasone, or dexamethasone were prescribed rarely, and for brief intervals. Replacement of one corticosteroid by another, at equivalent dosage, occasionally appeared beneficial clinically. Concurrent therapy included antibacterial drugs and antidiarrheal sedative agents. Both the initial and long-term responses were evaluated on the basis of the following 5 criteria: an *excellent* response indicated sustained relief of all symptoms; a *good* response, almost complete relief of symptoms, but with at least one remaining identifiable manifestation; a *fair* response, partial relief of symptoms; a *poor* response, no improvement; and operation performed during treatment with corticosteroids.

## RESULTS

### Initial Effects

The response was excellent in 45, good in 11, and fair in 2 of the 58 courses initially, regardless of the extent of involvement (Table 1). However, inherent selection is evident, since only courses of longer than 6 months were chosen. Patients not responding favorably either were operated upon earlier or corticosteroids were discontinued before 6 months had elapsed. There was no correlation between the initial and the long-term responses.

TABLE 1. INITIAL AND LONG-TERM RESPONSE TO 58 COURSES OF CORTICOSTEROID THERAPY IN RELATION TO ANATOMIC EXTENT OF DISEASE (NO. OF PATIENTS)

| | | *Long-term effect* | | | |
|---|---|---|---|---|---|
| *Response* | *Initial effect* | *Terminal ileum* | *Ileum extensive* | *Jejuno-ileitis* | *Total* |
| Excellent | 97% 45 | 46% 10 | 67% 4 | 42% 5 | 50% 19 |
| Good | 11 | 7 | 2 | 1 | 10 |
| Fair | 2 | 5 | 0 | 0 | 5 |
| Poor | 0 | 4 | 1 | 0 | 5 |
| Operation | 0 | 11 | 2 | 6 | 19 |
| TOTAL | 58 | 37 | 9 | 12 | 58 |

### Long-Term Effects

At the conclusion of the survey, among 58 courses of therapy, the response was evaluated as excellent in 19, good in 10, fair in 5, and poor in 5; 19 required surgery (Table 1). Corticosteroid therapy had been continued without operation in 20 courses; discontinued without surgery in 20, continued after operation in 6, and discontinued after operation in 12.

Among 40 courses treated without operation, 20 individuals continued to receive corticosteroids at the termination of the study; 10 had an excellent response to therapy, 3 a good response, 4 a fair response, and 3 a poor response. Corticosteroid therapy was discontinued in 20 courses. At the termination of such therapy, the response was excellent in 10, good in 7, fair in 1, and poor in 2.

### Extent of Involvement

On the roentgenographic evidence of the extent of small bowel involvement, the patients were separated into three groups: 33 had involvement of the terminal ileum only, 9 had extensive disease of the ileum, and 12 had jejunoileitis. Recurrence at the anastomotic site between small and large bowel was classified arbitrarily as "terminal ileum." The roentgenologic extent of regional enteritis did not appear to correlate with the response to long-term corticosteroid therapy (Table 1). Excellent or favorable responses were observed in approximately 50% of the courses in each category.

### Symptoms

The most common symptoms were diarrhea, abdominal pain, weight loss, and fever, respectively (Table 2). No correlation could be established between therapeutic response and individual symptoms (Table 2) or symptom complex (Table 3). Patients with one symptom fared no better than those with multiple complaints. Patients with intestinal obstruction, malabsorption, or hemorrhage did not respond as well as those with the symptoms listed above.

### Prior Therapy

Corticosteroids or ACTH had been employed previously in 16 of the 54 patients (30%), but information regarding dosage or duration of administration was insufficient to evaluate the previous therapy or compare past with present responses.

Previous resection or bypass operation had been performed in 30 of 58 courses (Table 4). A larger number of favorable therapeutic responses occurred in patients not operated upon previously. Furthermore, a prior extensive resection (exceeding 100 cm. of intestine) appeared to be associated with a poorer response than the removal of a shorter segment of bowel. Opera-

TABLE 2. LONG-TERM RESPONSE IN 58 COURSES OF CORTICOSTEROID THERAPY IN RELATION TO INDIVIDUAL SYMPTOMS (NO. OF PATIENTS)

| *Response* | *Diarrhea* | *Abdominal pain* | *Weight loss* | *Fever* | *Intestinal obstruction* | *Malabsorption* | *Hemorrhage* | *Erythema nodosum* |
|---|---|---|---|---|---|---|---|---|
| Excellent | 52% 16 | 55% 12 | 48% 11 | 54% 6 | 28% 2 | 40% 1 | 0 | 50% 0 |
| Good | 9 | 9 | 1 | 1 | 0 | 1 | 0 | 1 |
| Fair | 5 | 2 | 1 | 0 | 2 | 0 | 1 | 1 |
| Poor | 5 | 3 | 3 | 1 | 0 | 0 | 1 | 0 |
| Operation | 13 | 12 | 9 | 5 | 3 | 3 | 0 | 0 |
| TOTAL | 48 | 38 | 25 | 13 | 7 | 5 | 2 | 2 |

TABLE 3. LONG-TERM RESPONSE OF CORTICOSTEROID THERAPY IN 46 COURSES IN RELATION TO SYMPTOM COMPLEX (NO. OF PATIENTS)

| *Response* | *Diarrhea alone** | *Pain alone†* | *Diarrhea, pain* | *Diarrhea, wt. loss* | *Pain, wt. loss* | *Diarrhea, pain, wt. loss* | *Diarrhea, pain, fever* | *Diarrhea, pain, wt. loss, fever* |
|---|---|---|---|---|---|---|---|---|
| Excellent | 2 | 0 | 1 | 1 | 2 | 5 | 3 | 2 |
| Good | 1 | 0 | 7 | 0 | 0 | 0 | 0 | 1 |
| Fair | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Poor | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 1 |
| Operation | 0 | 1 | 3 | 3 | 1 | 2 | 2 | 2 |
| TOTAL | 5 | 1 | 13 | 4 | 3 | 9 | 5 | 6 |

*Excluding patients with malabsorption.
†Excluding patients with intestinal obstruction.

TABLE 4. LONG-TERM RESPONSE IN 58 COURSES OF CORTICOSTEROID THERAPY IN RELATION TO PRIOR SURGERY AND ITS EXTENT (NO. OF PATIENTS)

| *Response* | *No prior surgery* | *Prior Surgery* | | | |
|---|---|---|---|---|---|
| | | *Total* | *Short resection (less than 100 cm.)* | *Extensive resection (over 100 cm.)* | *Bypass* |
| Excellent | 50% { 14 | 37% { 5 | 41% { 4 | 30% { 0 | 33% { 1 |
| Good | { 4 | { 6 | { 3 | { 3 | { 0 |
| Fair | 0 | 5 | 2 | 2 | 1 |
| Poor | 0 | 5 | 4 | 1 | 0 |
| Operation | 10 | 9 | 4 | 4 | 1 |
| TOTAL | 28 | 30 | 17 | 10 | 3 |

tions were necessary in approximately one-third of patients receiving long-term treatment with corticosteroids, regardless of whether surgery had been performed previously or not.

## CORTICOSTEROID DOSAGE

Analysis of the response in relation to the highest dose of steroids revealed that favorable responses occasionally could be achieved with smaller quantities than are usually prescribed. However, the majority of courses required 30 mg. or more of prednisone daily in divided doses. A substantial number utilized 50 mg. or more per day, but this quantity did not produce a better response than lower doses (Table 5). More important was the lowest amount to which corticosteroid dosage could be decreased, without return of symptoms. In the majority of courses, a definite dosage level was found, below which symptoms reappeared; this dose usually was 7.5 mg. of prednisone daily or higher, and

TABLE 5. LONG-TERM RESPONSE IN 58 COURSES OF CORTICOSTEROID THERAPY IN RELATION TO HIGHEST DAILY DOSE (OR EQUIVALENT AMOUNT) OF PREDNISONE (NO. OF PATIENTS)

| *Response* | *Daily dose (mg.)* | | | |
|---|---|---|---|---|
| | *10* | *15–25* | *30–45* | *50 or more* |
| Excellent | 50% { 0 | 45% { 4 | 61% { 10 | 37% { 5 |
| Good | { 1 | { 1 | { 6 | { 2 |
| Fair | 0 | 0 | 1 | 4 |
| Poor | 0 | 0 | 3 | 1 |
| Operation | 1 | 5 | 6 | 7 |
| TOTAL | 2 | 11 | 26 | 19 |

in approximately half the courses, 15 mg. or higher. Although mild symptoms usually reappeared on reduction of dosage, corticosteroid therapy could be decreased and discontinued for some patients without adverse effect.

The average duration of continued therapy was 38 months, ranging from 7 to 120 months. Forty courses were longer than 2 years, and 11 exceeded 5 years. No correlation existed between the duration of therapy and the therapeutic response.

## Age

The average age at onset of regional enteritis was 28 years, ranging from 10 to 61 years. The average age at which corticosteroid therapy was instituted was 36 years, ranging from 14 to 65 years. The interval between the onset of disease and the inception of corticosteroid therapy averaged 7 years, ranging from 0 to 32 years. Corticosteroids administered soon after the onset of regional enteritis appeared to exert a more favorable effect than when the disease had been present for many years. Favorable responses were more prevalent among patients below the age of 45. Of 45 courses initiated in patients below age 45, responses in 19 were evaluated as excellent and in 8 as good; in the remaining 18, responses were evaluated as fair, poor, or requiring operation. Of the 12 courses administered to patients above age 45, in only 2 were responses evaluated as good (Table 6).

## Relapses After Therapy

Long-term corticosteroid therapy was discontinued for 16 patients without operation. Twelve patients were asymptomatic; 2 had not received significant benefit; and 2 developed side effects severe enough to warrant discontinuation. Seven of the 12 asymptomatic patients had recurrences after cessation of corticosteroid therapy, 4 requiring operation. The remaining 5 patients continue asymptomatic, but have been observed for less than 5 years.

TABLE 6. LONG-TERM RESPONSE IN 58 COURSES OF CORTICOSTEROID THERAPY IN RELATION TO AGE OF PATIENT AT ONSET OF THERAPY (NO. OF PATIENTS)

| | *Age (years)* | | | | |
|---|---|---|---|---|---|
| *Response* | *14–25* | *26–35* | *36–45* | *46–55* | *56 and over* |
| Excellent | 50% 9 | 38% 2 | 65% 8 | 11% 0 | 25% 0 |
| Good | 2 | 1 | 5 | 1 | 1 |
| Fair | 0 | 1 | 2 | 1 | 1 |
| Poor | 0 | 0 | 0 | 3 | 1 |
| Operation | 7 | 3 | 5 | 4 | 1 |
| Total | 18 | 7 | 20 | 9 | 4 |

Corticosteroid therapy was discontinued after operation for regional enteritis in 13 patients. Three of them subsequently experienced recurrences, 1 requiring another operation. In general, the natural tendency for regional enteritis to recur appears to be unchanged despite a long-term course of corticosteroids.

### Influence on Abdominal Mass

Seven of the patients with involvement of the terminal ileum and 1 with more extensive involvement of the ileum had a palpable abdominal mass, in addition to two or more symptoms. In 3 patients, all symptoms remitted, with the mass remaining unchanged or becoming smaller and firmer. Four of the 7 patients were operated upon; the mass was identified as a walled-off abscess in 2 and as thickened bowel loops and adhesions in 2. One patient with an abdominal mass, treated for 15 months with corticosteroids, died of peritonitis after perforation of a gangrenous segment of ileum.

### Roentgenographic Course

Serial roentgenographic studies of the small bowel before and after therapy were available for 39 patients, with the following results: no change in 19; definite improvement in 7, including 4 with involvement of the terminal ileum; and either more extensive disease or more severe involvement in the segment initially affected, such as the development of fistulae, in the remaining 13 patients. There was no correlation between symptomatic and roentgenographic improvement.

### Complications

#### *Corticosteroid Therapy*

No complications of corticosteroid therapy developed in 21 patients. The minor complications of acne, excessive weight gain, and severe Cushing-like facies were observed in 11 patients. Twenty-two patients had a total of 35 major complications; these complications included peptic ulcer in 9, hypertension in 7, edema in 3, electrolyte imbalance in 2, severe emotional disturbance in 2, corticosteroid myopathy in 2, free perforation of the ileum in 2, hepatic abscess in 1, and pulmonary embolism in 1. The vast majority of these complications were reversible on decreasing the quantity of steroids. The case of the patient with regional enteritis and hepatic abscess has been reported elsewhere.[11] Two individuals developed perforation at the ileum and generalized peritonitis (see Cases 7 and 8, reported below). Since walled-off perforation with abscess formation is not uncommon in regional enteritis, corticosteroids may have facilitated the spread of an ordinarily localized inflammatory reaction.

*Postoperative*

Nineteen patients required operation while receiving corticosteroids, after 6 months or more of therapy. Five patients developed complications possibly related to long-term administration of corticosteroids. One individual developed leakage at the anastomosis, with abscess formation, requiring further operation. Two patients were suspected of having developed an anastomotic leakage because of fever and abdominal pain in the early postoperative period; 1 patient was not operated upon and the symptoms resolved; the other was operated upon and no evidence of leakage could be found. However, symptoms persisted and soon thereafter a retroperitoneal abscess was identified at operation and drained; the patient recovered. The fourth patient developed a wound infection, and the fifth, a psychosis postoperation.

Corticosteroid dosage was decreased slowly for 15 patients without adverse reactions, including 2 patients with extensive disease demonstrated at operation and at least one instance of a partial resection with the anastomosis of diseased bowel (see Case 4, below). Corticosteroid dosage was decreased rapidly for 4 patients, with the development of fever, diarrhea, and hypotension in 1 patient and high fever in another; the symptoms resolved on increasing the dosage of corticosteroids. A third patient, mentioned above, developed leakage of the anastomosis after rapid decrease in the dosage of corticosteroids. The fourth patient, also mentioned above, developed a wound infection that probably was unrelated to the rapidity of the decrease in corticosteroid dosage.

Postoperative diarrhea continued in 10 patients; 8 of them responded to an increase in the dosage of corticosteroids. For 3 patients, dosage of corticosteroids was then reduced slowly, with eventual subsidence of the diarrhea and discontinuation of the medication. For 2 patients, dosage of corticosteroids was then discontinued more rapidly and the diarrhea subsided over a much longer period.

## "Prophylactic" Use After Operation

Corticosteroids were administered immediately after bowel resection in 8 patients, either in an attempt to prevent recurrent disease or to control diarrhea (Table 7). All 8 patients developed recurrent regional enteritis while receiving corticosteroids; there was roentgenographic evidence in 7 cases. The initial dosage of prednisone in this postsurgical recurrence group varied from 5 to 80 mg. daily.

## COMMENT

The limitations of this study are evident: the retrospective approach, the lack of paired controls, and the elimination of patients not responding to corticosteroids for whom therapy was discontinued before 6 months had

TABLE 7. OUTCOME OF "PROPHYLACTIC" USE OF CORTICOSTEROIDS AFTER APPARENTLY COMPLETE RESECTION OF DISEASED BOWEL

| *Patient* | *Postoperative symptoms* | *Highest dose (mg. prednisone or equivalent)* | *Evidence for recurrence* | |
|---|---|---|---|---|
| | | | *Roentgenographic* | *Clinical* |
| L.M. | Diarrhea | 80 | Positive | Rectovaginal fistula |
| T.B. | Diarrhea, fever, weight loss | 5 | Positive | Perforated terminal ileum |
| M.K. | Diarrhea | 10 | Positive | Abdominal mass |
| S.S. | Diarrhea | 40 | Positive | Erythema nodosum |
| B.R. | None | 15 | Positive | None |
| A.M. | Diarrhea | 15 | Positive | Anemia, hypoproteinemia |
| H.R. | Diarrhea | 25 | Not done | Perforated terminal ileum |
| E.H. | Diarrhea, weight loss | 80 | Positive | Diarrhea if dose less than 30 mg. daily |

elapsed. However, since corticosteroids were prescribed frequently in the management of regional enteritis, information regarding their potential usefulness seems desirable, especially, as in this study, when the results appear so definitive despite the absence of "double-blind" conditions. Nineteen of the 54 patients (35%) ultimately required operation during long-term corticosteroid therapy. The incidence of operation in regional enteritis at this hospital is 70%, reflecting the severity of the disease in patients referred for treatment. Thus, a decrease in the incidence of surgical intervention appears to have been achieved with long-term corticosteroid therapy. However, once corticosteroid administration was discontinued, recurrences were common, indicating that the natural history of the disease was modified only temporarily, perhaps by suppression rather than resolution of the tissue reaction during the administration of corticosteroids.

The response to corticosteroids was extremely variable; of the multiple parameters examined, very few criteria for prognosticating the potential response to long-term corticosteroid therapy emerged. The age of the patient at the time of steroid therapy seemed useful prognostically because of the larger proportion of favorable responses among patients below the age of 45. Corticosteroids administered relatively soon after the onset of symptoms appeared to be more beneficial than when prescribed for chronic disease. More favorable results were achieved in the absence of prior operation; and patients with previous extensive intestinal resections, often unable to undergo further operation, unfortunately did not respond as well as patients with more limited resections of small intestine.

Corticosteroids usually were employed after the failure of a "standard"

medical program. Intestinal obstruction did not invariably necessitate operation; and in obstruction secondary to acute inflammation, corticosteroids often were helpful in reducing the inflammation. Malabsorption secondary to regional enteritis usually is attributable to the combination of inflammation and prior extensive bowel resection; corticosteroids were disappointing in this situation, as noted also by others.[12] A palpable abdominal mass was not a contraindication to corticosteroid therapy. Corticosteroids may have prevented recurrent hemorrhage secondary to regional enteritis in one case, but failed to do so in another. Large doses of corticosteroids controlled erythema nodosum in one instance, but were ineffectual in another.

All but one of the patients with jejunoileitis had the onset of symptoms below age 23. Although corticosteroids in large amounts were required for many years in a few patients with jejunoileitis, as described by Crohn and Yarnis,[13] several eventually were able to discontinue taking corticosteroids completely.

An effective dosage level, below which symptoms returned, was defined for the majority of patients. Since this dosage usually was too high for prolonged maintenance therapy, either operation was undertaken or the amount of corticosteroids was decreased, despite the reappearance of mild symptoms. Maintenance of higher corticosteroid dosages for longer periods, rather than attempts to reach a minimal effective dose, might have been wiser for several patients.

The complications of long-term corticosteroid therapy were common, but not as frequent as has been anticipated.[14] The development or exacerbation of peptic ulcer and the appearance of mild hypertension were most frequent. Peptic ulcer complicating the use of corticotrophin and corticosteroids in ulcerative colitis is rare.[1] The majority of the complications, major and minor, could be reversed by decreasing the amount of corticosteroid. Complications following operation performed after long-term corticosteroid therapy were few and almost always were related to excessively rapid reductions in steroid dosage, with resultant adrenal insufficiency.

Intra-abdominal and perineal abscesses are so common in the natural course of regional enteritis as not to be classified necessarily as direct complications of therapy. On the other hand, free perforation of the bowel is unusual; and the 2 such cases in this small series may incriminate corticosteroids. The development of a hepatic abscess during corticosteroid therapy may represent another instance of decreased ability to localize infection, attributable to the action of corticosteroids.

Diarrhea after resection of the small bowel and the ileocecal valve is common.[15] Since this symptom is controlled by administration of corticosteroids and since slow reduction of the medication is indicated after long-term therapy, the continued administration of corticosteroids postoperation is indicated for variable but temporary intervals. The use of corticosteroids in preventing

recurrent regional enteritis after resection of disease was unsuccessful for 8 patients.

The mechanism of corticosteroid action in regional enteritis has not been elucidated, but probably involves an anti-inflammatory rather than an immunosuppressive effect. Little is known of the effect of corticosteroids on the lymphangiectasia and granuloma formation characterizing regional enteritis. Corticosteroids do not influence fibrosis associated with chronic disease. The immediate symptomatic response is striking, particularly in the subsidence of diarrhea, abdominal pain, weight loss, and fever. The sense of well-being associated with the use of corticosteroids probably is responsible in part for the symptomatic improvement; but the striking defervescence and fall in sedimentation rate indicate a direct effect upon the tissue reaction. The occasional improvement in the roentgenologic appearance of the bowel also is noteworthy.

## SELECTED CASE REPORTS

### *Case 1. Excellent Result in Jejunoileitis*

L.K. (85-04-22), a 16-year-old white boy, developed severe cramping abdominal pain associated with borborygmi, palpable loops of bowel, and a 10-16 lb. weight loss. There was no diarrhea. Roentgenograms 1 years later revealed a regional enteritis involving the entire jejunum and proximal ileum, with a delay in transit time. The hemoglobin was 9.7 gm./100 ml.; the sedimentation rate 33 mm./hr. Therapy with diet, sulfonamides, antispasmodics, sedatives, and blood transfusions for 3 weeks produced little or no clinical improvement. Prednisone, 40 mg. daily, then was added; there was prompt weight gain, cessation of abdominal pain, and a fall in the sedimentation rate to 2 mm./hr. Subsequently the patient remained asymptomatic and gained 36 lb. Corticosteroid therapy was discontinued after 15 months of gradually decreasing medication.

#### COMMENT

This favorable response to corticosteroids appears to be more prevalent in young individuals who have not had prior operations and are treated relatively soon after onset of the illness.

### *Case 2. Excellent Response in Regional Enteritis Involving Terminal Ileum*

A.R. (58-49-29), a 21-year-old white housewife, developed diarrhea and abdominal pain and had a 16-lb. weight loss over a 4-month period. Her temperature rose to 39.2° C. daily. Roentgenograms demonstrated regional enteritis involving 20 cm. of terminal ileum. Therapy with cortisone, 300 mg. daily, was instituted; there was immediate defervescence, cessation of diarrhea and abdominal pain, and a weight gain of 35 lb. Rapid reduction of the cortisone dosage to 25 mg. daily resulted in a return of abdominal pain and weight loss; there symptoms were controlled by increasing the dose to 100 mg. daily. Corticosteroid dosage was then decresed slowly and eventually discontinued after 8 months, with no recurrence of symptoms. The patient remained well without corticosteroids for 6 years, when an episode of obstruction required the resection of 72 cm. of terminal ileum and colon.

### Comment

The defervescence on corticosteroid therapy was striking. As in Case 1, the beneficial results correlate with the youthfulness of the patient, the absence of prior operation, and the prompt institution of therapy after onset of illness.

### *Case 3. Three Long-Term Courses of Corticosteroid Therapy*

S.S. (55-71-94), an 18-year-old white girl, developed periumbilical and lower abdominal cramping pain, intermittent watery diarrhea, and fever to 39.5° C., as well as having weight loss. Barium enema revealed regional enteritis involving the terminal ileum. A course of cortisone, 75 mg. daily, resulted in decrease in abdominal cramps, defervescence, weight gain, and regulation of bowel activity with one formed stool daily. Symptoms returned when the dosage of cortisone was reduced to 50 mg. daily but remitted when the dosage was increased. Despite recurrence of symptoms, corticosteroid therapy was discontinued after 19 months, because of pregnancy. The patient remained symptom-free except for stress-induced diarrhea for 7 years, when severe postprandial cramping abdominal pain and diarrhea began. A small, tender mass was present in the right lower abdominal quadrant. Administration of prednisone, 30 mg. daily for 4 weeks, did not control symptoms; but an increase to 60 mg. daily completely relieved the pain and diarrhea. The mass became smaller and less tender. A gradual reduction of prednisone dosage to 5 mg. daily over the next 11 months was followed by a return of symptoms, controlled by temporarily increasing the dose to 30 mg. daily. Administration of prednisone was discontinued gradually after 18 months. A return of symptoms 4 months later was treated by a brief course of prednisone, again discontinued because of pregnancy. A postpartum exacerbation of regional enteritis initially responded to 60 mg. of prednisone daily. While the patient was asymptomatic on therapy, during a routine cholecystectomy, 75 cm. of terminal ileum and 15 cm. of cecum were resected. The abdominal mass was composed of thickened bowel loops. Postoperative severe diarrhea ensued and was treated with 40 mg. of prednisone daily, in addition to standard treatment. Recurrent disease was demonstrated several months later. Erythema nodosum developed while the patient was receiving 30 mg. of prednisone daily. She is continuing to receive 40 mg. of prednisone daily.

### Comment

An initially small dose of corticosteroid controlled symptoms; however, a larger dose was required for symptomatic control after each exacerbation. The decrease in the inflammatory abdominal mass is noteworthy.

### *Case 4. No Difficulties During or After Partial Resection*

M.K. (82-85-59), a 12-year-old white girl, experienced lower abdominal cramping pain, followed in several months by mild diarrhea. At laparotomy, the entire small bowel was found to be dilated, thickened, and edematous except for the proximal 2 ft. of jejunum, and the mesentery was filled with large lymph nodes; 3 ft. of jejunum and 1 ft. of ileum were resected. Six months after operation, cramping pain returned, associated with a failure to gain weight. Symptoms improved briefly after intermittent injections of ACTH. Sustained symptomatic improvement and weight gain for 30 months followed the administration of 15 mg. of prednisone daily. After the dose was reduced to 2.5 mg. daily, an episode of intestinal obstruction occurred, not relieved by 200 mg. of hydrocortisone intravenously, daily. At operation, the entire jejunum and proximal half of the ileum were involved with regional

enteritis. A 20-cm. stenotic segment of jejunum was resected, with a primary anastomosis of diseased bowel. The postoperative course was uneventful. Therapy with hydrocortisone, 200 mg. daily, was continued, and decreased very slowly for the first month and then more rapidly. Corticosteroid therapy was discontinued 4 months postoperation. The patient remains asymptomatic 8 months later.

### Comment

The initial reduction in corticosteroid dosage may have promoted the episode of intestinal obstruction in that the inflammatory process was no longer suppressed. The prompt and uneventful healing of the anastomosis constructed with diseased bowel, in the presence of high doses of corticosteroid, is noteworthy.

### *Case 5. Regional Enteritis with Abdominal Mass, Requiring Slow Postoperative Therapy Reduction*

B.L. (84-73-31), a 43-year-old white woman, developed diarrhea and right lower quadrant pain. Regional enteritis was diagnosed and treated by diet alone, without relief of symptoms. At age 52, after the death of her husband, cramping abdominal pain, fever, and diarrhea began. Regional enteritis involving the terminal ileum was present roentgenographically. Symptoms were not controlled by a "standard" medical program. One year later, an 8-cm. tender mass in the right lower quadrant was detected, and 30 mg. of prednisone daily was added to a program which included sedatives, an anticholinergic, and sulfonamide medication. All symptoms were relieved within 2 weeks and the abdominal mass became smaller and less tender. Prednisone dosage was reduced gradually to 17.5 mg. daily; there was a return of fever, abdominal pain, and diarrhea, and an increase in the size of the abdominal mass. An intravenous pyelogram demonstrated deviation of the right ureter by a pelvic mass. An increase in prednisone dosage to 30 mg. daily again relieved symptoms and the mass decreased. Despite the high dose of prednisone, fever and diarrhea returned. At laparotomy, 9 months after beginning prednisone therapy, the abdominal mass was seen to be thickened bowel and a small abscess; 38 cm. of terminal ileum and 5 cm. of cecum were resected. Postoperation, hypotension, fever, and diarrhea occurred and responded to increased amounts of corticosteroids and antibiotics. Repeated attempts at rapid corticosteroid reduction were attended by diarrhea. Corticosteroid therapy finally was discontinued 6 months after operation.

### Comment

Although an initially excellent response was obtained, symptoms returned at a reduced level of prednisone, remitting only temporarily when the dose was increased. The abdominal mass, a combination of thickened bowel and walled-off abscess, decreased with corticosteroid therapy, but it did not disappear. Postoperative diarrhea responded only to increased corticosteroid dosage; and 6 months of further therapy were necessary before this medication could be discontinued.

### *Case 6. Failure of Corticosteroids Prophylactically*

B.R. (67-13-32), a white salesman, developed a perirectal abscess at age 19, followed by weakness, diarrhea, nausea, emesis, and weight loss. Regional enteritis involving the terminal

ileum was diagnosed. Symptoms recurred intermittently and he was treated with 15 mg. of prednisone daily for a short time without relief. The terminal ileum was resected but an ileosigmoid fistula was repaired at age 27. Three years later, intestinal obstruction due to recurrent disease at the operative site necessitated further resection of bowel. Abdominal discomfort and diarrhea persisted after operation and studies repeated 1 year later demonstrated recurrent regional enteritis at the anastomotic site. Administration of betamethasone, 2.4 mg. daily, produced almost immediate relief of symptoms. Abdominal cramping followed a decrease to 0.6 mg. daily, and was relieved when the dose was increased to 1.8 mg. daily. While the patient was receiving betamethasone, 1.2 mg. daily, intestinal obstruction occurred and a third resection was performed, 4 years after the previous operation. Administration of prednisone, 10 mg. daily, was continued after operation, although the patient was asymptomatic, in an attempt to prevent recurrent disease. Small bowel roentgenographs repeated 11 months after operation revealed a markedly abnormal pattern, particularly in the distal 30 cm. of small bowel and including the anastomotic site. At this time the patient was almost asymptomatic except for occasional diarrhea.

### Comment

An attempt to prevent an almost inevitable recurrence with a substantial maintenance dose of prednisone was unsuccessful.

### *Case 7. Perforation of Terminal Ileum*

T.B. (76-43-11), a 62-year-old white man, developed abdominal pain and diarrhea and had weight loss. A resection of 76 cm. of terminal ileum was performed the following year. Postoperation, administration of 5 mg. of prednisone daily was begun and the dose increased to 25 mg. 4 months later, because of diarrhea, weight loss, fever, and abdominal pain. Small bowel roentgenographs demonstrated recurrent regional enteritis involving a 30-cm. segment proximal to the anastomosis. The response to corticosteroids was poor; there was continuing diarrhea and abdominal pain. Twenty-seven months after the beginning of corticosteroid therapy, the abdominal pain suddenly became severe and the patient died in shock in the emergency room. At autopsy, generalized peritonitis was found due to several perforations of the distal small bowel, proximal to the ileotransverse colostomy.

### Comment

Corticosteroid therapy may have prevented localization of the free perforations and thus may have promoted generalized peritonitis. The failure of prophylactic corticosteroids again is evident.

### *Case 8. Perforation of the Terminal Ileum*

H.R. (73-41-91), a 39-year-old white man, developed diarrhea and cramping lower abdominal pain. Eight years later, an abscess in the right lower quadrant was incised and followed by persistent drainage, increasing abdominal pain, and fever up to 40° C. Small bowel roentgenograms demonstrated extensive regional enteritis of the ileum with multiple fistulous tracts from the ileum to the colon. Administration of prednisone, 40 mg. daily, induced pronounced improvement in symptoms prior to the resection of 70 cm. of ileum and 10 cm. of cecum.

The postoperative course was uneventful, and therapy with prednisone, 40 mg. daily, was

continued. Mild diarrhea occurred when the dosage was reduced to 20 mg. daily because of severe diarrhea. Prednisone therapy was discontinued briefly 40 months after surgery, but was reinstituted after diarrhea and abdominal pain returned. Severe abdominal pain and intestinal obstruction 2 months later prompted another abdominal operation, now demonstrating perforation of a gangrenous segment of bowel. An extremely stormy postoperative course ensued, with the development of an enterocutaneous fistula, subdiaphragmatic abscess, anastomotic rupture, and death from peritonitis. At autopsy, the entire small bowel was involved with regional enteritis.

## Comment

Corticosteroid therapy, continued postoperation because of diarrhea, should have prevented recurrent disease if it were effective in this capacity, but unfortunately did not prove helpful. The perforation of the terminal ileum may not have been due to corticosteroid therapy, but secondary to gangrenous bowel.

## SUMMARY

Among 58 courses of corticosteroids administered for 6 months or longer, complete or almost complete relief of symptoms occurred in 50% and operation was required in 33%. The response was variable and unpredictable. The initial response to steroids, the type or number of symptoms, the roentgenographically evidenced extent of the disease, or the initial dosage of corticosteroids did not influence the long-term response. The only factors that correlated with a favorable response were the absence of prior operation, a short duration of symptoms, and a patient age of less than 45 years. Roentgenographically evident improvement was unusual. Symptoms often recurred after a reduction of prednisone dosage to below 15 mg. daily, indicating a suppressive rather than a curative effect. Prolonged corticosteroid therapy did not influence the tendency for the disease to recur once the therapy was discontinued. Complications attributable to long-term corticosteroid administration were common, but reversible. There were two instances of free perforation of the ileum. Postoperative complications following long-term corticosteroid administration were uncommon, and were related usually to excessive rapid reduction in steroid dosage. The "prophylactic" use of corticosteroids postoperation did not prevent the recurrence of regional enteritis in a small group of patients.

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## REFERENCES

1. Spencer, J. A., Kirsner, J. B., Mlynaryk, P., Reed, P. I., and Palmer, W. L. Immediate and prolonged therapeutic effects of corticotrophin and adrenal steroids in ulcerative colitis: Observations in 340 cases for periods up to ten years. *Gastroenterology 42*:113, 1962.

2. Sparberg, M., and Kirsner, J. B. Corticosteroid therapy of ulcerative colitis: Status after 15 years. *Curr Ther Res 7*:324, 1965.
3. Gray, S. J., Reifenstein, R. W., Benson, J. A., Jr., and Young, J. C. G. Treatment of ulcerative colitis and regional enteritis with ACTH. *AMA Arch Int Med 87*:646, 1951.
4. Machella, T. E., and Hollan, O. R. The effect of cortisone on the clinical course of chronic regional enteritis and chronic idiopathic ulcerative colitis. *Am J Med Sc 221*:501, 1951.
5. Stanley, M. M., Rosenberg, I. N., and Cleroux, A. P. The use of corticotrophin (ACTH) in the treatment of chronic regional enteritis. *Med Clin N Amer 35*:1255, 1951.
6. Kirsner, J. B., Palmer, W. L., and Klotz, A. P. ACTH in severe chronic regional enteritis: Observations in four patients. *Gastroenterology 20*:229, 1952.
7. Sauer, W. G., Brown, P. W., and Dearing, W. H. Experiences with the use of corticotrophin in regional enteritis. *Gastroenterology 22*:550, 1952.
8. Redish, M. H. Failure of cortisone in chronic ulcerative disease of the large and small bowel. *Gastroenterology 18*:179, 1951.
9. Crohn, B. B. Current status of therapy in regional ileitis. *JAMA 166*:1479, 1958.
10. Kirsner, J. B., and Dooley, J. E. Management of regional enteritis. *Mod Med Ann 1*:25, 1959.
11. Sparberg, M., and Kirsner, J. B. Liver abscess complicating regional enteritis: Report of two cases. *Gastroenterology 49*:548, 1965.
12. Pimparkar, B. D., Mouhran, Y., and Bockus, H. L. Nutritional and metabolic studies in nonspecific regional enteritis and enterocolitis: Correlation with anatomic site of involvement. *Proc Internat Congr Gastroenterology*. Leyden, 1960, p. 227.
13. Crohn, B. B., and Yarnis, H. *Regional Ileitis* (rev. ed. 2), Grune, New York, 1958.
14. Bargen, J. A. Nonsurgical management of regional enteritis. *JAMA 165*:2045, 1957.
15. Singleton, A. D., Jr., Redwood, D. C., II, and McMurray, J. E. Ileocecal resection and small bowel transit and absorption. *Ann Surg 159*:690. 1964.