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CLINICAL TRENDS AND TOPICS

Healing of Perineal Crohn's Disease with Metronidazole

LESLIE H. BERNSTEIN, MICHAEL S. FRANK, LAWRENCE J. BRANDT, and SCOTT J. BOLEY

The Division of Gastroenterology, Department of Medicine and the Department of Surgery, Montefiore Hospital and Medical Center, Albert Einstein College of Medicine, Bronx, New York

The effect of metronidazole was studied in 21 consecutive patients with chronic unremitting perineal Crohn's disease. Drainage, erythema, and induration diminished dramatically in all patients, and complete healing was obtained in 10 of 18 patients maintained on therapy. Five others have shown advanced healing; in 2 patients the inflammation is improved, but healing is minimal. Side effects of metallic taste, dark urine, and mild gastrointestinal upset occurred in many patients. However, the dosage had to be decreased in only 4 patients and the drug discontinued in only 1 patient, all because of peripheral neuropathy that proved to be reversible. In 2 other patients, metronidazole was discontinued because of poor compliance. If further experience corroborates this prompt and striking response in patients with extreme, disabling, and otherwise unmanageable disease, metronidazole will play an important role in the therapy of perineal Crohn's disease.

The perineal manifestations of Crohn's disease are frequently disabling, socially crippling, and particularly unresponsive to treatment. These lesions usually complicate the colonic and ileocolonic forms of the disease, but may be associated with only small bowel involvement or may be the initial manifestation of Crohn's disease.[1-3] The perineal lesions often persist or even progress despite local operations or extensive resections of diseased bowel.

In 1975, Ursing and Kamme first reported the use of metronidazole in the treatment of 5 patients with Crohn's disease.[4] Since that study, there have been reports of at least 155 patients treated with the drug in differing dosage regimens and treatment schedules.[5-10] Although the response of the intestinal disease has been variable, improvement in the associated perineal disease is briefly mentioned in four studies.[4,5,8,9] These isolated observations prompted us to evaluate metronidazole in the treatment of the chronic perineal manifestations of Crohn's disease.

Patients, Materials, and Methods

Twenty-one consecutive patients with perineal Crohn's disease were studied; these included 5 men and 16 women ranging in age from 19 to 75 yr with a mean of 39.5 yr. Roentgenograms, biopsy material, and surgical specimens were reviewed, when available, to confirm the diagnosis of Crohn's disease. In 8 of the patients the disease had involved the colon, and in 11 patients both the colon and small bowel were involved. Five patients had rectal involvement. In 4 patients the involved intestine had been resected, and no active residual bowel disease was known to be present at the time of the study. Two patients who had never had intestinal involvement had perineal disease for 3 and 15 yr, respectively. The average duration of Crohn's disease was 11.4 yr (range: 1.5–40 yr, median: 10 yr) and the average duration of perineal disease was 5 yr (range: 1.5–15 yr, median 3 yr).

Nineteen patients had received one or more forms of medical treatment without healing of the perineal disease (Table 1). Twelve patients were on medications to which metronidazole was added, including prednisone alone in 5, sulfasalazine and prednisone in 6, and sulfasalazine alone in 1. Seventeen patients had had prior surgical treatment, including one or more intestinal operations in 9 and one or more perineal surgical procedures in 10 (Table 2). Two patients who had had no prior medical or surgical treatment

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Address requests for reprints to: Leslie H. Bernstein, M.D., Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, New York 10467.

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Table 1. Medical Therapy Before Metronidazole (19 Patients)

Steroids	16
Sulfasalazine	11
Antibiotics	10
Parenteral nutrition	5
Antimetabolites	2

were started on metronidazole after our initial encouraging experience suggested the efficacy of the drug.

An informed consent to a protocol approved by the Medical Center Human Research Committee was obtained from all patients. Pregnancy was excluded in all women, and they were cautioned against becoming pregnant while on metronidazole. Patients were warned not to drink alcoholic beverages while on metronidazole because of its reported disulfuramlike effect. They were continued under the care of their referring physicians, and the protocol did not require any changes in medications. In some patients, steroid therapy was discontinued during the study when a good response to metronidazole was noted.

The nature of the perineal disease varied. Eight patients had multiple simple sinuses and fistulas with chronic purulent drainage. Nine patients had complicated fistulas with associated abscesses, including 2 with rectovaginal and 3 with rectolabial fistulas. One patient had multiple unhealed wounds after excision of hypertrophied anal skin tags containing granulomata. Two patients had unhealed proctectomy wounds and "metastatic Crohn's ulcers" in the groin, and 1 patient had an unhealed proctectomy wound and multiple draining perineal and labial sinuses.

During the initial visit a complete history was obtained, and physical examination was performed. Laboratory studies included a complete blood count and serum chemistries (SMA 20). When present, purulent material was cultured under aerobic and anaerobic conditions.

The patient's immunologic reactivity was studied by several methods. Delayed hypersensitivity was assessed by the intradermal injection of five different antigens. In vitro lymphocyte stimulation was studied in mixed leukocyte culture utilizing phytohemagglutinin stimulation,[11] and circulating immune complexes were quantitated by a modified ^{125}I-C1q binding test.[12]

Photographs were taken before and at varying intervals after the institution of therapy.

After the initial visit, 20 mg/kg/day metronidazole [Flagyl (Searle, 250 mg tablet)] were administered orally in 3-5 doses/day. Patients were interviewed by telephone weekly and were examined monthly. They were questioned and evaluated as to adherence to the drug dosage, side effects of therapy, response of the intestinal symptoms, and their clinical condition, including fever, tenderness, discharge, induration, and erythema.

Periodic blood studies and repeat cultures of purulent drainage were obtained. Metronidazole levels were also determined using a modification of the bioassay of Ralph et al.[13]

Results

The initial response to metronidazole was objectively and subjectively striking. Nineteen patients reported a decrease in pain and tenderness within 1-2 wk after starting therapy and the other 2 patients noted improvement after 6 and 8 wk, respectively. Objective improvement, as evidenced by a clearly discernible decrease in erythema and swelling, a decrease or cessation of drainage, and beginning epithelialization of open wounds was observed in 18 patients, 15 within 2 mo and 3 within 4 mo. Improvement was most striking in those patients with "metastatic Crohn's ulcers" in whom the ulcerative process was rapidly arrested and healing began within 2 wk (Figure 1).

Continued healing and diminution in drainage was noted in 15 of the 18 patients maintained on therapy for more than 2 mo. Seventeen of the 18 patients have been maintained on metronidazole for 5-21 mo; 6 of these have been on the drug for more than 1 yr. Ten patients have shown complete healing of the perineal disease, with epithelialization of ulcerations and closure of draining fistulas. Five other patients have shown advanced, but not complete healing of the perineum. One of these 5 had a rectovaginal fistula and perineal fistulas. The perineal wounds have healed, but she continues to pass gas through the vagina, although roentgenologically the rectovaginal fistula is closed. Other than the passage of gas through the vagina she remains asympto-

Table 2. Surgical Therapy Before Metronidazole (17 Patients)

Intestinal	No.	Perineal	No.
Ileotransverse colostomy	3	Incision and drainage	9[a]
Ileocolectomy	2	Fistulotomy	3
Subtotal colectomy	3	"Hemorrhoidectomy"	2
Total colectomy	2	Skin grafting	2
Proctectomy (second stage)	2		
Ileal resection	1		
	13 (in 9 patients)		16 (in 10 patients)

[a] Most had mutiple procedures.

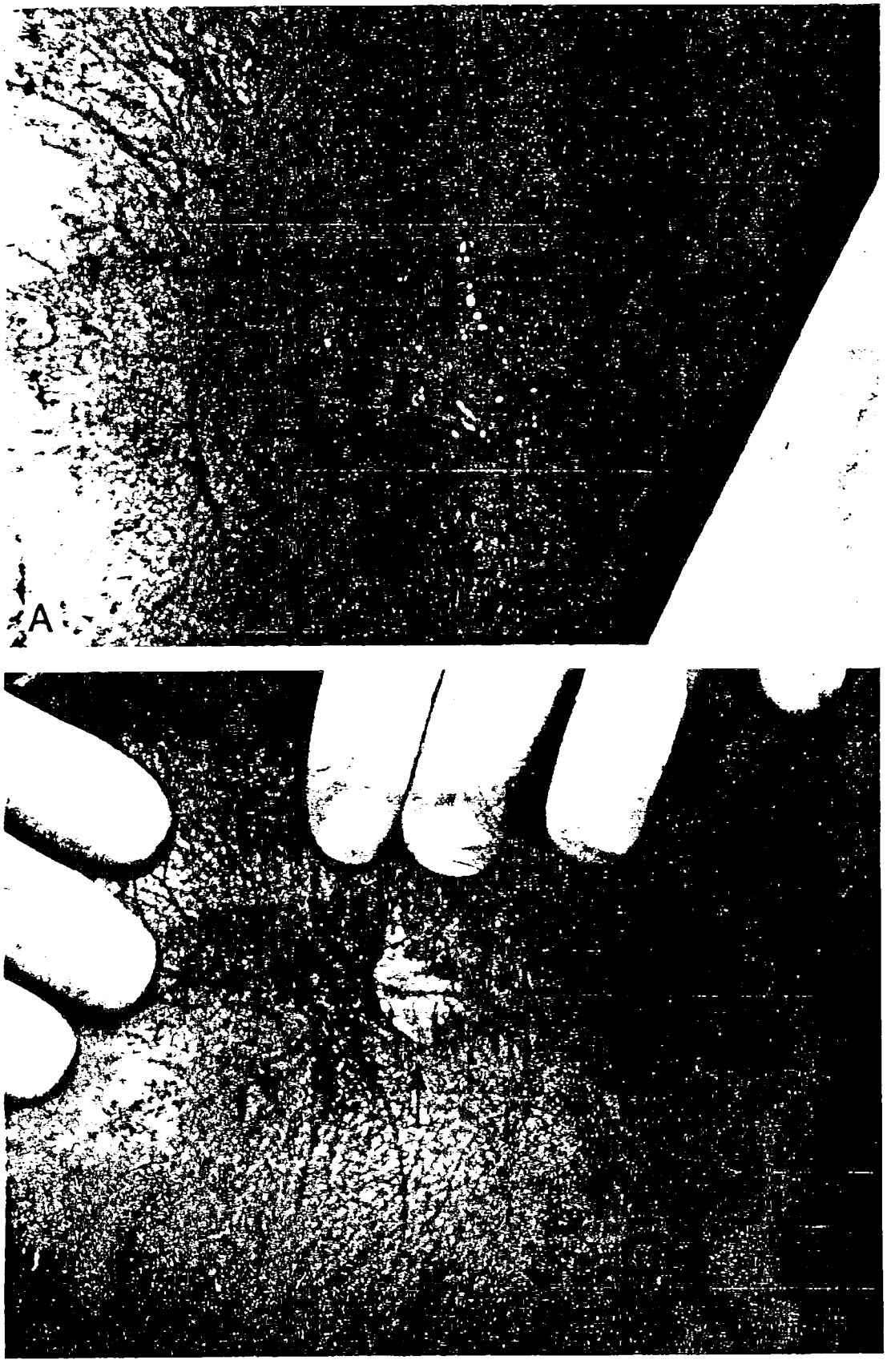

Figure 1. "Metastatic" Crohn's ulcer of the groin in a 36-yr-old woman with unhealed perineal wounds after proctocolectomy. *A.* Before metronidazole. *B.* After 6 mo of metronidazole the ulcer (*single arrow*) is completely healed; dimple (*double arrow*) indicates healed site of previous fistula.

matic. Two patients have had intermittent subjective improvement, but on examination their perineal disease continues to be active. The 1 patient who showed a transient and limited subjective response when maintained on therapy for more than 2 mo had far advanced perineal disease and a post-proctectomy sinus. In this patient the drug was discontinued after 6 mo, and a radical perineal excision was performed with excellent healing. Her perineal lesions strongly resembled lymphogranuloma venerium (i.e., esthiomene), however, her serologic studies were not diagnostic and histologic sections from her resected colon were most consistent with Crohn's colitis.

Metronidazole was discontinued in 3 patients during the initial 2 mo of treatment. In the 1st of these patients, the perineal disease was improving when she developed painful neuropathy of the feet. Therapy was discontinued because of our lack of knowledge regarding the reversibility of this complication after reduction in the daily dose of metronidazole. After cessation of the drug her neuropathy disappeared, but her perineal disease worsened. In a 2nd patient we discontinued therapy in spite of a good response because of her failure to adhere to the regimen. The 3rd patient discontinued the drug on her own, claiming the disease was "cured" after closure of a rectoforchette fistula and improvement in bowel function. Relapse occurred 4 mo later, and she was restarted on the drug with almost complete healing after 4 mo of therapy.

During healing, purulent discharge became serous or serosanguineous. Fistulous openings frequently developed elevated nipplelike projections of granulation tissue (Figures 2 and 3), which later resolved, leaving a dimple as the only evidence of previous fistulous disease (Figure 2).

In patients with large ulcers, where there was extensive loss of cutaneous and subcutaneous tissue, complete epithelialization occurred leaving a depressed area with a rolled edge (Figure 4).

Improvement of the perineal disease was accompanied by an improved sense of well being in 20 patients. This subjective improvement persisted in 16 of the 17 patients maintained on therapy. Eleven of 12 patients who had had diarrhea before therapy reported improvement in both consistency of stool and number of bowel movements. In 8 of these, bowel

Figure 2. Simple fistulas in a 29-yr-old woman 2 mo after beginning metronidazole. The nipple of granulation tissue (arrow) is typical of the intermediate phase of healing. A healed fistula is seen below the finger at left.

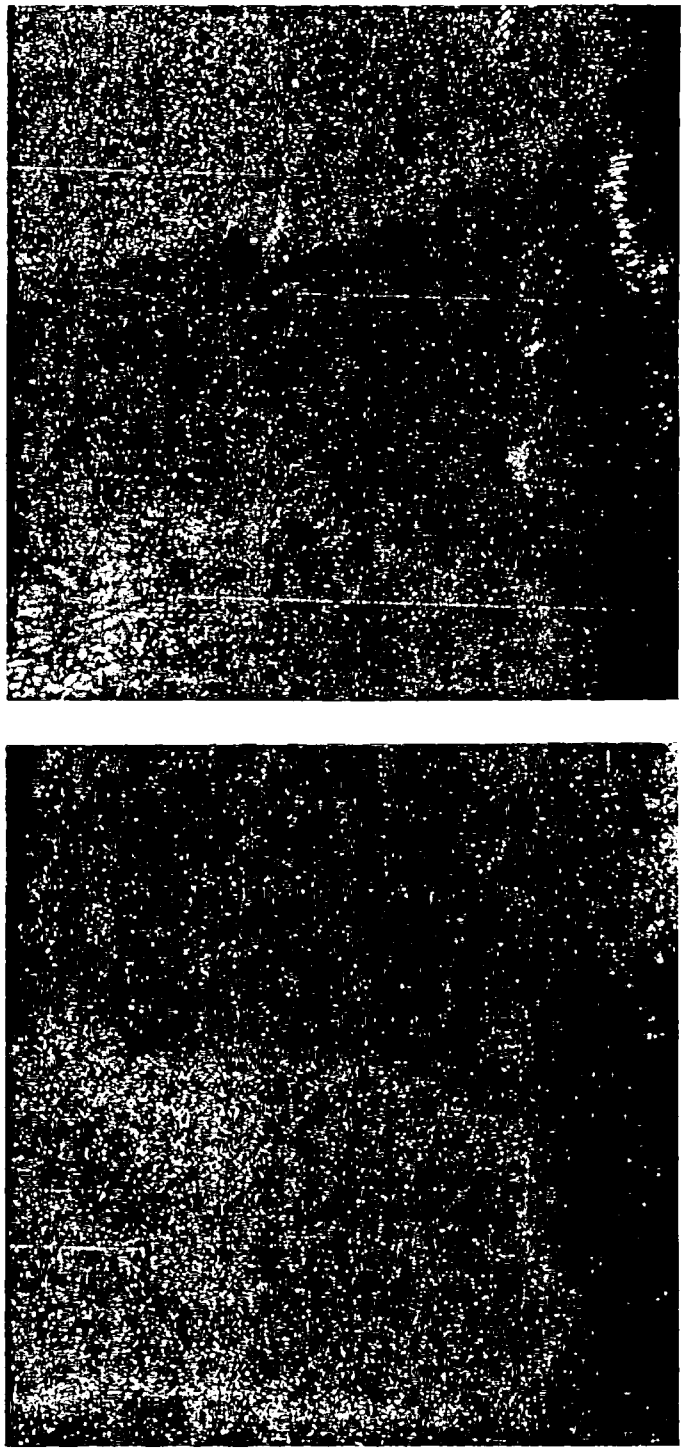

Figure 3 Multiple perineal fistulas in a 31-yr-old man. *A*. Before metronidazole the entire buttock is involved and the fistulas are draining pus. *B*. After 4 mo of metronidazole the inflammation has localized and healing is progressing but is not complete.

function returned to normal. Body weight increased or remained unchanged in all but 2 patients.

Objective evidence of systemic improvement was reflected by a rise in hematocrit in all 17 patients maintained on therapy. A rise in serum albumin of 24.5% of the initial value was noted when pretreatment levels were less than 3.5 g/dl and an increase of 7.1% was noted in those patients with a pretreatment albumin between 3.5 and 4.0 g/dl.

Fourteen of 21 patients were anergic before therapy, as evidenced by a failure to show skin reaction to intradermal injection with several antigens. Six of these patients were on prednisone, and 8 were not. While on metronidazole, 1 of the 7 patients who had

Figure 4. Healed postproctectomy wound after 6 mo of metronidazole therapy. The wound is completely epithelialized with a ridge of skin at its periphery.

reacted became anergic, and 1 of the 14 patients who had been anergic reacted to a single antigen.

Lymphocyte reactivity to mitogenic stimulation was assessed in 16 patients, including 11 before and after therapy. No pattern of change after the administration of metronidazole was noted.

C1q binding, a postulated marker for circulating immune complexes, was determined in 17 patients; 7 showed an elevated value. Six patients were tested both before and while on therapy; 4 of these showed a fall in C1q binding on metronidazole.

Organisms found in aerobic cultures are shown in Table 3. In 12 patients, cultures of aerobic organisms were obtained before therapy. In 2 of these, therapy was discontinued. Four of the remaining 10 patients healed, and no drainage could be cultured. In the 6 others, aerobic cultures of the drainage remained positive while on therapy, although the organisms cultured were not always the same as those found before treatment.

Organisms found in anaerobic cultures obtained before therapy in 6 patients are shown in Table 3. Two of these patients healed, but in 3 of the 4 in whom drainage continued, anaerobic cultures were positive while on metronidazole. Cultures obtained from 2 other patients after therapy was instituted showed no anaerobic growth.

Most patients tolerated therapy without significant side effects. Five patients on the drug for 3–7 mo developed peripheral neuropathy, characterized by numbness and tingling of the lower extremities. In 1 of these patients therapy was discontinued and the neuropathy disappeared. In 2 other patients the neuropathy promptly reversed when the daily dose was lowered by 250 mg. One patient whose dose was lowered by 500 mg continues to have numbness although it has improved. The last patient had minimal numbness of the tips of the toes and has been maintained on the same dosage although this symptom has persisted. Other side effects included a metallic taste (12), darkening of the urine (15), anorexia (3), nausea (2), vomiting (1), and vertigo (1). In spite of being warned to avoid alcohol beverages because of a possible disulfuramlike effect of the drug, the majority of patients admitted to having tried alcoholic beverages with no untoward effects.

Serum concentrations of metronidazole were determined in 16 patients at various times. The average serum concentration was 15.5 μg/ml (median: 14.8 μg/ml, range: 3.1–30.1 μg/ml). Concentrations of metronidazole were greater than 18.8 μg/ml in 4 of the 5 patients with peripheral neuropathy, although 2 patients who had levels greater than 19 μg/ml did not complain of neuropathy.

Discussion

This study strongly suggests that metronidazole is effective in the therapy of chronic unremitting perineal Crohn's disease. Nineteen of the patients had not responded to previous treatments over months to years. However, it is a retrospective study and not a randomized, double-blind controlled one. Thus, while the rapid and striking subjective im-

provement in 20 of 21 consecutive patients and the complete or almost complete healing in 15 of 18 patients maintained on the drug are not likely to be chance occurrences, corroboratory prospective studies will be necessary.

The chronic and unremitting nature of perineal Crohn's disease has been a source of frustration to both patients and physicians. Perineal forms of the disease include: (a) anal fistulas, abscesses, polyps, and ulceration[14]; (b) metastatic Crohn's disease, a term used to describe an indolent granulomatous ulceration of the skin separated from the perianal area by normal skin[15]; and (c) unhealed surgical perineal wounds.[16] These lesions occur in approximately 60%–80% of patients with Crohn's disease of the large intestine and in 25% of those with only small bowel involvement,[17] and are independent of the intestinal disease. They may precede the intestinal manifestations[3] or persist, and even progress, after the intestinal disease has been successfully controlled medically or removed surgically.

Local surgical procedures for the perianal abscesses and fistulas are usually followed by delay or failure of wound healing. Typical poor results are those in Baker and Milton-Thompson's series[18] in which 43% of 111 patients with fistulas-in-ano ultimately required excision of the rectum. Even after proctectomy, 48% of 180 patients from multiple series failed to heal their perineal wounds after 6 or more months.[16]

The dismal results with standard surgical techniques have prompted studies using both nonoperative modalities and combined surgical and medical approaches. Conventional therapies such as steriods, sulfasalazine, and broad spectrum antibiotics have not been effective in perineal Crohn's disease.[19] Total parenteral nutrition, originally recommended in the treatment of Crohn's disease by Dudrick et al.,[20] has now been widely used for preoperative preparation of complicated gastrointestinal cutaneous fistulas and as a primary therapy. Cohen et al.[21] from our institution reported on the use of total parenteral nutrition in 7 children with Crohn's disease, and noted marked improvement in perianal disease in all 3 patients with this complication; in 2, complete healing occurred. After continued use of this modality for perineal Crohn's disease, we have found that temporary improvement can be expected in most patients and that complete healing occurs; however, in most instances the disease recurs. Immunosuppressive agents such as azathioprine and 6-mercaptopurine have also been used in the management of Crohn's disease, but not specifically for its perineal complications. The results of numerous anecdotal and several controlled studies are contradictory.[22,23]

Table 3. Organisms Cultured from Perineal Wounds

	Prior to Therapy (12 patients)	On Therapy (7 patients)
Aerobic		
E. coli	8	5
Proteus mirabilis	6	6
Proteus morganii	1	—
Enterococcus	3	2
Staphylococcus		
aureus	2	3
epidermidis	6	1
Streptococcus		
beta hemolytic	1	—
bovis	1	—
Corynebacterium	2	1
Enterobacteriacae	1	—
Klebsiella	—	2
Citrobacter species	—	1
Anaerobic	(6 patients)	(6 patients)
Bacteroides		
fragilis	3	—
melaninogenicus	3	1
thetaiotaomicron	—	1
corrodens	1	—
other species	3	2
Fusobacterium nucleatum	1	—
Fusobacterium mortiferum	1	—
Peptococcus	2	—
Propionibacterium	2	1
No growth	1	4

Various surgical procedures have been advocated for perineal Crohn's disease. Diverting ileostomy or colostomy were of little benefit in patients with severe perirectal complications in McIlrath's study.[24] Persistence or worsening of the lesions led to proctocolectomy in 4 of 8 patients. As previously stated, even proctocolectomy has resulted in unhealed perineal wounds in one-half of the patients.[16] Wide debridement and unroofing,[25] saucerization with skin grafting combined with parenteral ACTH,[26] muscle flaps,[27] and myocutaneous flaps have all been used with varying degrees of success for unhealed perineal wounds.

Against the background of treatment difficulties and failures, the response of our patients to metronidazole is at least very encouraging. However, several questions remain unanswered. Although many patients have remained healed or mostly healed for up to 21 mo, we do not know what will happen over longer periods. Nor do we know if the perineal lesions will recur if the drug is discontinued or the dosage decreased. One patient discontinued the drug after 2 wk and the disease recurred after 3 mo. On the other hand, in 2 patients on metronidazole for 6 and 12 mo the drug was first tapered and then discontinued with no recurrence of disease after 5 and 3 mo, respectively. The effects of lowering dosage,

length of treatment, and discontinuation of the drug are being studied, but at this point sustained good responses have only been clearly documented with patients on continuous treatment with 20 mg/kg/day of metronidazole.

The pathogenesis of the side effects of metronidazole have not been established. They do not appear to be hypersensitivity reactions, as they have appeared after weeks or months of therapy.[28,29] The neuropathy seen in 5 of our patients all occurred after at least 3 mo of treatment. The high blood levels above 18.8 μg/ml in 4 of the 5 patients with neuropathy suggest a correlation of this complication with blood levels; the subsidence of symptoms when the dosage was lowered would support this concept. However, two patients with blood levels over 20 μg/ml did not develop a neuropathy, so other factors such as duration of treatment may also play a role.

Experimental studies have shown that metronidazole is carcinogenic in rodents and mutagenic in bacteria.[30-33] However, there have been no reported cases in which cancer has been attributed to metronidazole in humans. In the only long-term study, 771 women with documented exposure to metronidazole were retrospectively evaluated.[34] After a 10-yr follow-up, no appreciable increase in cancer was detected. While even the remote possibility of this complication must be considered in a group of patients whose primary disease has its own malignant potential,[35,36] we believe that the chronically incapacitating effect of the disease in our patients justified the risk of this therapy.

Another intriguing, but unanswered, question is the mechanism of metronidazole's effect in perineal Crohn's disease. Three possibilities can be postulated: (a) its antimicrobial effect,[37] (b) its immunosuppressive effect,[38] and (c) a direct effect upon tissue healing.[39]

Initially, use of the drug was suggested for Crohn's disease because of its antimicrobial action. It was postulated that metronidazole would control the overgrowth of organisms in the small intestine and thus improve absorption or, alternatively, by decreasing the intestinal flora, remove a source of antigen that might be of immunologic significance in the pathogenesis of disease. Although we have eradicated anaerobic organisms in several of our patients with perineal disease, in others, anaerobes persisted in spite of long-term therapy.

Later, investigators found that metronidazole effectively suppressed cell-mediated immunity, especially granuloma formation, and suggested that this action of the drug explained its effectiveness in Crohn's disease.[38] Our immunologic studies show no significant change in cell-mediated immunity as manifested by either anergy screening or in vivo lymphocyte stimulation tests. Measurements of circulating immune complexes, however, were decreased after metronidazole therapy, as demonstrated by the mean fall in C1q level from 20.9% to 11.3%.

The third possible mechanism by which metronidazole may work is by an as yet undemonstrated direct effect on wound healing. In a preliminary investigation of this possibility in rats, metronidazole had no beneficial effect on the rate of epithelialization and healing of skin wounds. Moreover, there was a significant interference with healing of fascial incisions after 6 days. While this was only a preliminary study, no positive effect of metronidazole was demonstrated.[39]

This study was undertaken to evaluate metronidazole in the treatment of the perineal manifestations of Crohn's disease. We did not radiographically or endoscopically follow the status of intestinal lesions when they were present and, therefore, cannot reach any conclusion on the beneficial effects of the drug on the gastrointestinal disease. However, the rise of the hematocrit and serum albumin levels, and the decrease in diarrheal symptoms can be construed as indirect evidence of systemic improvement.

If our early results with metronidazole for perineal Crohn's disease continue in more extensive and longer term trials, the drug will offer a promising form of therapy for this chronic unresponsive form of the disease. Confirmatory prospective studies are obviously necessary, as are the valuations of the necessity for continuous therapy, of the possibility of using lower dosages, and of the development of late resistance to the effects of the drug. Finally, if logistically possible in this disease, and morally justified in these chronically disabled patients, a randomized double-blind study should be undertaken.

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