Metronidazole in Periodontitis*

I. Clinical and Bacteriological Results after 15 to 30 Weeks

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THE STATISTICAL ASSOCIATION of certain anaerobic organisms such as black pigmented bacteroides (BPB) species and spirochetes with clinical signs of active periodontitis, i.e. bleeding upon probing and bone loss, suggests that the lesions may actually reflect a "specific infection" involving these or unidentified species. All the known oral species of BPB and spirochetes are anaerobes which suggests that antimicrobial treatment directed specifically against anaerobes might be effective in periodontal therapy. In this report, the short-term results of metronidazole treatment plus mechanical debridement in patients with extensive periodontal disease and of a double-blind clinical study in which metronidazole plus mechanical debridement is compared to placebo plus mechanical debridement are described. The findings indicate that 1 week of systemic metronidazole can optimize the clinical reduction of pockets and increase the apparent attachment in periodontitis patients who receive concurrent mechanical debridement of their root surfaces. In patients with extensive clinical involvement, metronidazole resulted in a significant reduction in the number of sites exhibiting pocket depths and attachment loss ≥ 7 mm. When metronidazole plus mechanical debridement was compared with placebo plus mechanical debridement in a double-blind study, the metronidazole patients exhibited a significant improvement in those sites initially ≥ 7 mm. The beneficial effect of the metronidazole was associated with a significant and sustained reduction of certain anaerobic organisms such as Bacteroides gingivalis and the large spirochetes. These data indicate that treatment aimed specifically toward the anaerobic component of the plaque flora can be associated with impressive clinical improvements 15 to 30 weeks after the initiation of treatment.

Periodontal disease is the foremost cause of tooth loss in adult populations.[1] In recent years the essential role of bacterial plaque in initiating and propagating a host inflammatory response in the periodontal tissues has been documented both in experimental gingivitis in humans[2,3] and in periodontitis in animals.[4-6] Moreover there appears to be an element of bacterial specificity in these periodontal infections as spirochetes[7,8] and black pigmented bacteroides (BPB)[9,10] are signifi-cantly elevated in plaques removed from sites of active periodontitis, and Actinobacillus actinomycetemcomitans is either present, or in high proportions in plaques taken from sites of bone loss in patients diagnosed as exhibiting localized juvenile periodontitis[11,12] or rapidly progressing periodontitis.[13] Peripheral blood taken from periodontal patients reveals significant increases in specific antibodies to the above organisms.[14,15]

The statistical association of certain organisms with clinical signs of active disease, i.e., bleeding upon probing and bone loss, suggests that the observed lesions may actually reflect a "specific infection" involving these or possibly unidentified bacterial species. These observations led to the formulation of the specific plaque hypothesis (SPH), which views certain plaques as being periodontopathic because they are colonized and/or dominated by one or more bacterial types. These bacterial types are presumed, on the basis of association-type data and animal studies, to be responsible for a measurable amount of periodontal tissue

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destruction.[16] The SPH does not state that these bacterial species are responsible for all forms of periodontal disease, but rather that they are responsible for a measurable amount of the tissue destruction with the expectation that this amount will be biologically and clinically significant. Implicit in the SPH is the concept of nondisease-associated plaque.[17] For practical purposes the nondisease-associated plaque is simply plaque which is not colonized and/or dominated by the known or suspected periodontopathogens. It can be readily identified by microscopic examination as plaque that is dominated by cocci and nonmotile rods.[7,18]

BPB species, such as *Bacteroides gingivalis* and *Bacteroides intermedius*, and spirochetes are invariably elevated in periodontopathic plaques to the extent that if they are not contributors to the pathogenesis, they at least are diagnostic indicators of active disease.[10,19] All the known oral species of BPB and spirochetes are anaerobes which suggests that antimicrobial treatment directed specifically against anaerobes might be effective in periodontal therapy. The efficacy of the antiprotozoa agent metronidazole in acute necrotizing gingivitis (ANUG)[20] led to the discovery that metronidazole has a unique bacteriocidal action against anaerobes.[21] Subsequently it was shown that the curative effect of metronidazole in ANUG was associated with the significant and sustained suppression of spirochetes and *B intermedius* in plaque samples removed from the ANUG lesions.[22]

This action of metronidazole against the type of anaerobes associated with active periodontitis led to a clinical trial of metronidazole in selected periodontitis patients.[10] A 1-week treatment of metronidazole with and without scaling was associated with a sustained suppression of *B gingivalis* and spirochetes for periods of 6 months or more. In addition the sites with an initial probing depth of 6 mm or more exhibited a probing depth reduction of 2 mm or more and an apparent attachment gain of 1.5 mm.[10] In a study conducted in Sweden, metronidazole, given for three 2-week periods, each separated by an interval of 8 weeks, was found to give clinical and bacteriological results comparable to that obtained by rigorous mechanical debridement which was delivered in a series of four visits.[23] Both of these clinical studies indicate that metronidazole may be an antimicrobial agent of therapeutic value in the treatment of active periodontal infections.

In the present report, the short-term results of metronidazole treatment plus mechanical debridement in patients with advanced periodontal disease are presented, and a double-blind clinical study in which metronidazole plus mechanical debridement is compared to placebo plus mechanical debridement is described.

MATERIALS AND METHODS

Individuals with clinical evidence of bone loss were recruited into the study after being diagnosed as having an anaerobic periodontal infection, i.e., ten per cent spirochetes in one or more subgingival plaque samples. They were told of metronidazole's spectrum of activity against anaerobes and that we were evaluating whether metronidazole would be efficacious in the treatment of anaerobic periodontal infections. Patients were advised of the mutagenicity of metronidazole in bacterial systems,[24] and of the potential adverse reactions of metronidazole with alcohol consumption in some individuals. They were also told that in certain, but not all, rodent species, lifetime administration of high dosages of metronidazole, i.e., up to 0.6% of the diet, was associated with both tumors and longevity.[25,26] The lifetime dosage used in some of the animal studies[26] was about 3,500 times the total dosage used in the present investigation. This therapeutic dosage for humans has not been associated with human tumors[27,28] or with birth defects.[29,30] They were told that we were investigating this usage of metronidazole under an investigational new drug exemption from the Food and Drug Administration (FDA).

Metronidazole-Mechanical Groups. Forty patients with multiple sites of periodontal bone loss were assigned to one of two groups depending on the initial severity of their periodontal condition. If the number of sites with bone loss was extensive, i.e., an average of 20 or more sites per patient with apparent attachment loss of 7 mm or more, the patients were placed in an advanced disease group which received both metronidazole and meticulous root surface debridement. If the number of sites with bone loss was moderate, i.e. an average of about 10 sites per patient with attachment loss of 7 mm or more, the patients were placed into a double-blind group. The patients in the double-blind group received the same meticulous root surface debridement as the advanced disease group, but had a 50% chance of receiving either metronidazole or a placebo medication. All patients were given 21 tablets containing either metronidazole or placebo (250 mg) (both metronidazole, Flagyl®, and placebo were gratuitously provided by the G. D. Searle Co) at the first session of root scaling with instructions to take three tablets a day for 7 days. Compliance was monitored by history.

This method of patient assignment resulted in three groups who each received all the mechanical debridement and oral hygiene instruction that was deemed necessary to bring them successfully through the hygienic phase of periodontal therapy. The groups differed in that a more severely diseased set of individuals was known to have received metronidazole (metronidazole-mechanical group), whereas a less diseased set of individuals was randomly assigned in a double-blind fashion to either metronidazole (double-blind, metronidazole-mechanical group) or to placebo (double-blind placebo-mechanical group).

Bacteriological Procedures. Subgingival plaque was removed from one periodontal pocket per quadrant in

each patient for a total of four samples per patient. The sites chosen appeared from x-ray examination to be the most severely involved in each quadrant and were usually about molar teeth. The supragingival plaque about the sample site was removed with a curette and discarded. The root surface was then scaled and the adherent plaque on the scaler tip was transferred to a vial containing 0.5 ml of reduced transport fluid (RTF) without EDTA.[31] The plaque sample was immediately placed within the anaerobic chamber and after dispersing for 20 seconds with a Vortex mixer, a 50 μl aliquot was removed for microscopic examination. The remaining sample was diluted to 4 ml, sonically dispersed for 20 seconds with a Kontes sonifier,* serially diluted in RTF and plated automatically with a spiral plater† on a variety of selective and nonselective media. The method enabled us to obtain microscopic and cultural data on the same plaque sample.

The total anaerobic count, the count of BPB species, *Capnocytophaga* species, *Fusobacterium nucleatum* and *Actinomyces odontolyticus* were obtained by identification of their distinctive colonies on enriched trypticase soy agar (ETSA).[32] Either all or representative colonies of BPB were identified as *B gingivalis*, *B intermedius* and *Bacteroides melaninogenicus* initially by their ability to use glucose, to hydrolyze esculin and to produce indole,[22] and subsequently by a rapid test using chromogenic enzyme substrates.[33,34] *Actinomyces viscosus* and *Actinomyces naeslundii* were differentiated by catalase activity of colonies growing on a selective GMC agar.[35] The total count of facultative organisms, *Streptococcus sanguis* and *Streptococcus mutans* were obtained from growth on ETSA agar containing 2% sucrose and 20 μg/ml of metronidazole, which was incubated anaerobically. *Veillonella* colonies were enumerated on a medium containing MM10 base, minus blood but supplemented with lactate, vancomycin and a 0.004% bromocresol purple indicator.

Ten μl of the aliquot removed for microscopic examination was placed on a glass slide, covered with a 22 × 30 mm cover slip, sealed and viewed by dark-field microscopy. Either 200 organisms or the number of organisms in 20 high power fields (HPF) were enumerated, depending on which event occurred first. The single cells were identified as spirochetes, selenomonads, motile rods, fusiforms, nonmotile rods or cocci.[7,22] The spirochetes were further subdivided into large, intermediate and small size spirochetes.

Clinical Evaluation. All teeth, including molars with furcation involvement, were scored for pocket depth (probing depth) and loss of attachment using procedures previously described.[36] All readings were obtained by one individual (ECM), who was not aware of the medications given to participants in the double-blind study.

Statistical Analysis. The counts for each organism enumerated culturally and microscopically were recorded on forms suitable for computer processing.

The proportions of these organisms were calculated by dividing the viable count of the specific organism by the total viable count on the ETSA agar plate in the case of the cultural data, and by dividing the microscopic count of the specific organism by the total microscopic count in the case of the microscopic data. If there were less than 20 colony-forming units (CFU) on the ETSA plate or in the microscopic count, no proportions were calculated. This was to eliminate distortions of the data which can occur when the denominator is very low, as can be the case for microscopic counts following treatment.

The total counts and the proportions of organisms in each cultural and microscopic sample were statistically analyzed using the computer programs available in the Michigan terminal system. Comparisons between the placebo and metronidazole samples in the double-blind study were analyzed by the parametric student *t* test. The effect of metronidazole or placebo plus mechanical debridement on bacterial and clinical parameters within each group was evaluated by the paired *t* test.

RESULTS

All patients reported that they used the entire supply of medication that was provided them. A few patients noted a metallic taste. Otherwise no complaints were recorded. Some patients were unable to, or did not, return for clinical examinations of pocket depth and attachment loss that were specially scheduled following completion of the hygienic phase of therapy. This meant that in some cases we had posttreatment bacteriological data for patients in whom we had no posttreatment clinical measurements. We chose to analyze all the available bacteriological data within a group, but to restrict our bacteriological comparisons between groups to only those subjects for whom we had complete clinical data.

The patients assigned to the known metronidazole group initially had significantly more sites per dentition that had pocket depths or attachment loss greater than 7 mm, than did those patients assigned to the double-blind groups, (Figs. 1 and 2). This increased clinical involvement was the justification for placement of these patients into a distinct group.

These advanced-disease patients responded favorably to treatment in that 15 to 30 weeks after usage of metronidazole and about 10 to 20 weeks after the completion of the mechanical debridement of the root surfaces, the number of pocket sites per patient that were ≥7 mm had decreased from 22.8 to 4 (mean values) and the number of sites with attachment loss ≥7 mm decreased from 25.3 to 14.6 (mean values). The magnitude of this change was greater than that observed in the double-blind groups (Figs. 1 and 2).
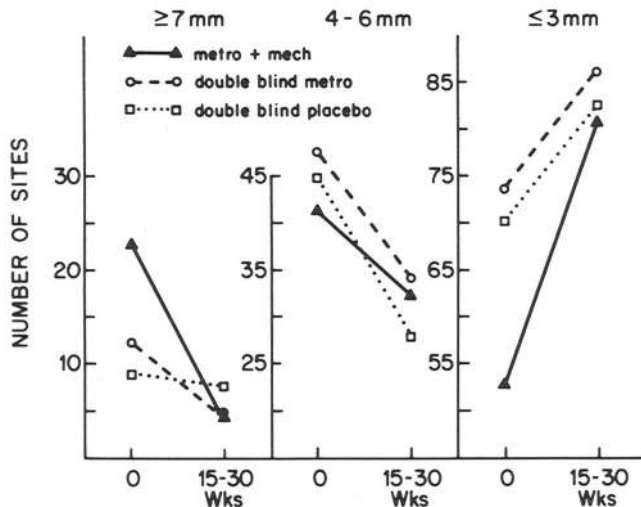
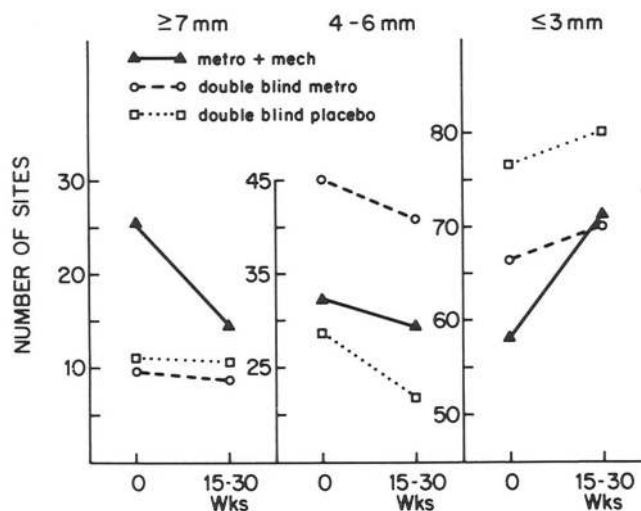**Figure 1.** *Frequency distribution of number of sites with pockets.*

Figure 2. *Frequency distribution of number of sites with attachment loss.*

Treatment also resulted in a pronounced increase in the number of sites in which the pocket depths and attachment loss were ≤3 mm (Figs. 1 and 2).

Metronidazole treatment in the double-blind patients reduced the number of pockets that were ≥7 mm from 12 per patient to 4 per patient (mean values) and the number of sites with attachment loss ≥7 mm from 9.7 to 8.8 (mean values). Placebo treatment reduced the number of pockets that were ≥7 mm from 8.9 per patient to 7.7 per patient (mean values) and the number of sites with attachment loss ≥7 mm from 11.3 to 10.1 (mean values) (Figs. 1 and 2).

The magnitude of probing depth (pocket) reduction and the apparent attachment gain in each site found in these double-blind patients were determined. In sites that were initially 4 to 6 mm in depth or which exhibited 4 to 6 mm attachment loss, both metronidazole and placebo treatments caused about a 1-mm decrease in pocket depth and about a 0.3 mm apparent gain in attachment (Table 1). The slight advantage observed in

the metronidazole group was not significant. However, in the deeper pockets and in sites with greater attachment loss, there was a significant advantage associated with metronidazole treatment (Table 1). Thus while placebo plus mechanical treatment reduced pocket depth 1.6 mm and increased attachment gain by 0.3 mm, the metronidazole plus mechanical treatment reduced pocket depth by 3.2 mm and increased apparent attachment gain by 1.4 mm.

The reasons for the apparent clinical effectiveness of the various treatments were sought in the analysis of the bacterial composition of the subgingival plaque in the most clinically diseased site per quadrant. All treatments reduced the levels of bacteria in the plaque samples as judged by total viable counts on anaerobically incubated ETSA plates, and by the number of bacteria observed per high-power field (HPF) of the darkfield microscope (Table 2). The high viable counts noted posttreatment in the double-blind metronidazole group reflected a few very high counts that raised the mean value, but not the median value. These outlying

Table 1
*Effect of Metronidazole or Placebo Treatment Superimposed Upon Instrumentation—Double Blind Study**

Original measure-ment	Change in measurement		
	Metronidazole	Placebo	Difference
Pocket depth			
4–6 mm	−1.19 mm	−1.05 mm	0.14 mm
>6 mm	−3.19 0.03†	−1.55	1.64
Attachment distance			
4–6 mm	+0.38	+0.28	0.10
>6 mm	+1.42 0.05†	+0.23	1.19
No. of patients	7		

* Results are 2 to 4 months after completion of hygienic phase.
† Difference between groups is significant, *t* test.

Table 2
Effect of Metronidazole or Placebo Plus Mechanical Debridement on Size of Pocket Flora

Treatment regimen*	Pretreatment	Posttreatment	
		0–2 wks	15–30 wks
Total Count × 10⁶/ plaque			
Metro + Mech	31.3ᴾ	8.6	8.4
DB Metro + Mech	24.1	24.1	20.3
DB Placebo + Mech	31.1	15.5	7.9
% Facultative			
Metro + Mech	19.8ᴾ	91.8	44.2
DB Metro + Mech	42.0ᴾ	63.3ᴾ	44.2
DB Placebo + Mech	33.3	53.4	57.8
Microscopic Counts/ HPF			
Metro + Mech	15.2	5.8	5.7
DB Metro + Mech	20.9	6.9	6.3
DB Placebo + Mech	19.4	7.6	6.0

* Metro = metronidazole; Mech = mechanical; DB = double-blind.

P = paired *t* test; values with these superscripts or ☐ are significantly different from other values in row.

values could be due to the non- or underutilization of the metronidazole by certain participants.

The patients with advanced disease differed initially from the double-blind patients in having a reduced percentage of facultative bacteria in their plaques (Table 2). Treatment in these patients resulted in a significant increase in the proportions of facultative bacteria that was still evident 15 to 30 weeks after the administration of metronidazole. The double-blind patients also exhibited an increase in the proportions of facultative bacteria as a result of treatment, but this increase was not significant, probably due to the relatively high initial proportions of facultative organisms in these patients (Table 2).

The effect of the various treatments on selected cultivable anaerobes is shown in Table 3. All treatments resulted in a decrease in the proportions of *B intermedius* in the immediate postmedication period (Table 3). The reductions observed in the metronidazole groups were still evident 15 to 30 weeks after treatment, whereas the reduction in the placebo group did not persist. All treatments also reduced the proportions of *B gingivalis*, but only those in the metronidazole groups were significant. The proportions of *F nucleatum* declined significantly following medication in the known metronidazole group but then significantly increased 15 to 30 weeks later. The proportions of *A odontolyticus* increased following treatment in all groups (Table 3).

The effect of the treatments on selected facultative

or microaerophilic species is shown in Table 4. Metronidazole should not affect these organisms so that a proportional increase would be expected. This was particularly evident in the case of *S mutans* and *S sanguis*, but less evident in *A viscosus* and *A naeslundii* and not observed in the case of the *Capnocytophaga* species (Table 4). Some of this increase was due to the mechanical treatment, as proportional increases were observed in the placebo plus mechanical group, especially in the proportions of *S sanguis*. The proportions of *A viscosus*, *S sanguis* and *S mutans* declined with time posttreatment. Nevertheless the proportions of *S mutans* were still elevated from baseline values some 15 to 30 weeks after metronidazole treatment (Table 4).

Spirochetes comprised about 35% of the organisms in these plaque samples (Table 5). Their proportions decreased in all treatment groups, but significantly so only in the metronidazole groups. Fifteen to 30 weeks after medication, the metronidazole groups still exhibited about a 50% reduction in spirochetes, but the placebo group had returned to pretreatment values.

The spirochetes were differentiated into large, intermediate and small sizes. Metronidazole significantly reduced the proportions of large spirochetes in both groups, often to undetectable levels for the entire period of observation. The mechanical treatment reduced the proportions of the large spirochetes initially, but then

Table 3

Effect of Metronidazole and/or Mechanical Debridement on Subgingival Proportions of Selected Anaerobes

Treatment regimen*	Pretreat-ment	Posttreatment	
		0–2 wks	15–30 wks
% *B intermedius*			
Metro + Mech	15.8 (40)^P	3.4 (40)†	3.1 (32)†
DB Metro + Mech	10.0 (35)	2.5 (35)	5.9 (22)
DB Placebo + Mech	9.6 (51)	4.5 (51)	8.6 (32)
% *B gingivalis*			
Metro + Mech	3.8 (41)^P	0.1 (41)^P	1.4
DB Metro + Mech	5.9 ^{P}	0.3	0.9
DB Placebo + Mech	5.8	1.4	2.0
% *F nucleatum*			
Metro + Mech	3.6 ^{P}	1.3 ^{P}	4.2 ^{P}
DB Metro + Mech	3.4	3.0	9.8 ^{P}
DB Placebo + Mech	4.6	4.5	3.0
% *Veillonella*			
Metro + Mech	2.4	0.9	1.9
DB Metro + Mech	3.2	1.4	4.1
DB Placebo + Mech	1.7	2.8	1.7
% *A odontolyticus*			
Metro + Mech	2.0	4.0 ^{P}	0.6 ^{P}
DB Metro + Mech	1.3 ^{P}	1.7	2.9 ^{P}
DB Placebo + Mech	0.4	2.0	0.3

* Metro = metronidazole; Mech = mechanical; DB = double-blind.

† Number of plaque samples involved in paired comparison.

P = paired test; values containing these superscripts or ☐ are significantly different from other values in row.

Table 4

Effect of Metronidazole and/or Mechanical Debridement on Subgingival Proportions of Selected Facultative and Microaerophilic Species

Treatment regimen*	Pretreat-ment	Posttreatment	
		0–2 wks	15–30 wks
% *Capnocytophaga*			
Metro + Mech	1.0 (40)†	0.9 (40)†	1.4 (32)†
DB Metro + Mech	4.6 (35)	4.0 (35)	3.0 (22)
DB Placebo + Mech	1.4 (51)	1.8 (51)	2.4 (32)
% *A viscosus*			
Metro + Mech	0.7	2.0	0.9
DB Metro + Mech	2.7	5.3	2.3
DB Placebo + Mech	2.2	3.9	2.9
% *A naeslundii*			
Metro + Mech	0.02	0.5	2.0
DB Metro + Mech	0.3	0.3	2.5
DB Placebo + Mech	0.3	1.3	0.2
% *S sanguis*			
Metro + Mech	4.1 ^{P}	15.3 ^{P}	6.8
DB Metro + Mech	2.0	14.1	1.9
DB Placebo + Mech	2.3	9.2 ^{P}	1.5
% *S mutans*			
Metro + Mech	0.2	1.1	0.5
DB Metro + Mech	0.4	17.7	5.3
DB Placebo + Mech	0.1	1.8	0.1

* Metro = metronidazole; Mech = mechanical; DB = double-blind.

† Number of plaque samples involved in paired comparison.

P = paired *t* test; values containing these superscripts or ☐ are significantly different from other values in row.

there was a rebound at the 15 to 30-week visit (Table 5).

All treatments significantly reduced the proportions of intermediate size spirochetes, but this reduction only persisted in the patients known to have received metronidazole. Metronidazole significantly reduced the proportions of small spirochetes, whereas only slight reductions were observed in the placebo group (Table 5).

The effect of the treatments on other morphotypes that could be distinguished on darkfield microscopy are presented in Table 6. All treatments caused an immediate increase in cocci, but this increase was only sustained in the known metronidazole patients. The selenomonads decreased in the metronidazole groups whereas the fusiforms increased in these patients. There was a significant transient increase in rods in the known metronidazole patients.

Between-group comparisons were limited to the participants in the double-blind study who were present for both clinical measurements (Figs. 1 and 2). Prior to treatment these two groups were balanced in terms of suspected periodontopathic organisms such as *B gingivalis, B intermedius, F nucleatum, A viscosus, A naeslundii* and the various *spirochetes* (Table 7). The patients destined to receive metronidazole had significantly higher proportions of *Veillonella, Capnocytophaga* species and *S mutans.*

Zero to 2 weeks after completion of treatment with either metronidazole or placebo there were significant

Table 5
Effect of Metronidazole or Placebo Plus Mechanical Debridement on Subgingival Proportions of Spirochetes; Microscopic Examination

Treatment regimen*	Pretreatment	Posttreatment	
		0–2 wks	15–30 wks
% Spirochetes			
Metro + Mech	37.8	4.7 P	17.9
DB Metro + Mech	37.8	6.8 P	19.6
DB Placebo + Mech	31.7	17.6	31.2
% Large spirochetes			
Metro + Mech	3.5 P	0	1.0
DB Metro + Mech	5.0 P	0.7	0.6
DB Placebo + Mech	4.3 P	1.1 P	11.5
% Intermediate spirochetes			
Metro + Mech	19.8 P	1.1	4.9
DB Metro + Mech	7.8	0.7 P	8.1
DB Placebo + Mech	8.8 P	2.2 P	7.0
% Small spirochetes			
Metro + Mech	14.7	3.6 P	8.7
DB Metro + Mech	23.6	5.5 P	11.1
DB Placebo + Mech	19.5	15.5	14.3

* Metro = metronidazole; Mech = mechanical; DB = double-blind.

P = paired *t* test; values containing these superscripts or □ are significantly different from other values in row.

Table 6
Effect of Metronidazole and/or Mechanical Debridement on Subgingival Organisms; Microscopic Examination

Treatment regimen*	Pretreatment	Posttreatment	
		0–2 wks	15–30 wks
% Selenomonads			
Metro + Mech	4.5	2.0	7.2
DB Metro + Mech	10.8	2.3 P	3.8
DB Placebo + Mech	5.0	4.8	6.0
% Motile rods			
Metro + Mech	4.9	3.2	3.2
DB Metro + Mech	4.6 P	2.0 P	3.4
DB Placebo + Mech	7.1	6.2	4.3
% Fusiforms			
Metro + Mech	6.4	9.5	8.5
DB Metro + Mech	4.8	5.1 P	8.0 P
DB Placebo + Mech	7.7	6.3	9.1
% Rods			
Metro + Mech	24.5 P	49.0 P	36.4
DB Metro + Mech	26.2	25.7	38.3
DB Placebo + Mech	28.9	30.6	32.6
% Cocci			
Metro + Mech	17.7 P	30.9	32.3
DB Metro + Mech	16.6	56.2 P	18.5
DB Placebo + Mech	19.5 P	31.7 P	16.4

* Metro = metronidazole; Mech = mechanical; DB = double-blind.

P = paired *t* test; values containing these superscripts or □ are significantly different from other values in row.

proportional changes in the plaque flora. The proportions of monitored anaerobes, such as spirochetes (all sizes), *B intermedius* and *Veillonella,* decreased significantly in the metronidazole patients relative to the placebo patients, whereas the proportions of *S mutans* and fusiforms increased significantly.

DISCUSSION

Several longitudinal studies have demonstrated that the maximal effect of mechanical-surgical procedures on pocket reduction and apparent attachment gain occurs during or shortly after the completion of active therapy.[37-42] This benefit can be maintained but not necessarily improved by mechanical debridement delivered at 2- to 3-month intervals.[38,42] If this is so, then a treatment strategy in periodontics should be to optimize the initial beneficial effects by tactics that are safe, effective and cost-efficient. One such tactic would be the judicious usage of antimicrobial agents in patients who are diagnosed as exhibiting an active infection or who are known to be at risk to such an infection.

The rationale behind the usage of antimicrobials in periodontal disease is valid to the extent that periodontal infections are specific infections.[16] In this case short-term intensive usage of antimicrobials may suppress the pathogenic flora, so that when the antimicrobial therapy stops, a nondiseased or normal flora may reestablish in the subgingival ecosystem. In the present investigation all patients exhibited elevated proportions

Table 7

Double-Blind Study: Effect of Metronidazole or Placebo Treatment Superimposed Upon Mechanical Root Planing*

Variable	Pretreatment		Posttreatment			
			0–2 wks		15–30 wks	
	Metro.	Placebo	Metro.	Placebo	Metro.	Placebo
No. of Plaques	25	30	22	30	23	30
Pocket Depth	5.2 mm	6.2 mm			4.5 mm	5.0 mm
Attachment Loss	5.4 mm	5.0 mm			5.1 mm	4.8 mm
Anaerobes						
Total Count × 10⁶	39.3	46.4	42.4 s→	11.4	20.3	7.6
% *B. intermedius*	6.7	10.2	0.8 s→	4.3	5.9	8.4
% *B. gingivalis*	9.4	11.6	0.2	2.3	0.9	2.0
% *Veillonella*	5.9 s→	1.5	1.5 s→	3.5	4.1	1.7
% *A. odontolyticus*	0.6	0.3	2.6	3.2	3.0 s→	0.3
% *F. nucleatum*	2.4	3.7	1.6	2.8	9.8 s→	2.9
% *B. melaninogenicus*	4.0	0.8	0.2	0.1	4.1	0.3
Facultative/Microaerophilic						
% *Capnocytophaga*	2.0 s→	0.4	1.4	1.4	3.0	2.4
% *A viscosus*	2.2	1.1	5.3	2.7	2.3	2.8
% *A. naeslundii*	0.4	0.2	0.1	1.8	2.5	0.3
% *S. sanguis*	2.8	2.1	11.4	9.0	1.8	2.4
% *S. mutans*	2.1 s→	0.1	23.2 st→	2.0	5.3	0.2
% Facultative	27.9	30.3	64.9	55.7	46.7	63.3
Microscopic						
Bacteria/HPF	23.1	20.1	8.2	5.2	9.9	6.0
% Spirochetes	27.3	29.1	2.3 st→	19.1	19.6	28.7
% large	2.9	3.6	0.04 st→	4.8	0.6 s→	10.9
% intermediate	10.8	12.2	0.5 st→	4.3	8.1	6.6
% small	12.5	15.1	1.8 st→	13.7	11.1	13.6
% Selenomonas	6.0	4.8	3.2	3.9	3.8	5.9
% Motile rods	4.6	5.0	4.3	6.6	3.4	4.3
% Fusiforms	5.6	8.6	7.7 s→	3.5	8.0	9.2
% Rods	31.3	32.8	30.7 ←s	30.1	38.2	32.6
% Cocci		20.6	49.0	31.4	18.5	16.5

* Values connected by → are significantly different by Student *t* test (S), *P* = 0.05.

† Signifies that significance *P* is less than 0.01.

of spirochetes and BPB in their plaques which permitted us to make a diagnosis of an active anaerobic infection. The patients differed in the number of sites which exhibited clinical morbidity such as pocket depth and attachment loss. It was this extent of morbidity, rather than obvious bacterial changes, that caused us to recognize two types of patients, those with numerous sites of attachment loss (advanced disease), and those with a moderate number of sites (Figs. 1 and 2). The former patients were given metronidazole, whereas the latter were entered into a double-blind study.

The advanced disease patients showed a profound clinical improvement following 1 week of metronidazole and rigorous mechanical debridement (Figs. 1 and 2). How much of this was due to the usage of metronidazole and how much to the mechanical debridement cannot be stated, other than to note that two of the

patients in this group had, in the past, received complete conventional periodontal therapy and thus might be considered as refractory patients. The bacteriological changes that occurred are consistent with a metronidazole effect as anaerobes such as BPB and spirochetes were suppressed for 15 to 30 weeks (Tables 3 and 5).

Of particular interest in these patients was the apparent increase in attachment that was detected clinically with the probe. If these measurements reflect accurately what is happening at the base of the pocket, then some of the pocket reduction that occurred in these patients occurred at the bottom of the pocket. If so, then x-rays might reflect this change in pocket configuration. Non-standardized x-rays taken of these patients suggested that the bone levels about some of these teeth did not decrease over time and may have improved (Fig. 3).

The patients assigned to the double-blind study were

similar to the advanced disease patients in terms of the proportions of spirochetes and BPB in their plaques. The metronidazole clearly suppressed the proportions of these indicator-organisms in the subgingival plaque immediately following medication both relative to pretreatment values and to placebo treatment values (Tables 3, 5 and 7). However, at the 15 to 30 week interval, only the proportions of the large spirochetes were still significantly suppressed in the metronidazole group relative to the placebo group (Table 7). This could indicate that the continued suppression of these organisms was contributing to or was responsible for the improved periodontal health in the metronidazole patients, or that the higher proportions of these organisms in the placebo patients were an early indicator of recurrence of an infection. In this regard it should be noted that only a few of the many anaerobic species present in plaque[43] are identified by our bacteriological approach. Thus unidentified anaerobes such as *Eubacterium* species and *Peptostreptococcal* species[43] should have been suppressed by the metronidazole, but the duration of this suppression is not known.

Metronidazole is not an antiplaque agent. In fact,

metronidazole should select for plaque-forming organisms such as *S mutans*, *S sanguis*, *A viscosus* and *A naeslundii*, because these organisms are microaerophilic and/or facultative. This occurred in the short run for *S mutans*, *S sanguis* and *A viscosus*, but with the exception of *S mutans* this selection was not evident in plaques removed 15 to 30 weeks after medication.

The patients destined to receive metronidazole initially had low proportions of *S mutans*, but the proportions were significantly higher than those found in patients destined to receive placebo (Table 7). Metronidazole led to a large proportional increase in *S mutans* in those plaques removed 0 to 2 weeks after medication, and this increase, while somewhat subdued, was still evident some 15 to 30 weeks after the metronidazole (Table 7). This selection for *S mutans* was without apparent clinical significance in our patients but does indicate that the usage of metronidazole in caries-active patients might be contraindicated, or that supplemental topical fluoride treatments should be used.

The *Capnocytophaga* species and *A actinomycetemcomitans* are also resistant to metronidazole. The levels of the *Capnocytophaga* species but not their proportions
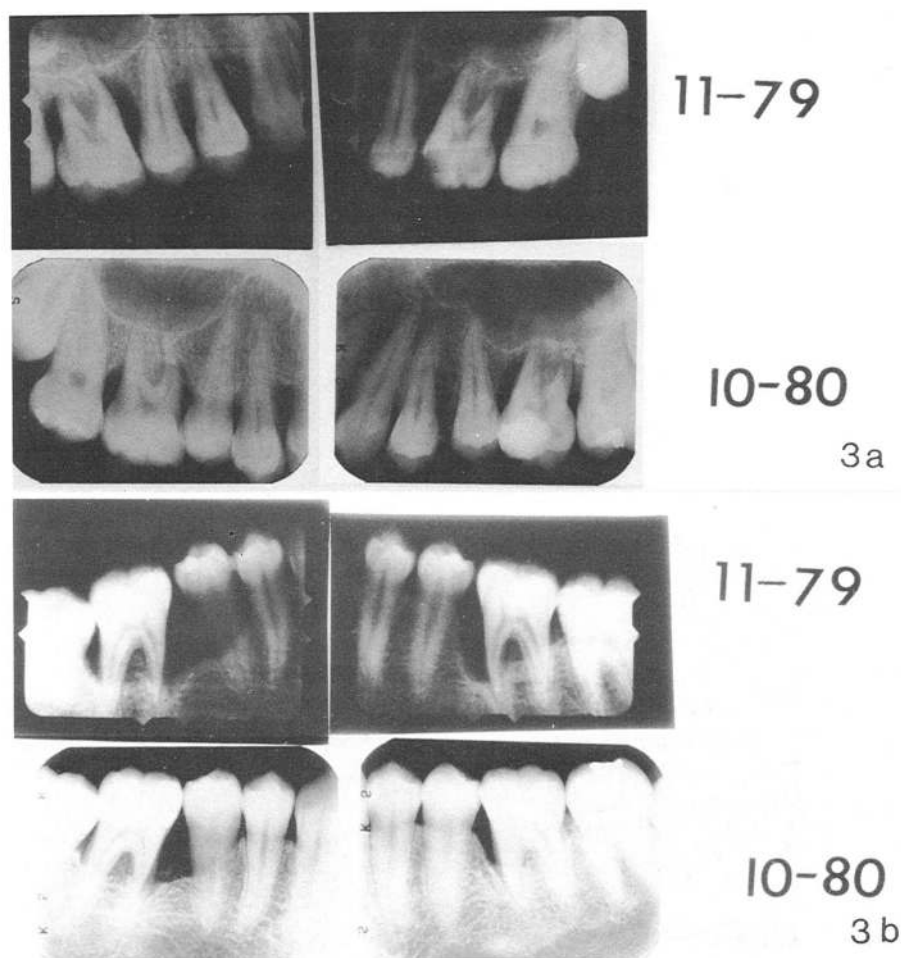

Figure 3. *X-rays of 19-year-old patient with generalized bone loss about molars and premolars when seen in November of 1979. Patient was treated for 1 week with metronidazole and had teeth mechanically debrided in November 1979. X-rays taken 1 year later suggest that no further bone loss occurred. The large carious lesion in the upper right first molar was restored.*

increased transiently in the plaques immediately following therapy. *A actinomycetemcomitans* **was not found in these patients either before or after treatment.**

At the 15- to 30-week interval, the proportions of certain anaerobes such as *F nucleatum*, *A odontolyticus* and *Veillonella* had increased proportionately in the metronidazole group relative to the placebo group (Table 7). As this increase was associated with a sustained clinical improvement in the metronidazole patients, these anaerobes would appear to be members of the nondisease flora.

The placebo plus mechanical treatment also exhibited some degree of selectivity against anaerobes. Thus the proportions of both *B intermedius* and *B gingivalis* (Table 3) and total spirochetes decreased initially (Table 5). However this reduction was not sustained. Ongoing studies in our laboratory involving other patients indicated that rigorous mechanical debridement selectively decreases the proportions of BPB and spirochetes.[44] Thus it may be that nonspecific

treatments such as scaling and root planing are successful because in practice they discriminate against anaerobes and select for a facultative flora. If so, then their mechanism of action is comparable to the mechanism of action of metronidazole, i.e. the conversion of a periodontopathic flora to a nondisease-associated flora by the selective deletion of certain anaerobic organisms.

This similarity of mechanism could explain why the metronidazole and placebo treatments were essentially equivalent in the clinical resolution of pockets initially 4 to 6 mm in depth (Table 1). The mechanical treatment could be delivered at these pocket depths with such effectiveness that only a minimal additional benefit could be derived from the metronidazole. However at pockets greater than 6 mm, the efficacy of mechanical debridement decreases due to instrument inaccessibility of deep root surfaces and furcations. These sites however are apparently bathed by sufficient levels of metronidazole to effect a significant improvement in apparent attachment gain and pocket reduction (Table 1).
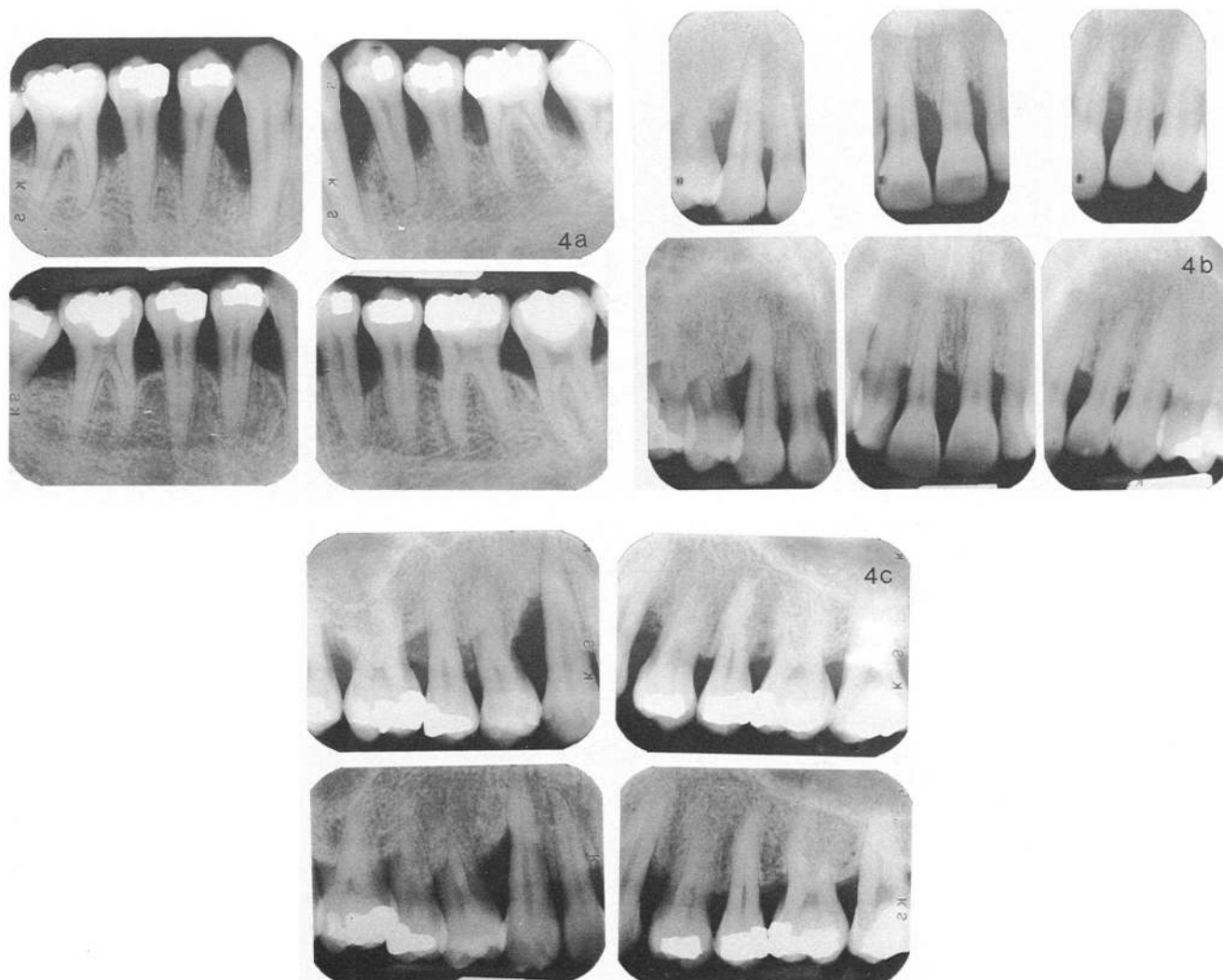

Figure 4. *X-rays of 28-year-old patient taken in February 1981 (top row) and in March of 1983 (bottom row).* **4a,** *mandibular teeth,* **4b,** *maxillary anterior teeth.* **4c,** *maxillary teeth. Patient received metronidazole for 1 week and had teeth mechanically debrided in the spring of 1981. The x-rays taken in 1983 suggest that no further bone loss occurred.*

About half of the pocket reduction in these deep pockets in the metronidazole patients was associated with an apparent gain of attachment of about 1.4 mm, whereas in the placebo group the apparent gain in attachment contributed minimally to the pocket reduction (Table 1). This suggests that the metronidazole permitted a type of disease resolution in the base of these deep pockets which was not found with mechanical debridement plus placebo. Again, nonstandardized x-rays were suggestive of bone fill about some of the teeth in these patients (Fig. 4). The implication of this finding caused us to terminate the present study and to initiate a second double-blind study in which standardized x-rays would be taken[45] and then analyzed by subtraction radiography[46] in order to assess any change in bone levels and/or density.

In conclusion, the results reported in this investigation indicate that short-term usage of systemic metronidazole can optimize the clinical reduction of pockets and increase attachment gain in periodontitis patients who receive concurrent mechanical debridement of their root surfaces. In the case of patients with extensive clinical involvement, the metronidazole treatment results in a significant reduction in the number of sites exhibiting pocket depths and attachment loss ≥ 7 mm. When metronidazole plus mechanical debridement was compared with placebo plus mechanical debridement in a double-blind study, the metronidazole patients exhibited a significant improvement in those sites initially ≥ 7 mm. In both the advanced periodontitis patients and the double-blind patients, the beneficial effect of the metronidazole was associated with a significant and sustained reduction of certain anaerobic organisms such as *B gingivalis* and the large spirochetes. These data indicate that the periodontal infections present in these patients had a dominant anaerobic component.

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In Memoriam

Frank M. Wentz
1917–1984

Dr. Frank Wentz, 67, a life member of the Academy of Periodontology, passed away January 8, 1984.

Dr. Wentz received his DDS degree from Temple University in 1939, his Masters degree in dental histology in 1948 and his PhD in anatomy and pathology in 1954 from the University of Illinois. He embarked on an academic career which spanned 30 years of outstanding accomplishments in periodontics. Clinical application of biologic information was the subject of most of his many scientific articles and numerous textbook contributions.

The measure of Dr. Wentz's enthusiasm for knowledge and universal curiosity was manifest in 1977 when he was stricken with an undiagnosed disease which left him paralyzed. He perceived the disability as just another challenge to be conquered and proceeded with his productive career in teaching, administration and scholarly pursuits.