

Microbial Complexes Detected in the Second/Third Molar Region in Patients With Asymptomatic Third Molars

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Purpose: Our goal was to report the detection and levels of pathogenic bacteria in subgingival plaque samples taken from the distal of all second molars in 295 patients with asymptomatic third molars.

Patients and Methods: Data assessing oral health were collected from each of these healthy patients (ASA Classes I and II). Probing depth (PD), at 6 sites per tooth, including third molars, was obtained to determine periodontal status. Subgingival plaque samples were taken from the distal of all second molars before periodontal probing. The presence and levels of 11 bacterial species were determined using whole chromosomal DNA probes and checkerboard DNA-DNA hybridization. Detected bacterial species were grouped into clusters of periodontal pathogens designated as “red” or “orange” complex microorganisms as described by Socransky et al (J Clin Periodontol 25:134, 1998) who found an association of these specific microorganisms with periodontitis.

Results: As a group these relatively young patients were periodontally healthy. “Orange and red” complex microorganisms were detected at levels equal to or greater than 10^5 more often if patients had a PD equal to or greater than 5 mm with periodontal attachment loss at the distal of second molars or around third molars at their entry examination. In patients with no PD equal to or greater than 5 mm in the third molar region, “orange and red” complex microorganisms were detected at levels equal to or greater than 10^5 more frequently than would be anticipated in patients with little clinical evidence of periodontal disease.

Conclusions: The clinical findings of increased periodontal PDs and periodontal attachment loss coupled with colonization of periodontal pathogens support the concept that clinical and microbial changes associated with the initiation of periodontitis may present first in the third molar region in young adults.

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Current models of periodontal disease implicate specific microbiologic species in the pathogenesis of

periodontitis and relate these periodontal pathogens to clinical measures of periodontitis such as increased

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periodontal probing depth (PD).^{1,2} Socransky et al³ have shown that the bacteria involved most often exist in complexes, particularly *Bacteroides forsythus*, *Porphyromonas gingivalis*, and *Treponema denticola*. Blakey et al⁴ reported that 25% (82 of 329) of patients with asymptomatic third molars, enrolled in a longitudinal clinical trial, had at least 1 PD equal to or greater than 5 mm with periodontal attachment loss at the distal of second molars or around third molars at their entry examination. These subjects were young (median age, 25 years), systemically healthy (ASA Classes I and II), and periodontally healthy. Only 4 of the 329 patients had 3 or more teeth with PD equal to or greater than 5 mm other than second or third molars. These findings were surprising because Blakey et al's data on the prevalence of periodontitis in the third molar region exceeded current epidemiologic estimates based on the Third National Health and Nutrition Estimates Survey (NHANES III) of the prevalence of periodontitis in young patients. However, the distal of second molars or third molars were not studied in NHANES III. This report focuses on the detection and quantification of microbial species in subgingival plaque samples taken from the distal of all second molars in Blakey et al's patients with asymptomatic third molars.

Patients and Methods

The 329 patients in Blakey et al's study were enrolled in an institutional review board-approved trial at 2 clinical centers (University of Kentucky and University of North Carolina) over a 30-month period.⁴ Inclusion criteria dictated that patients be healthy (ASA Classes I and II), between the ages of 14 and 45 years, and have 4 asymptomatic third molars with adjacent second molars. Patients with the most severe form of periodontal disease (AAP Class IV), who were pregnant, who had taken antibiotics within the past 3 months, or who had a history of treatment for a psychiatric disorder within the past 12 months were excluded from participation.

Demographic data and data assessing oral health were collected from each patient. Full mouth periodontal probing, at 6 sites per tooth, including third molars, was conducted to determine periodontal status.

Subgingival plaque samples were taken from the distal of second molars in all 4 quadrants of the mouth before periodontal probing. The presence and levels of 11 bacterial species were determined using whole chromosomal DNA probes and checkerboard DNA-DNA hybridization.³ Based on the findings of Socransky et al,³ the detected bacterial species were grouped into "red" or "orange" complex microorganisms, all associated with periodontitis. For our study "red" complex microorganisms included *B forsythus*,

P gingivalis, and *T denticola*; "orange" complex microorganisms included *P intermedia* and *C rectus*. The presence or absence of "orange" and "red" complexes of microorganisms at levels of equal to or greater than 10^3 and equal to or greater than 10^5 in the third molar region was tabulated for each patient enrolled in the clinical trial; "red" or "orange" complexes of microorganisms were considered present in a patient if the microorganisms could be detected by sampling at the distal of any second molar. Four patients with 3 or more teeth with PD equal to or greater than 5 mm other than second or third molars were not included in the tabulation. Of the remaining 325 patients who had fewer than 3 teeth with PD equal to or greater than 5 mm other than second or third molars, microbiology data were available for 295. Microbiology data were available for all except 1 patient with PD equal to or greater than 5 mm in the third molar region; data were missing for 29 patients with PD of less than 5 mm. PD equal to or greater than 5 mm in the third molar region was associated with at least 1 mm of periodontal attachment loss in all 77 patients; PD equal to or greater than 5 mm was associated with at least 2 mm of periodontal attachment loss in 76 of 77 patients. The detection and levels of "orange" and "red" complex microorganisms were compared by patients who had PD less than 5 mm or equal to or greater than 5 mm in the third molar region, the distal of second molars or around third molars. Because more patients 25 years old or older had at least 1 PD equal to or greater than 5 mm at the distal of second molars or around third molars at their entry examination, results also are reported for ages less than 25 years and 25 years or older. Blakey et al reported that third molars at or above the occlusal plane and vertical or distal in angulation were at equal risk for increased periodontal PD as were third molars below the occlusal plane and mesial or horizontal in angulation.⁴ The detection and levels of "orange" and "red" complex microorganisms sampled from the distal of second molars adjacent to these third molars were compared by third molar position and angulation.

Results

Patients with a PD equal to or greater than 5 mm at the distal of second molars or around third molars were older than those without increased PD, median age 28 years versus 24 years (Table 1). A higher percentage of black patients, 21% versus 9%, had a PD equal to or greater than 5 mm. "Orange and red" complex microorganisms were detected at levels equal to or greater than 10^5 in plaque samples from the distal of second molars more often if patients had a PD equal to or greater than 5 mm in the third molar

Table 1. CHARACTERISTICS OF 295 PATIENTS WITH ASYMPTOMATIC THIRD MOLARS AND MICROBIOLOGY DATA AVAILABLE FOR ANALYSIS, DIVIDED BY PERIODONTAL PROBING DEPTH (PD) <5 OR ≥5 MM IN THE THIRD MOLAR REGION, DISTAL OF SECOND MOLARS OR AROUND THIRD MOLARS

	PD <5 mm		PD ≥5 mm	
	n	%	n	%
Patients	218	100	77	100
Female	116	53	34	44
Male	102	47	43	56
White	179	82	53	69
Black	19	9	16	21
Other	20	9	8	10
Age (yr)	24 (IQ, 21-30)		28 (IQ, 24-35)	
Use tobacco	26	12	10	13
White	20	11	7	13
Black	3	16	1	6

NOTE. Four patients with ≥3 teeth with PD ≥5 mm other than second or third molars were excluded from analysis. Microbiology data were missing from Blakey's sample for 29 patients with PD <5 mm and 1 patient with PD ≥5 mm.⁴

Abbreviation: IQ, interquartile range, 25th to 75th percentile.

region at their entry examination. Conversely, if patients had no PD equal to or greater than 5 mm in the third molar region, "orange and red" complex microorganisms were more likely to be detected at levels less than 10³ (Fig 1, Tables 2, 3).

If patients had a PD equal to or greater than 5 mm in the third molar region, "orange" complex microorganisms were detected at levels equal to or greater than 10³, with "red" complex microorganisms less than 10³ in 13 of 77 patients (17%) versus 20 of 218 patients (9%) with no PD equal to or greater than 5 mm in the third molar region. Similarly, when a PD equal to or greater than 5 mm was found in the third molar region 34 of 77 patients (44%) had "orange and red" complex microorganisms at levels equal to or greater than 10⁵ versus 79 of 218 patients (36%) with

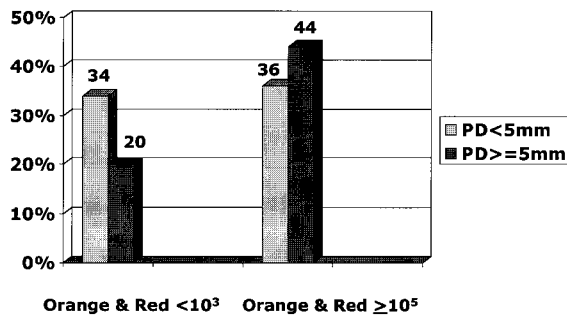


FIGURE 1. Prevalence of asymptomatic patients with "orange and red" microbial complexes detected at levels less than 10³ or equal to or greater than 10⁵ in subgingival plaque samples from distal of second molars by PD less than or equal to or greater than 5 mm in the third molar region.

Table 2. PREVALENCE OF PATIENTS WITH MICROBIOLOGIC COMPLEXES DETECTED IN SUBGINGIVAL PLAQUE SAMPLES FROM THE DISTAL OF SECOND MOLARS WITH ADJACENT ASYMPTOMATIC THIRD MOLARS, COMPARED BY PROBING DEPTH (PD) <5 OR ≥5 MM IN THE THIRD MOLAR REGION, DISTAL OF SECOND MOLARS OR AROUND THIRD MOLARS

Detected Levels of "Orange" and "Red" Microbial Complexes	Periodontal PD <5 mm		Periodontal PD ≥5 mm	
	n	%	n	%
Total	218	100	77	100
Orange and red <10 ³	73	34	15	20
Orange* ≥10 ³ and red <10 ³	20	9	13	17
Orange* <, ≥10 ³ and red ≥10 ³	41	19	15	19
Orange* <, ≥10 ³ and red ≥10 ⁵	5	2	—	—
Orange and red ≥10 ⁵	79	36	34	44

NOTE. Microbiology data are from Blakey's sample missing for 29 patients with PD <5 mm and 1 patient with PD ≥5 mm.⁴

*Detected levels of orange complex may be ≥10⁵.

no PD equal to or greater than 5 mm in the third molar region (Table 2). In the 77 patients with a PD equal to or greater than 5 mm in the third molar region, "red" complex microorganisms were not detected at levels equal to or greater than 10³ without the presence of "orange" complex microorganisms at levels equal to or greater than 10³. Results followed a similar pattern whether the PD equal to or greater than 5 mm was on the distal of the second molar or only around a third molar.

Results were similar if the detection at levels equal to or greater than 10³ and presence of one to all 3 "red" complex bacteria are compared by PD in the third molar region. If all 3 "red" complex bacteria are detected at levels equal to or greater than 10³ it is more likely that patients will have a PD equal to or

Table 3. PREVALENCE OF PATIENTS WITH SINGLE OR MULTIPLE "RED" COMPLEX BACTERIA DETECTED IN SUBGINGIVAL PLAQUE SAMPLES FROM THE DISTAL OF SECOND MOLARS WITH ADJACENT ASYMPTOMATIC THIRD MOLARS, COMPARED BY PROBING DEPTH (PD) <5 OR ≥5 MM IN THE THIRD MOLAR REGION, DISTAL OF SECOND MOLARS OR AROUND THIRD MOLARS

Detected Levels of "Red" Complex Bacteria	Periodontal PD <5 mm		Periodontal PD >5 mm	
	n	%	n	%
Total	218	100	77	100
No red, <10 ³	93	43	28	37
One red,* ≥10 ³	24	11	7	9
Two red,* ≥10 ³	20	9	8	10
Three red,* ≥10 ³	81	37	34	44

NOTE. Microbiology data are from Blakey's sample missing for 29 patients with PD <5 mm and 1 patient with PD ≥5 mm.⁴

*Detected levels of orange complex may be ≥10⁵.

greater than 5 mm in the third molar region (Table 3). Conversely, if no PD equal to or greater than 5 mm was found in the third molar region, it more likely that no "red" complex bacteria will be detected. A higher than anticipated prevalence of bacterial complexes ("orange and red" equal to or greater than 10^5 and all 3 "red" equal to or greater than 10^3) was detected in patients with no PD equal to or greater than 5 mm.

Although Blakey et al⁴ found that twice as many patients 25 years old or older had at least 1 PD equal to or greater than 5 mm at the distal of second molars or around third molars as compared to those younger than 25 years, the presence and levels of "orange and red" complex microorganisms did not appear to differ much by age group (Fig 2).

If third molars were at or above the occlusal plane and vertical or distal in position, targeted microorganisms were as likely to be detected at levels of equal to or greater than 10^5 from subgingival plaque collected at the distal of adjacent second molars compared with third molars below the occlusal plane and mesioangular or horizontal in position. This was true whether a PD equal to or greater than 5 mm was found in the third molar region or not (Fig 3).

Discussion

Salvi¹ presented a current model of periodontitis and discussed risk factors for the disease. The model indicates that the acquisition of recognized periodontal pathogens is critical for the progression of periodontal disease. If a patient's neutrophils control these microorganisms colonized in the accumulated plaque, gingivitis does not progress to periodontitis. Specific bacterial species, including *P gingivalis* and *B forsythus*, possess a virulence trait empowering the microorganisms to bypass the immune system of the host patient. A key component of the transition from

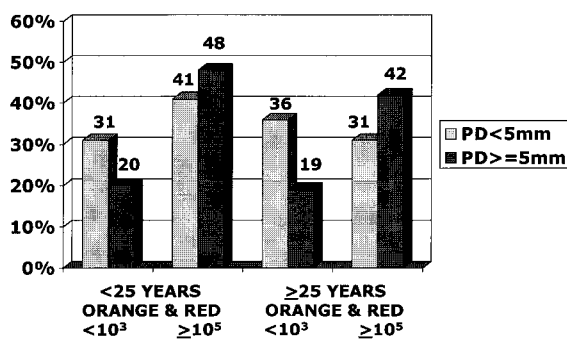


FIGURE 2. Prevalence of asymptomatic patients with "orange and red" microbial complexes detected at levels less than 10^3 or equal to or greater than 10^5 in subgingival plaque samples from distal of second molars by PD less than or equal to or greater than 5 mm in the third molar region and age younger than 25 years or 25 years old or older.

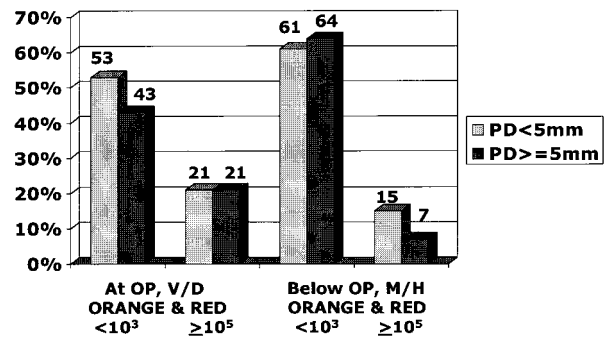


FIGURE 3. Prevalence of asymptomatic patients with "orange and red" microbial complexes detected at levels less than 10^3 or equal to or greater than 10^5 in subgingival plaque samples from distal of second molars by PD less than or equal to or greater than 5 mm in the third molar region and third molar below occlusal plane and mesial/horizontal angulation or at occlusal plane and vertical/distal angulation.

gingivitis to periodontitis is the ability of the bacteria to evade clearance by the host neutrophil.

The detection of specific microorganisms and quantification of their level is facilitated by technology using whole chromosomal DNA probes and checkerboard DNA-DNA hybridization. Haffajee et al,² using this technology with the potential to identify 40 different microorganisms, studied 3 groups: periodontally healthy patients (mean age, 36 years), elders (mean age, 77 years) with a well-maintained periodontium, and adult patients with periodontitis (mean age, 46 years). Subgingival plaque samples were taken from the mesial of all teeth present except third molars. *P gingivalis*, *B forsythus*, and *T denticola* were detected at elevated levels in multiple sampling sites in the adult periodontitis patients compared with the other 2 groups studied. These 3 species were detected more often at sampling sites with deeper periodontal pockets, particularly pocket depths equal to or greater than 5 mm. However, these same bacteria were also found in shallow periodontal pocket depths of 0 to 4 mm in all 3 groups of patients, particularly in the adult periodontitis group. Haffajee et al's data implicate *P gingivalis*, *B forsythus*, and *T denticola* in the etiology of periodontitis. The presence of these microorganisms in shallow pockets raises new questions regarding the relationship between the detection of suspected pathogens and incipient periodontitis.

Socransky et al³ used the same technology to detect and quantify microorganisms from subgingival plaque samples taken from the mesial of all teeth present except third molars. Their 185 subjects (mean age, 51 years) included 25 without evidence of periodontitis. By cluster analysis techniques, a "red" complex of 3 microorganisms, *P gingivalis*, *B forsythus*, and *T denticola*, was identified. This complex was found with increasing frequency as periodontal pocket depths

increased. The presence of any or all 3 of the “red” complex microorganisms appears to be strongly related to clinical measures of periodontitis, including increased PD. An “orange” complex of 9 microorganisms was identified, including *P intermedia*, *C rectus*, *P nigrescens*, and *F nucleatum* subspecies. The presence of “orange” complex microorganisms also was associated with increased PD, although the relationship was not as strong as with the “red” complex microorganisms. Using community ordination techniques, Socransky et al showed that “red” complex and “orange” complex microorganisms were closely related. Bacteria in the “red” complex are rarely found in the absence of bacteria from the “orange” complex. As increasing levels of “orange” complex bacteria are detected, “red” complex bacteria are found more often. Socransky et al’s³ data suggest that the colonization of “orange” complex bacteria precedes colonization of “red” complex bacteria.

In our study PD equal to or greater than 5 mm in the third molar region was associated with a pattern of increased levels of pathogenic periodontal microorganisms even though patients had no symptoms. The detection of increased levels of “orange” and “red” complex microorganisms from patients with periodontal PD equal to or greater than 5 mm at the distal of second molars or around third molars is consistent with the data presented by Haffajee et al² and Socransky et al.³ These findings add weight to the conclusions reached by Blakey et al⁴ that periodontitis in young adults may present initially in the third molar region.

Data from Haffajee et al² indicate that *P gingivalis* and *B forsythus* can be detected in samples taken from sites anterior to the third molar region with a PD of less than 5 mm. The frequency of occurrence of “orange” and “red” complex microorganisms detected at levels equal to or greater than 10^5 in patients who had PD of less than 5 mm in the third molar region in our study was higher than was expected from Haffajee et al’s data. For example, in 21% of third molars at the occlusal plane and vertical or distal in angulation without increased PD, we found that “orange and red” complex microorganisms could be detected at levels equal to or greater than 10^5 from the distal of adjacent second molars (Fig 3). In Haffajee’s² periodontally healthy group, *P gingivalis* and *B forsythus* were detected in less than 10% of pocket depths of 0 to 4 mm. Direct comparisons cannot be made because we sampled the distal of second molars only. Haffajee et al obtained samples from the mesial of all teeth anterior to third molars but not the distal of second molars.

It is possible that elevated levels of microorganisms associated with periodontitis detected in the third molar region in the absence of increased PD may not

lead to destruction of the periodontal structures supporting the second and third molars. As such these would be considered “false-positive” findings. Alternatively, detection of increased levels of “orange” and “red” complex microorganisms, particularly at levels equal to or greater than 10^5 , may herald a progression of periodontal pathology. The detection of pathogenic bacteria may precede detection of periodontitis by clinical measures such as increased PD. The relationship over time between the detection of periodontal pathogens and PD is being pursued further in the longitudinal clinical trial.

Current views of periodontal disease would hold that the absence of “orange” and “red” complex microorganisms indicate a low risk for progressive periodontal disease and a good prognosis for an individual patient treated for periodontitis.⁵ This may be true in the third molar region as well; 20% of the sample with PD equal to or greater than 5 mm had low levels, less than 10^3 , of “orange and red” complex microorganisms (Fig 1, Tables 2, 3). Clinical measures alone, such as increased PD, may not always be an accurate measure of periodontitis.

Haffajee² has shown that patients with periodontitis treated successfully and maintained over time have lower levels of the pathogenic bacteria. These data suggest that detecting increased PD and elevated levels of “orange and red” complex microorganisms may be an indication for third molar removal for affected patients. As has been discussed by Blakey et al,⁴ successfully treating the second-third molar region periodontally, with the goal of eliminating periodontal pocket depth without removing the third molar, is difficult. This issue deserves further investigation. A patient may be at higher risk if PD equal to or greater than 5 mm is coupled with the detection of “orange and red” bacteria at increased levels. Patients in the clinical trial will be monitored closely for increasing periodontal PD and attachment loss, increasing levels of pathogenic microorganisms, and symptoms such as spontaneous bleeding or drainage from third molar regions. If patients in the clinical trial with increased PD and elevated levels of “orange and red” complex microorganisms elect to have third molars removed, it will be important to see if removal of third molars will lead to decreased PD on the distal of second molars and reduced levels of periodontal pathogens.

Although Blakey et al⁴ found increased numbers of patients with at least 1 PD equal to or greater than 5 mm in the third molar region and increased numbers of teeth with a PD equal to or greater than 5 mm on the distal of second molars or around third molars when patients were 25 years old or older, the detection of “orange” and “red” complex bacteria did not appear to differ much with age in these same patients. Until recently, health professionals have assumed that

older patients as a group were more susceptible to periodontitis than those younger because epidemiologic surveys showed increasing prevalence of periodontitis with age. These studies are cross sectional in design, reporting the prevalence of clinical measures for periodontal disease; the same subjects are not followed over time. It is plausible that age is just a proxy for time. As a clinical measure for periodontitis, increased PD represents the cumulative effects of the disease process over time. What may be occurring clinically with third molars may begin with the eruption of these teeth in the late teens and early 20s. Once teeth are exposed in a region difficult to keep clean and with qualitatively poorer soft tissue, periodontal pathogens can accumulate, initiating periodontitis. As discussed by Salvi et al,¹ if neutrophil clearance of these microorganisms is evaded because of the virulence of the bacteria or host factors involving qualitatively altered neutrophils found in systemic diseases such as diabetes mellitus, the inflammation is self-perpetuating. The local environment with increased serum transudate seen as increased gingival crevicular fluid flow, bringing protein and heme, coupled with low oxygen tension facilitates the continued multiplication and resulting destructive activity of the pathogenic bacteria.¹ Increased PD would follow over time. If one region of the mouth could be singled out as a prime candidate for such a scenario, it is the mandibular third molar region. In addition to being difficult for patients to reach to keep clean, the horizontal shelf of thick cortical bone of the mandibular external oblique ridge and the easily traumatized covering mucosa lends itself to the accumulation of plaque and resulting inflammation.

Perhaps Blakey et al's⁴ finding of a greater prevalence of PD equal to or greater than 5 mm on the distal of second molars or around third molars in the mandible when patients were 25 years old or older is related to the sequelae over time of periodontal pathogens colonized in periodontal tissue in the susceptible mandibular third molar region. This destructive process may require a minimum level of pathogens, perhaps equal to or greater than 10^5 , but at some point an equilibrium is reached with the patient's immune system, which includes the presence at higher levels, but not an ever-increasing level, of "orange and red" complex bacteria. The result clinically in a cohort of patients 25 years old or older would be increasing PD in the mandibular third molar region in individual patients and an increased number of patients with PD equal to or greater than 5 mm on the distal of second molars or around third molars. Data collected over time in this longitudinal clinical trial where patients retain third molars may add further insight into our understanding of the initiation and progression of periodontitis. An effective moni-

toring protocol for periodontal disease whether the third molar region is involved or not may require both clinical measures and the detection and levels of biologic markers such as targeted pathogenic bacteria.

Clinicians intuitively expect symptoms and periodontal pathology if third molars are below the occlusal plane but not if third molars are erupted to the occlusal plane. We found the prevalence of "orange and red" complex bacteria detected at levels equal to or greater than 10^5 at the distal of second molars to be similar whether the third molar was erupted to the occlusal plane and vertical or distally inclined, or below the occlusal plane and angled mesial or horizontal. The findings in this study of colonization of pathogenic periodontal microorganisms with an increased risk of periodontitis in asymptomatic patients give further emphasis to the need to develop a data-based protocol for monitoring retained, erupted third molars as well as third molars below the occlusal plane.

In a previous study of patients with acute symptoms of pericoronitis, Blakey et al⁶ found that symptomatic third molars were most often erupted to the occlusal plane and vertical. None of the patients with acute pericoronitis had PD equal to or greater than 5 mm in the third molar region. "Orange" complex bacteria, *P nigrescens* and *F nucleatum* subspecies, were found at much higher levels at symptomatic third molars in Blakey et al's patients with pericoronitis, more than 1 SD above levels in subjects selected as controls. "Red" complex microorganisms were not detected at elevated levels at all in patients with acute pericoronitis. This suggests that symptomatic pericoronitis without increased periodontal PD is clinically and microbiologically more similar to a severe gingivitis than periodontitis. However, the same third molar position, erupted to the occlusal plane and vertical, was associated with increased PD equal to or greater than 5 mm in asymptomatic patients enrolled in our longitudinal clinical trial, and "orange and red" complex bacteria were often detected at high levels.⁴ It will be important to determine whether acute recurrent or chronic pericoronitis that include the colonization of "orange" complex microorganisms will lead to the colonization of "orange and red" complex microorganisms with accompanying clinical measures of periodontitis in the third molar region.

After collecting data and controlling symptoms of pericoronitis without antibiotics, all third molars were removed in Blakey et al's patients.⁶ Three months after surgery the "orange" complex microorganisms had fallen to the levels of the control patients. It will be important to determine if removal of a third molar with PD equal to or greater than 5 mm around it and the presence of elevated levels of "orange and red" complex microorganisms will lead to

decreased PD on the distal of the adjacent second molar and falling levels of the pathogenic bacteria. As mentioned, this outcome is being pursued in the longitudinal clinical trial.

Recent studies have suggested that periodontal infections may have a negative impact on general health, affecting the progression of cardiovascular disease and diabetes mellitus, and pregnancy outcomes. For example, studies in pregnant women show an association between increased periodontal probing depth and the premature delivery of low-birth-weight infants.⁷⁻⁹ The deleterious consequences of periodontal pathology may not be limited to the third molar region or to a negative impact on oral health. The possibility exists that increased PD in the third molar region coupled with colonization of high numbers of "orange and red" complex bacteria may constitute a nidus that continually seeds the circulation with toxic products leading to a harmful systemic impact on affected patients.

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