

# A Dentifrice for the 21st Century

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## ABSTRACT

This article reviews evidence of the clinical effectiveness and mechanism of action of Colgate® Total®.

Thirteen independent, 6-month plaque and gingivitis studies have demonstrated plaque and gingival bleeding reductions in the range of 12% to 98% and 38% to 88%, respectively, for Colgate Total. Six 3- to 6-month calculus studies have shown tartar reductions in the range of 23% to 55%. Four 2- to 3-year caries studies have demonstrated the effectiveness of the fluoride ingredient, one showing a reduction in new cavities of 16.6% with the addition of the triclosan copolymer system over fluoride alone. In addition, three 3-week organoleptic studies have shown reductions in oral malodor, 12 hours after brushing with Colgate Total, in the range of 40% to 53%. Colgate Total has also been shown to provide clinical benefits in reducing the progression of established periodontal disease.

In situ plaque viability studies have shown that significantly less viable bacteria were present in dental plaque collected 12 hours after brushing with Colgate Total compared with plaque collected 12 hours after brushing with a regular fluoride dentifrice. The effects of Colgate Total on clinical plaque scores and on levels of representative organisms in harvested plaque, 24 hours postbrushing, were compared to the effects of regular fluoride toothpaste. Colgate Total showed a 41% reduction in dental plaque coverage and fewer periodontal pathogens and early colonizers in harvested plaque compared to control. In vitro studies have demonstrated that triclosan has the potential to suppress a number of cytokine-initiated inflammatory pathways contributing to gingival inflammation. This is consistent with in vivo studies that show that Colgate Total can directly reduce gingival inflammation in addition to its effects on plaque bacteria.

In summary, clinical studies have demonstrated that Colgate Total delivers superior oral health benefits compared to regular fluoride toothpaste, including the prevention and control of plaque and gingivitis, reduced formation of calculus and oral malodor, and caries prevention. Colgate Total also provides benefits in preventing and controlling the progression of periodontal disease. Clinical and laboratory studies also show that Colgate Total provides 12-hour antibacterial protection and anti-inflammatory action, as well as 24-hour protection against plaque.

**T**his article reviews some of the unique properties and characteristics of Colgate® Total® toothpaste. A short background is followed by the mechanism of action, which covers both the antibacterial as well as the anti-inflammatory effects of Colgate Total. A summary of clinical studies is presented, including

the documented clinical effects of Colgate Total on periodontal disease.

## BACKGROUND

Colgate Total is a uniquely formulated dentifrice that possesses pronounced antibacterial and anti-inflammatory proper-

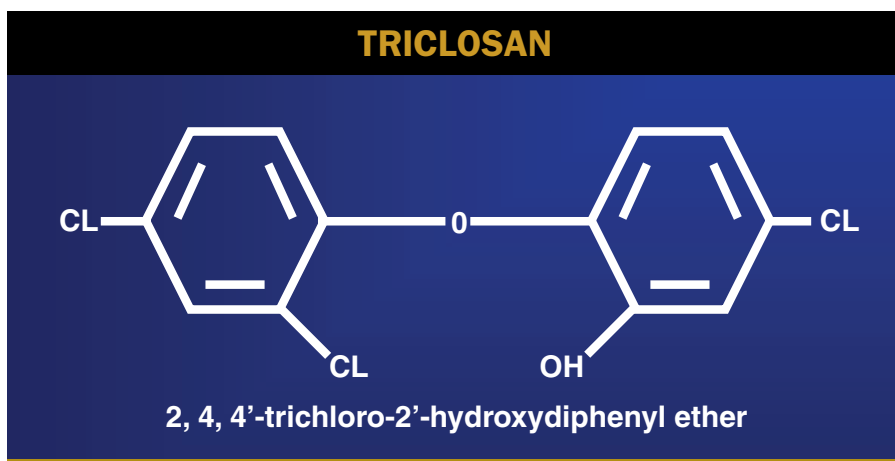
*This article may contain information regarding the use of Colgate® Total® that has not been approved by the US Food and Drug Administration. Please refer to the Colgate Total labeling for approved uses.*

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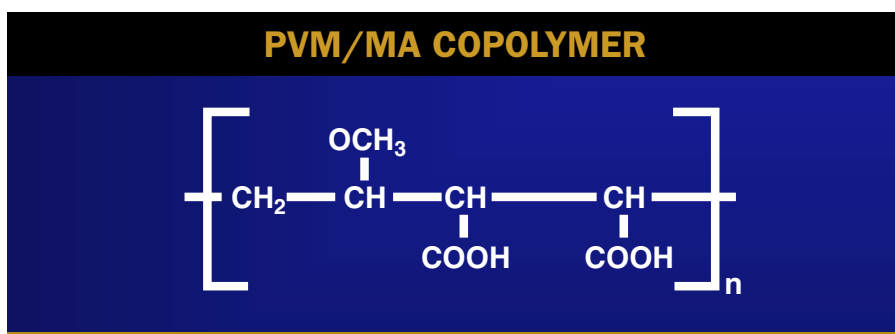
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**Figure 1** Chemical formula of triclosan. (Courtesy of Dr. Abdul Gaffar.)

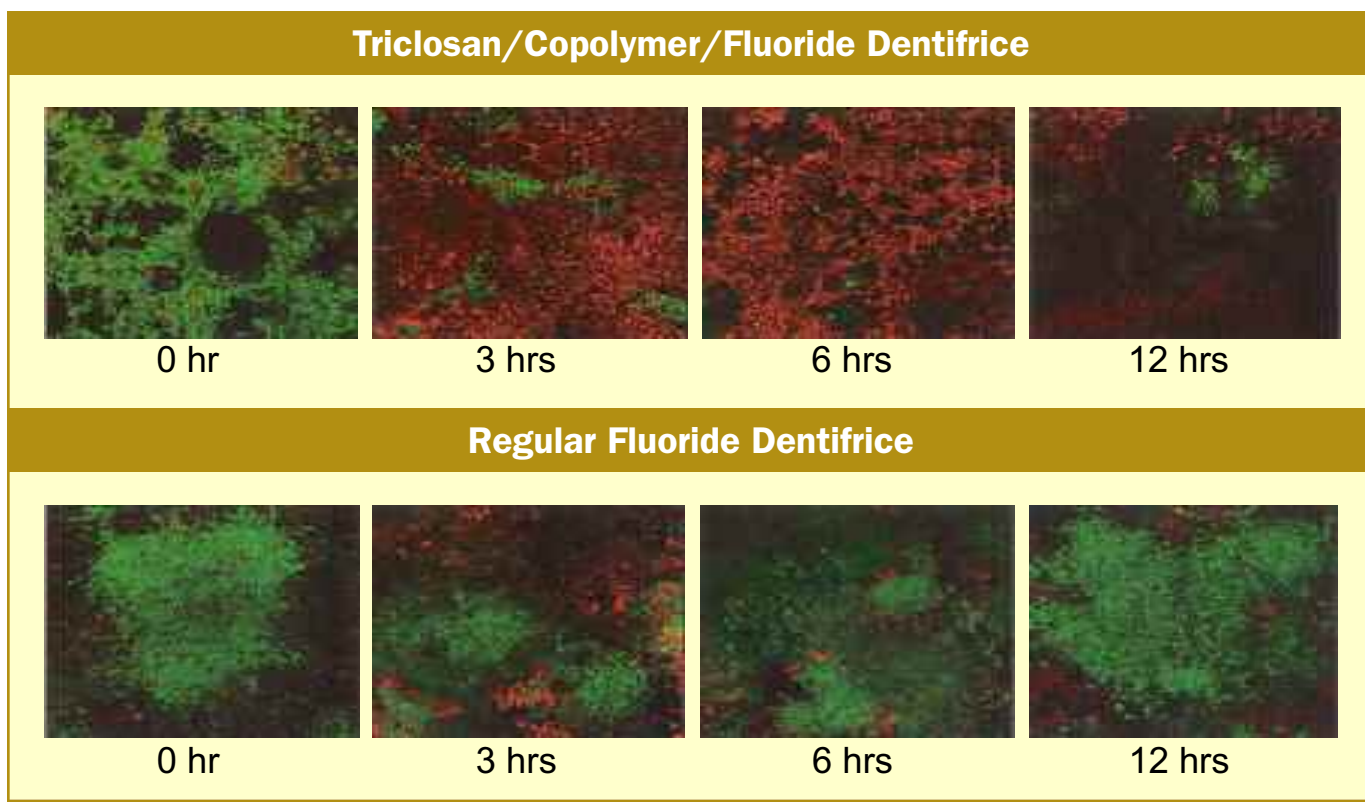


**Figure 2** Chemical formula of PVM/MA copolymer. (Courtesy of Dr. Abdul Gaffar.)

ties. The dentifrice formulation contains 0.3% triclosan and 2% of PVM/MA copolymer in a 0.243% sodium fluoride base. Triclosan is a broad-spectrum antibacterial agent marketed for use in oral products under the trade name Irgacare MP® (Ciba-Geigy corporation).<sup>1</sup> The chemical name is 2,4,4'-trichloro-2'-hydroxydiphenyl ether (Figure 1).

Triclosan is a useful antibacterial agent to incorporate into oral care products because it has a broad spectrum of activity against oral bacteria, is compatible with the ingredients in oral care products, and has a long history of safe use in consumer products.<sup>2</sup> After review of the available pharmacological and toxicological data, it was concluded that triclosan is safe for use in dentifrice and mouthrinse products.<sup>3</sup> Subsequently, a number of additional studies and reviews have attested to the safety of triclosan.<sup>4-7</sup>

PVM/MA is the nonproprietary designation for a polyvinylmethyl ether maleic acid copolymer. The chemical structure of this copolymer is presented in Figure 2. The results of in vitro studies reported showing greater uptake of triclosan to enamel and buccal epithelial



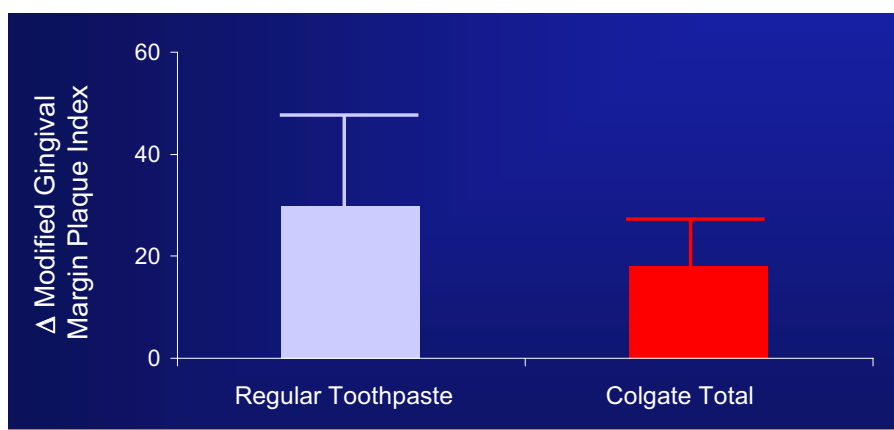
**Figure 3** In situ plaque viability over a 12-hour period visualized by confocal laser scanning microscopy. The upper panels show plaque viability after exposure to the triclosan/copolymer dentifrice. The lower panels show plaque viability after exposure to a regular fluoride dentifrice. (Courtesy of Dr. Richard Sullivan.)

cells for a fluoride dentifrice containing both triclosan and the PVM/MA copolymer compared with a dentifrice containing triclosan alone. It was also reported that the PVM/MA copolymer, in the presence of triclosan, inhibited crystal growth in vitro and in vivo<sup>8,9</sup> and a US patent on the triclosan and PVM/MA copolymer technology in oral products was granted.<sup>10</sup>

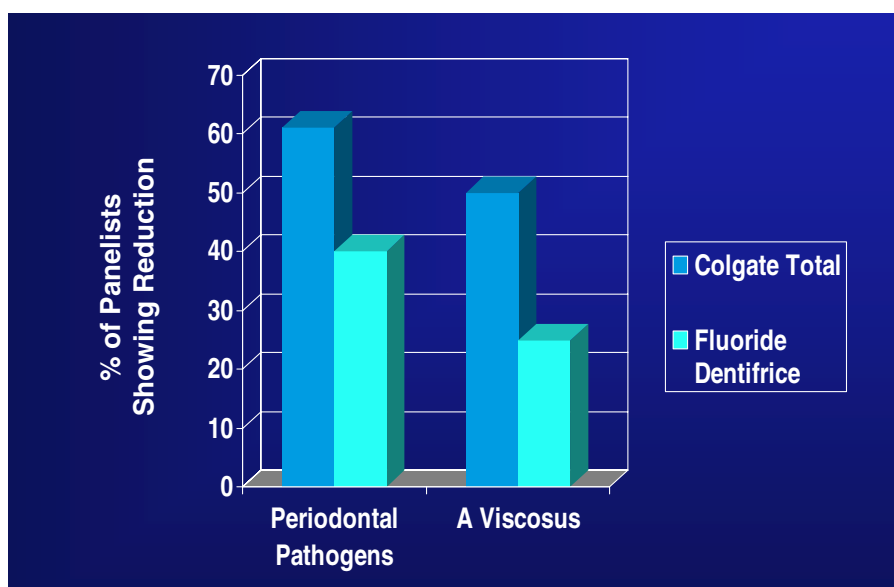
Colgate Total has been approved by the US Food and Drug Administration (FDA) as the only over-the-counter (OTC) oral care product that is clinically proven to reduce plaque and gingivitis. It has also been demonstrated to provide clinical benefits in preventing cavities and in controlling calculus and oral malodor.

More than 40 controlled clinical studies have demonstrated the efficacy of Colgate Total vs regular fluoride dentifrices. Thirteen independent, 6-month plaque and gingivitis studies have demonstrated reductions in plaque and gingival bleeding in the range of 12% to 98% and 38% to 88%, respectively.<sup>11-23</sup> Six calculus studies, 3 to 6 months in duration, have shown tartar reductions in the range of 23% to 55%.<sup>24-29</sup> Four caries clinical studies, ranging between 24 and 36 months, have demonstrated the effectiveness of the fluoride ingredient and, in one study, showed a reduction in the development of new cavities of 16.6%.<sup>30-33</sup> The caries studies demonstrated that Colgate Total is equal to or better than other dentifrices, containing the same type and level of fluoride, in promoting anticavity effects. Three organoleptic studies, and one study of volatile sulphur compounds (VSC), have shown reductions in oral malodor in the range of 40% to 53%, up to 12 hours after brushing with Colgate Total.<sup>34-37</sup> In conjunction with these oral malodor studies, investigation of the tongue and saliva microflora showed that Colgate Total has a pronounced effect in reducing the bacteria that produce VSC (the compounds that cause oral malodor).<sup>38</sup> No adverse effects on oral soft tissue or hard tissue resulting from the use of Colgate Total were observed in any of these clinical studies.

In addition to these clinical studies, microbiological safety studies have been conducted to examine the effects of



**Figure 4** Clinical effects of Colgate Total on dental plaque formation 24 hours postbrushing. (Courtesy of Dr. Tao Xu.)



**Figure 5** Effects of Colgate Total on the regrowth of periodontal pathogens and early colonizers over 24 hours. (Courtesy of Dr. Tao Xu.)

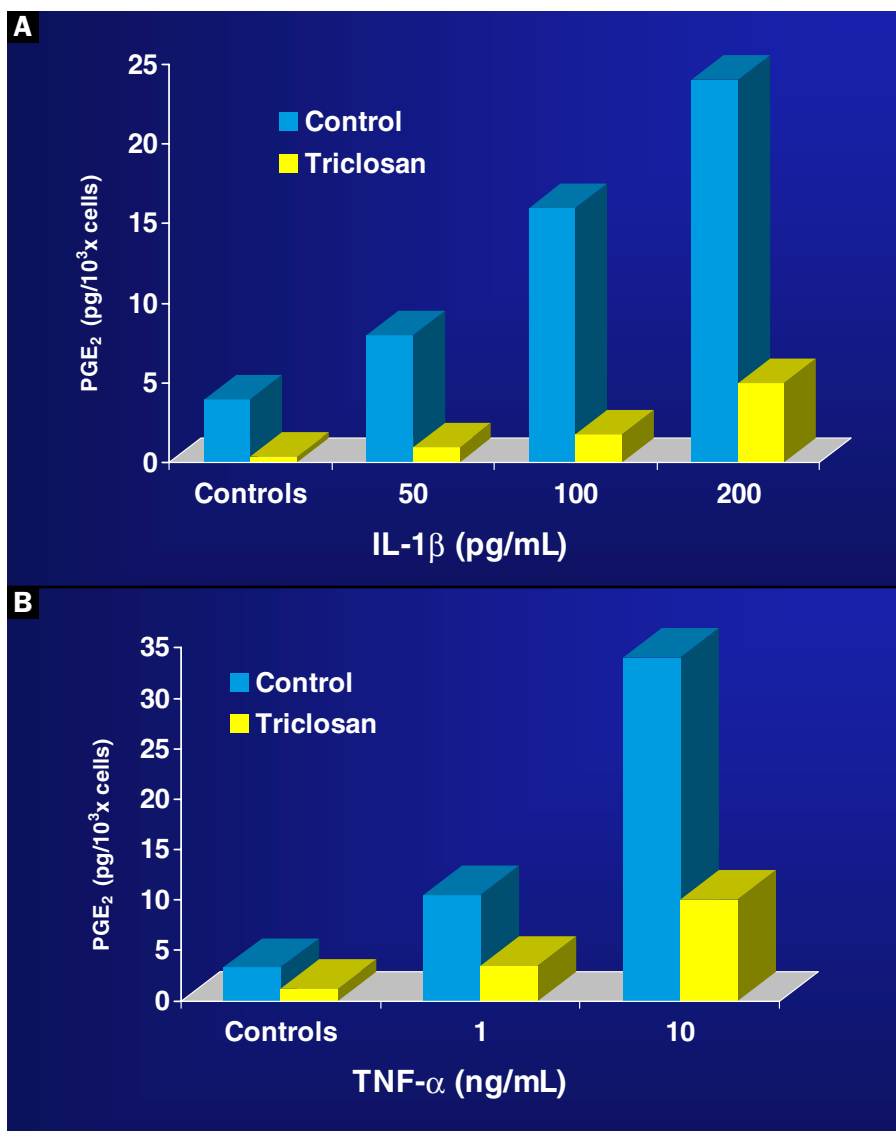
Colgate Total on oral ecology. Five studies were conducted, ranging in length from 6 to 12 months, in which the use of Colgate Total was compared to regular fluoride dentifrice. No differences in the presence or proportion of bacterial species were observed; no overgrowth of opportunistic bacteria, periodontal pathogens, or cariogenic flora was noted; and no bacterial resistance to triclosan was seen in these five studies.<sup>39-43</sup>

### ANTIBACTERIAL ACTIVITY

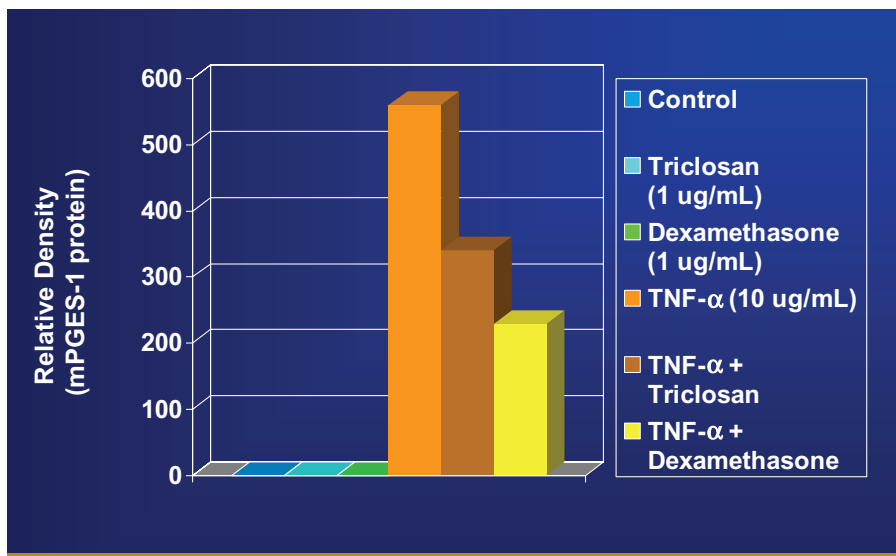
The minimum inhibitory concentrations (MIC) for triclosan for a range of oral bacteria have been reported to be in the range of 0.2- to 3- $\mu\text{g}/\text{ml}$ .<sup>44</sup> Further, a pilot clinical study showed that triclosan

was retained in both plaque and saliva after the use of a dentifrice containing triclosan and the PVM/MA copolymer.<sup>45</sup> A schematic diagram was published to illustrate the role of the PVM/MA copolymer in the delivery of triclosan to enamel and oral soft tissues.<sup>46</sup>

Subsequently, Colgate Total has been shown in several clinical studies to deliver antibacterial activity for 12 hours or more after brushing. In a pilot study, plaque samples harvested 14 hours after brushing with Colgate Total were shown to have retained  $> 4 \mu\text{g}/\text{ml}$  of triclosan, a level consistent with antibacterial activity. More importantly, plaque samples taken 12 hours after brushing with Colgate Total were shown to be  $\sim 30\%$  viable (30% live/70% dead) compared to samples taken



**Figure 6A and 6B** Inhibition of (A) IL-1 $\beta$ -stimulated and (B) TNF- $\alpha$ -stimulated PGE<sub>2</sub> production by triclosan in vitro. Adapted from Modeer et al, *J Clin Periodontol*.<sup>50</sup>



**Figure 7** Effect of triclosan on mPGES-1 protein expression induced by TNF- $\alpha$ . Adapted from Mustafa et al, *J Clin Periodontol*.<sup>54</sup>

12 hours after brushing with regular fluoride toothpaste, which were ~60% viable.<sup>47</sup> More recently, a double-blind, randomized, parallel-design clinical trial showed that 6 and 12 hours after brushing with Colgate Total, plaque samples had retained 6.6 and 5.2  $\mu\text{g/ml}$  of triclosan, respectively. Furthermore, 6 and 12 hours after brushing with Colgate Total, plaque viability was reduced to 44.5% and 38.0%, respectively, whereas 6 and 12 hours after brushing with regular fluoride toothpaste plaque viability was unchanged from baseline at ~70%.<sup>48</sup>

Plaque viability has also been visualized using confocal laser scanning microscopy (CLSM). Figure 3 shows the 3D CLSM images of plaque grown in situ on hydroxyapatite. Before brushing, plaque samples were dominated by the presence of live bacteria (seen as green fluorescence), as were plaque samples taken 3, 6, and 12 hours after brushing with regular fluoride toothpaste. In contrast, 3, 6, and 12 hours after brushing with Colgate Total, plaque samples are dominated by the presence of dead bacteria (seen as red fluorescence), demonstrating that Colgate Total provides significant antibacterial activity for at least 12 hours after brushing.

A recent study combined clinical assessment of plaque regrowth over a 24-hour period after dental prophylaxis and toothbrushing, with analysis of the effects of brushing on specific oral microorganisms using real-time polymerase chain reaction (PCR) methods. Twenty-four hours after brushing, dental plaque coverage increased 17.9% with Colgate Total compared with 30.4% for regular fluoride dentifrice (Figure 4). This represents a significant 41% reduction in plaque regrowth for Colgate Total compared to regular fluoride toothpaste. Real time PCR showed that plaque collected 24 hours after brushing with Colgate Total contained fewer representative periodontal pathogens (*F nucleatum*, *A actinomycetemcomitans*, *T forsythensis*, and *P gingivalis*) and fewer early colonizers (*A naeslundii*) than plaque before brushing, whereas regular fluoride toothpaste showed a moderate effect on these bacteria. Figure 5 shows the percentage of panelists showing reductions in these

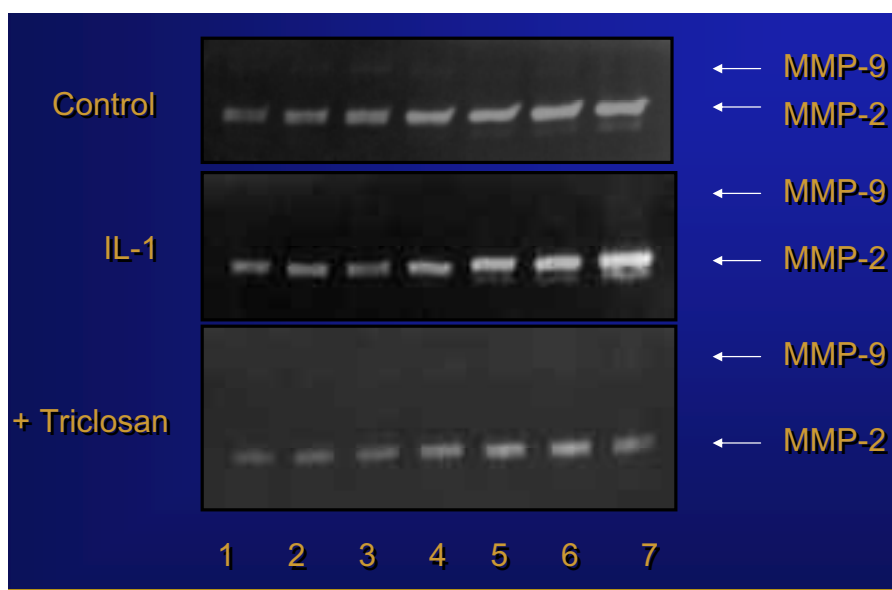
microorganisms for Colgate Total as compared to fluoride toothpaste.<sup>49</sup>

### ANTI-INFLAMMATORY ACTIVITY

In addition to studies of the antibacterial effects of Colgate Total, there have been a number of published studies to elucidate the anti-inflammatory action of triclosan.<sup>50-56</sup> Several of these studies involved gingival fibroblasts that were exposed *in vitro* to a known inflammation mediator, both in the presence and absence of triclosan, and a specific outcome was measured. The stimulants of particular interest have been interleukin-1beta (IL-1 $\beta$ ) and tumor necrosis factor alpha (TNF- $\alpha$ ), which are both well-known mediators of the inflammatory response and have been found in gingival tissue and gingival crevicular fluid (GCF) in patients who have gingivitis and periodontitis. Specific outcome variables were prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), cytokines, microsomal prostaglandin E synthase-1 (mPGES-1), and the production and secretion of matrix metalloproteinases (MMPs).

Figures 6A and 6B show that, in the presence of IL-1 $\beta$  and TNF- $\alpha$ , respectively, gingival fibroblasts produced elevated levels of PGE<sub>2</sub> which were dose-dependent. The addition of triclosan with the stimulant cytokine suppressed the increase in PGE<sub>2</sub> production by 70% or more, thereby demonstrating that triclosan inhibits IL-1 $\beta$ - and TNF- $\alpha$ -stimulated PGE<sub>2</sub> production.<sup>50</sup> More recently, TNF- $\alpha$ -induced mPGES-1 has been studied at both the messenger ribonucleic acid (mRNA) and the protein expression level. In the presence of TNF- $\alpha$ , there was an elevation in mPGE synthase mRNA and protein; whereas when triclosan was added along with the TNF- $\alpha$ , there was a reduction in the levels of mRNA and protein produced.<sup>54</sup> Figure 7 shows the results for protein expression.

Recent evidence indicates that triclosan can inhibit the major histocompatibility complex in macrophages, as well as IL-1 $\beta$ - and TNF- $\alpha$ -stimulated production and secretion of proteases by human bone and fibroblast cells.<sup>52</sup> Studies on the effects of triclosan on



**Figure 8** Gel zymography of conditioned medium from human osteoblast-like cells collected at various time points. Lane 1 = 1 hour, 2 = 2 hours, 3 = 4 hours, 4 = 8 hours, 5 = 16 hours, 6 = 24 hours, 7 = 48 hours.<sup>56</sup>

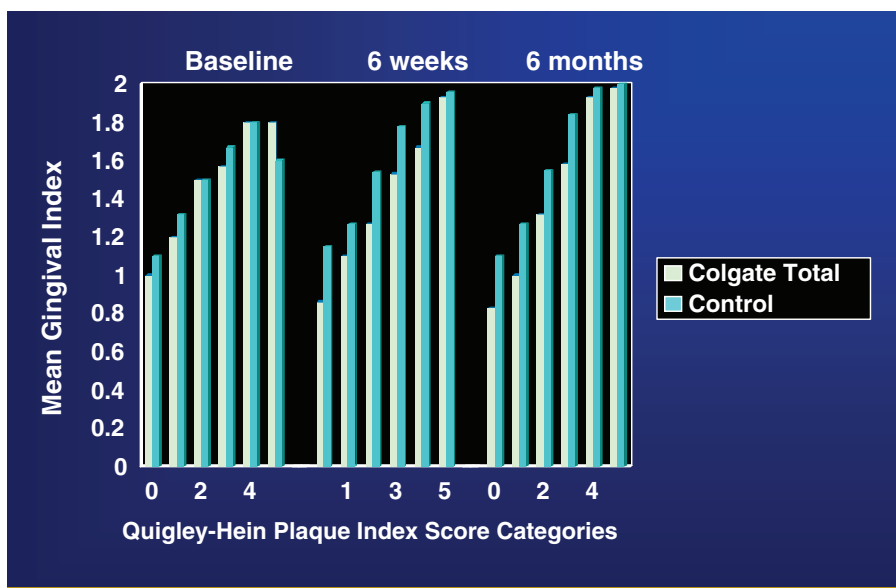


**Figure 9** Gel zymography of conditioned medium from human fibroblast-like cells. Lanes 1 to 3 = 24 hrs, Lanes 4 to 6 = 48 hrs, 1 = Control, 2 = TNF- $\alpha$ , 3 = TNF- $\alpha$  + triclosan, 4 = Control, 5 = TNF- $\alpha$ , 6 = TNF- $\alpha$  + triclosan.<sup>56</sup>

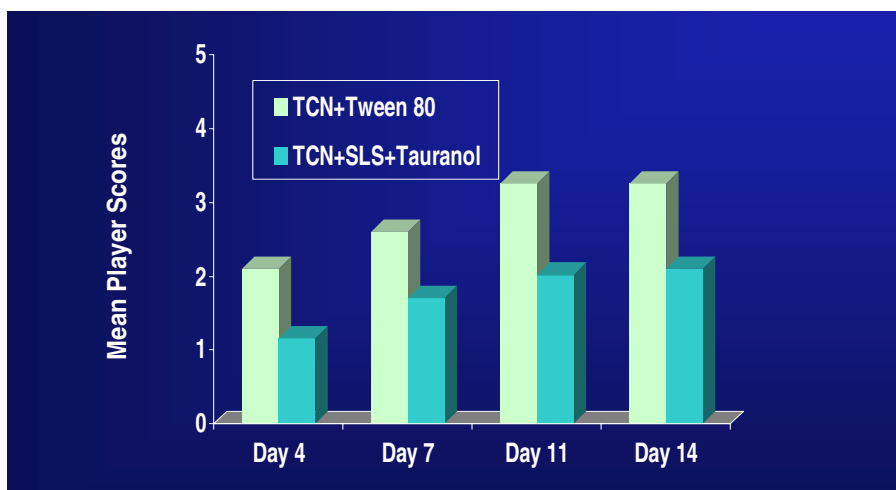
IL-1 $\beta$ - and TNF- $\alpha$ -stimulated MMP production showed that IL-1 $\beta$ -stimulated human osteoblast-like cells produce elevated levels of MMP-2 (Figure 8), whereas TNF- $\alpha$ -treated human fibroblast-like cells secreted elevated levels of MMP-2 (Figure 9). In each of these experiments, the addition of triclosan reduced MMP-2 production and accumulation in the media to levels similar to untreated control cells.<sup>56</sup>

Taken together, these results suggest that direct anti-inflammatory effects may contribute to the clinical effects delivered by Colgate Total toothpaste to gingival and periodontal tissues by controlling cytokine-stimulated inflammation pathways.

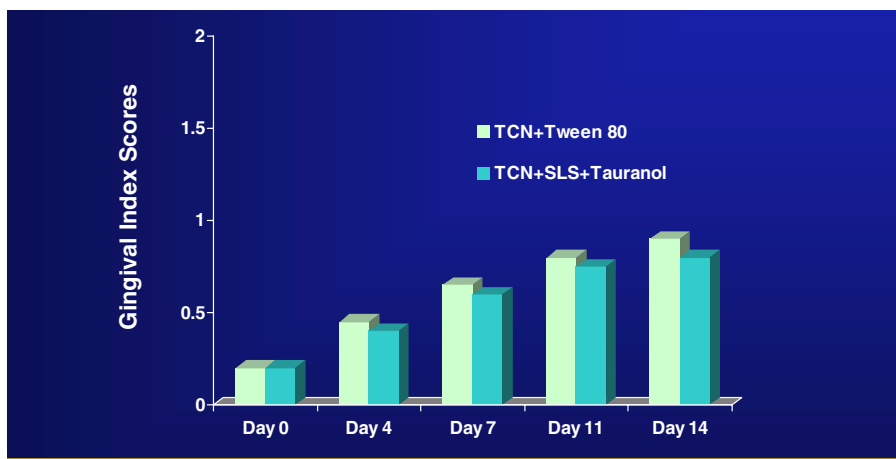
Clinical studies have been designed and conducted to probe the direct and indirect anti-inflammatory effects of triclosan on gingival inflammation.<sup>57,58</sup> In a 6-month plaque and gingivitis study, the effects of Colgate Total were compared to the effects of a fluoride dentifrice control on plaque-associated and plaque-independent gingival inflammation. The mean gingival index (GI) scores were presented for each incremental plaque index (QHI) score (Figure 10). At baseline, the two test groups were balanced for GI score at each QHI increment and the GI and plaque index followed a linear relationship. At 6 weeks and at 6 months, subjects who used Colgate Total had lower gingivitis scores



**Figure 10** Mean gingival index scores vs Quigley-Hein Plaque Index scores in subjects using either Colgate Total or a fluoride control dentifrice. Adapted from Lindhe et al, *J Clin Periodontol*.<sup>57</sup>



**Figure 11A** Mean Quigley-Hein Plaque Index scores in subjects using either a triclosan + Tween 80 mouthrinse vs subjects using a triclosan + SLS mouthrinse. Adapted from Ramberg et al, *J Clin Periodontol*.<sup>58</sup>



**Figure 11B** Mean gingival index scores in subjects using either a triclosan + Tween 80 mouthrinse vs subjects using a triclosan + SLS mouthrinse. Adapted from Ramberg et al, *J Clin Periodontol*.<sup>58</sup>

than subjects who used the control dentifrice. Importantly, the effects of Colgate Total were pronounced in sites where there was no plaque present (QHI = 0), suggesting that Colgate Total may deliver a pronounced and direct anti-inflammatory effect on the gingival tissue.<sup>57</sup>

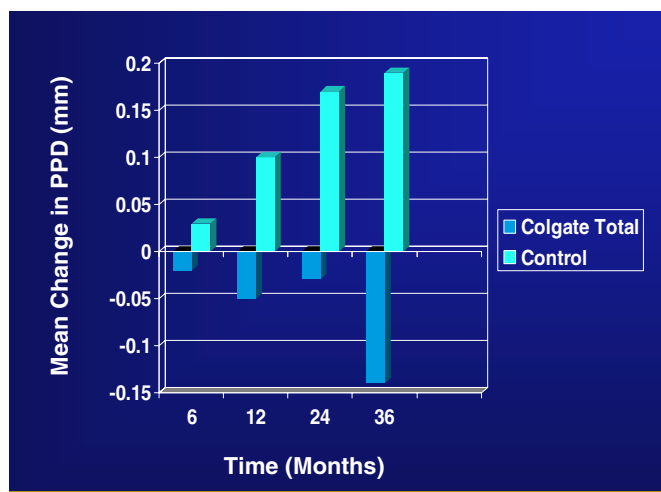
The second study compared the effects of two triclosan rinses on the development of gingivitis in the experimental gingivitis model. One rinse, with sodium lauryl sulfate (SLS), had a high level of antibacterial activity; the other, with Tween 80, had no antibacterial activity, allowing the investigators to examine the anti-inflammatory effects of triclosan independent of antibacterial effects. The mean plaque scores for the triclosan/Tween-80 group were much higher than those for the triclosan/SLS group after 4, 7, 11, and 14 days of use (Figure 11A). In contrast, the GI scores were almost identical for the two groups at all time points (Figure 11B). This result indicates that triclosan can moderate gingival inflammation through direct anti-inflammatory effects, regardless of the absence of an antibacterial effect.<sup>58</sup>

The clinical and laboratory studies on the anti-inflammatory properties of Colgate Total and triclosan are complimentary and support the view that Colgate Total reduces gingival inflammation in two ways: directly through anti-inflammatory effects on the gingival tissue and indirectly through its antibacterial effects on dental plaque.

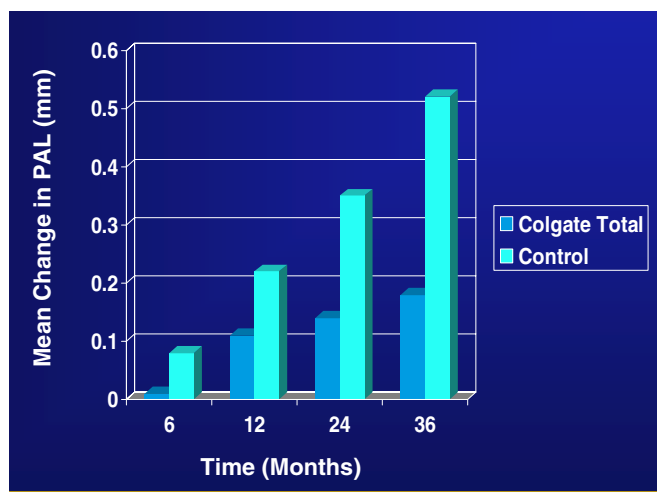
### CLINICAL EFFECTS ON PERIODONTAL DISEASE

Six independent clinical studies have examined the effects of extended use of Colgate Total on periodontal disease compared to the effects of regular fluoride toothpaste.<sup>59-65</sup>

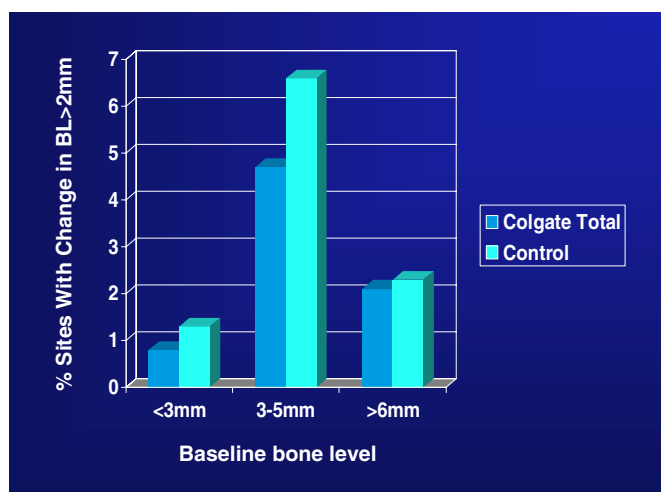
One study, of 2 weeks duration, was conducted in an adult population with advanced periodontal disease and a history of nonsurgical periodontal therapy and periodontal maintenance to determine the effects of adjunct therapy on healing after scaling and scaling and root planning (SRP). Subjects who used Colgate Total together with 0.3% triclosan/2% PVM/MA copolymer fluoride gel via stint experienced greater



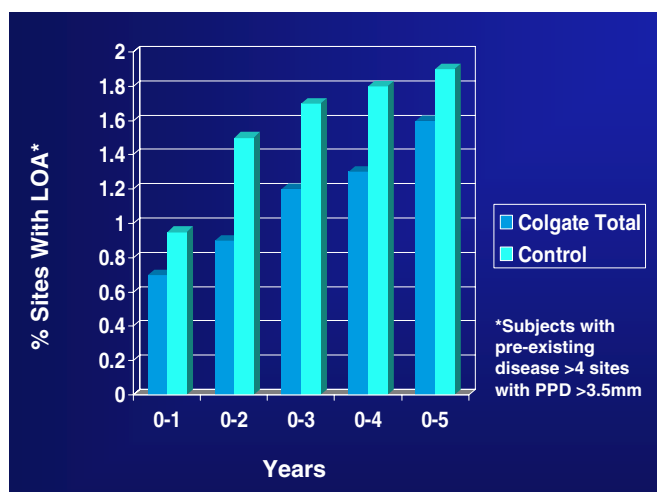
**Figure 12** Effects of Colgate Total on probing pocket depth vs a fluoride control dentifrice over 36 months. Adapted from Rosling et al, *J Clin Periodontol*.<sup>59</sup>



**Figure 13** Effects of Colgate Total on probing attachment level vs a fluoride control dentifrice over 36 months. Adapted from Rosling et al, *J Clin Periodontol*.<sup>59</sup>



**Figure 14** Effects of Colgate Total on bone loss vs a fluoride control dentifrice over 36 months. Adapted from Rosling et al, *J Clin Periodontol*.<sup>59</sup>



**Figure 15** Effects of Colgate Total on loss of attachment vs a fluoride control dentifrice over 5 years. Adapted from Cullinan et al, *J Clin Periodontol*.<sup>64</sup>

reductions in bleeding on probing (BOP) and GI scores than those who used the control dentifrice and gel. The results of this study indicate that use of triclosan/copolymer products may reduce gingival inflammation after routine SRP.<sup>61</sup> A second study conducted in an adult population with advanced periodontal disease evaluated the effects of Colgate Total on the progression of periodontal disease during a 3-year maintenance program after SRP. Colgate Total significantly reduced probing pocket depth (Figure 12) and changes in probing attachment levels (Figure 13) at 24 and 36 months, as well as the number of sites with change in bone loss > 2 mm (Figure 14) at 36 months compared with con-

rol.<sup>59</sup> A third study in a similar population evaluated the effects of Colgate Total on the progression of periodontal disease during a 3-year maintenance program which included professional therapy at individual sites that exhibited > 2 mm probing attachment loss at any of the examinations. There were fewer such sites in the group using Colgate Total (85) compared with control (126). In addition, there was a significant reduction in the number of sites with gingivitis, as well as a significant reduction in pocket probing depth and a significant improvement in probing attachment level for Colgate Total compared with control.<sup>63</sup>

In a fourth study, of 5 years duration, conducted in a normal adult population,

Colgate Total was shown to reduce the number of sites with probing depths > 3.5 mm and to significantly delay the progression of periodontal disease compared with regular fluoride toothpaste (Figure 15).<sup>64</sup> Two further studies were conducted in specialized populations. A 3-year study in a group of high-risk adolescents showed a significant difference in attachment loss for the group using Colgate Total compared with control.<sup>62</sup> In a group of smokers, significant differences in gingivitis, probing depth, and attachment loss were seen in favor of Colgate Total.<sup>65</sup> All studies indicated that use of Colgate Total resulted in an overall reduction in periodontal disease progression.

In addition, studies of the subgingival flora<sup>7,60</sup> were conducted in association with two of these studies of the effects of Colgate Total on the progression of periodontal disease.<sup>59,64</sup> These studies showed qualitative and quantitative reductions in subgingival microbiota<sup>60</sup> and, consistent with the microbiological studies of supragingival plaque in the plaque and gingivitis trials, showed no differences in the presence or proportion of bacterial species, no overgrowth of opportunistic or pathogens or organisms, and no increase in bacterial resistance to triclosan.<sup>7</sup>

## CONCLUSION

Clinical studies have clearly indicated that long-term, twice-daily use of Colgate Total provides significant oral health benefits beyond the “traditional” benefit of cavity prevention associated with conventional fluoride toothpaste. Specifically, studies have demonstrated that Colgate Total provides superior protection against plaque and gingivitis, cavities, oral malodor, and calculus compared to regular fluoride toothpaste. It also provides protection against the progression of periodontal disease.

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