EVALUATION OF ACTISITE® TETRACYCLINE FIBRES AROUND AILING DENTAL IMPLANTS.

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SUMMARY.

As the number of endosseous dental implants placed increases, the need for understanding failure modalities and treatment regimens is becoming essential. This preliminary clinical study was designed to assess an initial form of treatment for implants with early peri-implantitis, with the aim of arresting disease progression and improving prognoses.

The clinical, radiographic and microbiologic features associated with the ailing implant closely resembles that of chronic adult periodontitis . A concentrated local drug delivery system, Actisite® (tetracycline hydrochloride containing fibres) has been used around teeth in patients with chronic adult periodontitis with good success rates.

Patients with hydroxy-apatite cylindrical root form implants which exhibited signs of slight-moderate peri-implantitis (probing depths 5-7 mm, bleeding on probing and slight-moderate bone loss, but no mobility) from the Implant Maintenance Clinic at the School of Dentistry, Louisiana State University, were used in the study. Clinical parameters assessed were gingival margin position, probing depths, clinical probing attachment levels, bleeding on probing, neutral protease levels (Periochek®) and DNA probe analysis (Affirm®).

Actisite® fibres were applied to selected test implant sites. Patients were recalled at 10 days for fibre removal, then at 1 month for general evaluation and hygiene

review, and at 2 and 3 months to repeat clinical measurements obtained at baseline. Standardised oral hygiene procedures were provided to all patients at each visit. Thirteen patients provided twenty Actisite® fibre treated implants (69 surfaces) and eight control implants (18 surfaces).

A significant improvement ($P < 0.05$) in probing depths was observed between baseline and 3 months (-1.6 ± 2.4 mm vs. -0.9 ± 1.5) for Actisite® treated surfaces compared to the control implant surfaces.

As with probing depths, there was also a significant improvement ($P < 0.05$) in clinical probing attachment levels between baseline and 3 months (-1.8 ± 3.3 mm vs. -0.7 ± 1.6) for Actisite® treated surfaces compared to controls.

Bleeding on probing was reduced (though not significantly) in both groups between baseline and 3 months (Actisite® treated surfaces -0.3 ± 0.6 vs. Controls- 0.6 ± 0.4).

There were essentially no changes or differences in neutral protease or bacterial levels between treatments or between time periods.

The results of this study suggest that local delivery tetracycline fibres would indicate that they are useful in reducing probing depths and increasing attachment levels around implants with slight to moderate peri-implantitis for up to three months. Longer evaluations are underway.

DECLARATION.

This Research report contains no material which has been accepted for the award of any other degree or diploma in any University.

To the best of my knowledge and belief, this investigation contains no material previously published or written by another person except where due reference is made in the text.

This manuscript may be made available for photocopying or loan.

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PREFACE.

The use of endosseous dental implants has increased rapidly within the last 5-10 years, with most of the literature reporting excellent success rates. Little information, however, has been available concerning the management of the ailing implant. Previously, most implant problems were not detected until the later stages, by which time extensive remedial surgical therapy is required to attempt to arrest the disease process. It is both timely and important to initiate this study in order to establish an effective form of *initial* therapy for those implants that have developed periodontal-like problems or peri-implantitis. Effective, early interaction should ultimately prevent disease progression and implant loss.

More specifically, this project was designed to investigate the performance of a local antibiotic delivery technique involving Actisite® (tetracycline hydrochloride) Periodontal Fibre.

Since the development and clinical application of implant prosthodontics, many variations in implant design and coating, bridge design and the choice of metal alloys and suprastructure materials have evolved. Since this investigation was retrospective, it was not possible to assess any association of these clinical variables on the incidence of peri-implantitis within the confines of this study. Also, the influence

of operator and technical variables, together with patient variables such as occlusal factors, number of natural teeth present, parafunction and previous implant and dental hygiene practices prior to the commencement of the study could not be determined. As far as could be ascertained, no patients within the study were smokers. Limitations on time and patient availability has resulted in a relatively small sample size.

It is also possible that during occlusal loading of an implant that bone loss can occur. Patients exhibiting signs of bone loss but with no signs of peri-implant tissue inflammation were not included in this study.

The situation for implants with peri-implantitis is analogous to that of chronic periodontal disease, where the detection of past attachment and bone loss does not necessarily mean that sites will experience further breakdown.

The objective of this investigation was to assess the effectiveness of one form of early therapy for those implants with on-going peri-implantitis.

CHAPTER ONE

1. INTRODUCTION.

1.1 RESEARCH OBJECTIVES.

The purpose of this study was to evaluate the effectiveness of Actisite® (tetracycline hydrochloride) Periodontal Fiber around implants with slight to moderate peri-implantitis. The implant sites were monitored at baseline, two months and three months using specific clinical criteria and microbiological sampling techniques.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 AILING AND FAILING IMPLANTS

Today, studies involving the use of dental implants as abutments for the prosthetic rehabilitation of patients' dentitions abound in the dental literature (Adell et al., 1981; Adell, 1983; Astrand et al., 1991; Bahat, 1993; Bränemark et al., 1977; Henry et al., 1993; Jemt & Lekholm, 1993; Quirynen et al., 1992). Studies involving osseointegration have shown promising success rates (Adell et al., 1981; Adell, 1983; Albrektsson et al., 1988; Astrand et al., 1991; Bränemark et al., 1977; Friberg et al., 1991), encouraging an explosion in the rate of implant use. There has been less emphasis on factors that cause failures (ie, progressive loss of osseointegration) and, more importantly, the prevention, causation, detection and management of the ailing or failing implant.

The terms ailing and failing implants are used synonymously within the literature but there are very important differences between the two. The ailing implant may be treated, but the failing implant must be removed since it is nonfunctional and bone loss will continue (Meffert, 1992).

To best understand the literature on ailing and failing implants, the criteria used to assess a successful implant should be considered. Smith and Zarb (1989) examined the criteria proposed by other authors, and revised them as follows:

1. The individual unattached implant is immobile when tested clinically.
2. No evidence of peri-implant radiolucency is present as assessed on an undistorted radiograph.
3. The mean vertical bone loss is less than 0.2 mm annually after the first year of service.
4. No persistent pain, discomfort, or infection is attributable to the implant.
5. The implant design does not preclude placement of a crown or prosthesis with an appearance that is satisfactory to the patient and dentist.
6. By these criteria, a success rate of 85% at the end of a 5-year observation period, and 80% at the end of a 10-year period are minimum levels for success.

2.1.1. CRITERIA FOR IMPLANT FAILURE.

One of the most important aspects in preventing implant failure is proper patient case selection.

2.1.1.a Psychological, medical and social evaluation.

Patient selection should involve comprehensive psychological (expectations and demands of proposed implant treatment) and medical evaluation. The patient should be in good general health and be able to undergo routine oral surgery. The presence of any uncontrolled systemic problems is very important, and is determined after assessment of the patient's medical history and consultation with their physician if required. Individuals on medications (ie, tranquillisers) and conditions that seriously compromise bone healing, such as uncontrolled diabetes, alcoholism and immune disorders may need to be precluded from implant therapy (Gammage et al.,

1989). Few studies, however, show a lower implant success rate when patients are treated in the presence of such systemic factors (Bain and Moy, 1993).

In a study to determine the medical risks associated with implants, Smith et al. (1992) found that there did not appear to be an increased failure rate or an increase in peri-operative morbidity in patients with a compromised medical status (ie, age, sex, use of hypoglycaemic agents, supplemental female hormones and steroid usage). Though there was a limited number of patients studied, uncontrolled diabetics and patients on corticosteroid therapy do require close scrutiny to establish early diagnosis of infection. Smith et al. (1992) concluded that local factors such as bone quality and quantity as well as surgical and prosthetic technique were probably more significant indicators of outcome.

Dao et al. (1993) in a review of the literature regarding osteoporosis and a study of 129 patients, could not provide a compelling theoretical or practical basis to confirm osteoporosis as a risk factor for osseointegration of dental implants. It is presumed that radiation therapy is a contraindication to implant therapy, though there have been no significant reviews in the literature.

Studies by Bain & Moy (1993) and DeBruyn & Collaert (1994) reviewed the effects of smoking and its association with dental implant failure, with similar results. Bain & Moy (1993) reported a significantly greater percentage of failures in patients who smoked (11.28%), compared with nonsmokers (4.76%). These authors suggest that the patient stop smoking at least one week before surgery to eliminate nicotine-induced vasoconstriction, platelet adhesion and increased blood viscosity, and to allow flap

revascularisation. Smoking cessation should continue to at least two months after surgery by which time bony healing will have progressed to the osteoblastic phase, and early osseointegration should be established. It was concluded that moderate and heavy smoking has a negative influence on bone quality and such patients should be advised of the compromised prognosis for implant therapy. It seems likely that even upon smoking cessation, bone quality will be compromised for some time.

2.1.1.b Dental Health.

The patient's periodontal status is also critical, as plaque control must be meticulous and any periodontal disease in other areas of the mouth MUST be arrested. Individuals who cannot accept the responsibility to maintain their oral hygiene at a meticulous level should be placed on a maintenance phase or they should be prohibited from receiving implant therapy. Patients should be motivated and have a lifetime follow-up commitment in maintaining oral and implant care.

Patients with parafunctional habits, collapsed occlusions or craniomandibular /arthritic disorders should have the problem corrected before treatment begins (Johansson and Palmqvist, 1990).

2.1.1.c Treatment Planning.

During the case selection process, a pre-operative case conference, where the technical requirements of both surgery and prosthodontics are considered, should be held. The patient should be individually examined by both the surgeon and restorative dentist, with evaluations of an orthopantomogram and lateral cephalometric radiograph, and study casts mounted at the correct vertical dimension of occlusion. This is to ensure

that optimum results are achieved during the surgical and prosthodontic phases of treatment.

Some consequences of improper planning may involve, for example, the placement of six instead of five fixtures in the mandible, which results in overcrowding of the available space. If alignment is imperfect, one or more fixtures may not be used since the abutment sleeves and cylinders will demonstrate contact interference and prevent proper seating of the components. To maintain optimum oral hygiene between abutments that are too close will be very difficult for the patient. In addition, the effect of stress distribution to the bone between the abutments will result in unfavourable biomechanical loading (Henry, 1989).

With the partially edentulous patient, the presence of adjacent teeth greatly alters the biomechanical considerations of the implant restoration. Mechanically, bite force, tooth wear, abrasion resistance, occlusal scheme and differences in resiliency between the tooth and implant create a more complex scenario compared to the edentulous situation. The presence of adjacent teeth influences the anatomic variability of the edentulous residual ridge from the surgical viewpoint, and aesthetic requirements from the prosthetic viewpoint.

Other factors to consider in the partially edentulous patient are the limitations in the posterior regions. Anatomically, these areas are characterised by less favourable bone quality and smaller bone volumes than in the anterior region. As a result the selected implants are shorter and previous studies have shown that short implants fail more frequently than longer implants (van Steenberghe et al., 1990; Henry et al., 1993;

Friberg et al., 1991). The number of implants that can be placed in the posterior areas alone is frequently less than is other edentulous areas (van Steenberghe et al., 1990; Adell et al., 1981). Occluding force is increased the closer in the dental arch the teeth are placed to the temporomandibular joint (Book et al., 1992). All posterior implant supported partial prostheses are exposed to more loading than those in the anterior regions (Jemt & Lekholm, 1993).

The failure rates for individual fixtures supporting bridges have been reported in several short-term (Ericsson et al. 1986; van Steenberghe et al. 1987, 1989, 1990) and one long-term study (Jemt et al. 1989). The rates ranged from 1-8% in the mandible and 3-13% in the maxilla. Quirynen et al. (1992) and Jemt et al. (1989) both reported a 6% absolute failure rate for the maxilla and 1-6% for the mandible.

There are few longitudinal studies (van Steenberghe et al., 1989; Astrand et al., 1991) which provide compelling evidence of high success rates where the implant prosthesis is connected to an adjacent natural tooth. Most of the studies use a small number of patients and the period of evaluation is usually not very long. More research is required in this area, including whether a fixed or rigid connection, precision attachment or no connection should be recommended between natural teeth and osseointegrated abutments.

To evaluate occlusal overload, it must be determined whether the maximum number of fixtures of optimum length were used. Overload is most often encountered in patients with few and short (7.0 mm) fixtures (Jaffin & Berman, 1991). An implant should not be placed so that it is subjected to non-axial, especially faciolingual, loading

(ie, not directly compressive) as this results in overstressing the bone, irrespective of its structure. The implant is therefore at greater risk of osseointegrative mechanical failure (Bahat, 1993).

2.1.1.d Type of Bone.

It has been stated that the quality of bone stands out as the single greatest determinant in fixture loss (Friberg et al., 1991).

Bränemark et al. (1985) describes four types of alveolar bone that encompass most situations:

Type I: Homogeneous cortical bone.

Type II: Thick cortical bone with marrow cavity.

Type III: Thin cortical bone with dense trabecular bone of good strength.

Type IV: Very thin cortical bone with low density trabecular bone of poor strength.

Types I,II and III have enough cortex to stabilise the implant at installation and have sufficient strength to hold integrated implants in function. Type IV bone offers little cortex and minimal internal strength (Jaffin & Berman, 1991).

In a study by Jaffin & Berman (1991) involving a 5-year analysis, 90% of 1054 Bränemark implants were placed in Types I, II and III bone, and subsequently 3% of the fixtures were lost. Of the ten percent of fixtures placed in Type IV bone, 35% failed.

There have been numbers of reports illustrating the lower success rates of implants placed in the maxilla. Jaffin & Berman (1991) reported the loss of 8.3% of 444 titanium implants placed in the maxilla. In their 15-year analysis, Adell et al. (1981) observed a

failure rate of almost 20% for maxillary implants. In general, there is a decreased volume of bone available for fixture placement and for initial stabilisation and healing, compared to the mandible.

The results for the posterior maxilla have been less successful. DaSilva et al. (1992) found by lifetable analysis that the 6-year survival rate of posterior maxillary implants was 74%, compared to 94% with posterior mandibular implants.

Saadoun and LeGall (1992) in a five-year study of the Steri-Oss (Denar) endosseous implant system, found that the greatest failure rate was 12.9% in the posterior maxilla and the lowest failure rate was 1.4% in the anterior mandible. This difference was probably due to the difference in the quality (density) and quantity (depth) of bone. Deep bone (greater than 12 mm) favours a better initial stability for the implant and provides more surface area for osseointegration. The authors concluded that titanium screw implants should be used when bone quality is dense and immediate implant stabilisation can be achieved. In areas where the density of bone decreases and approaches Type IV, especially in the posterior maxilla, hydroxyapatite-coated implants are recommended.

2.1.2. FAILURES BEFORE OSSEOINTEGRATION.

Early failures can be described as occurring within 3-5 months post-surgically, that is before osseointegration has taken place, and have been attributed to surgical trauma, operative error, bone of insufficient quality and quantity, lack of primary stability, bacterial contamination of the recipient site and masticatory loading forces during

healing (Adell et al., 1981; Jaffin & Berman, 1991).

Failure of osseointegration (ie, the formation of a connective tissue interface or fibro-integration) may be due to any of the following situations (Meffert et al., 1992):

A. Overheating the bone during surgery and/or accidental contamination of the fixture surfaces.

B. The implant is placed with too much pressure.

C. Apical migration of epithelium into the interface, followed by connective tissue elements.

D. The implant does not exactly fit the site. The most important factor here is that no micromovement occurs between the implant and bone during periods of load transfer.

E. The system is prematurely loaded (earlier than 3-6 months).

Infection may contaminate a site, and so all carious infections and periodontal disease should be eradicated before fixture installation (Jaffin & Berman, 1991).

2.1.3. FAILURES AFTER OSSEOINTEGRATION.

2.1.3.a. Periodontal Considerations of Implants.

Progressive peri-implant bone loss together with a soft tissue inflammatory lesion can be defined as peri-implantitis (Jovanovic etal., 1993).

The soft and hard tissues surrounding an osseointegrated implant show some similarities with the periodontium. The coronal portion of the implant is surrounded by a thin layer of collagen fibres arranged circumferentially and with minimal vascular structures. The fibres are not attached to the implant and are parallel to the implant surface, in contrast to the gingival fibres around teeth which are perpendicular and attached to cementum. The low vascularity of the soft tissue band around the implant may adversely affect the defence mechanisms when compared with those associated with the teeth. Furthermore, if plaque was allowed to accumulate, then the number of inflammatory cells infiltrating the connective tissue around implants was found to be much larger and more extensive than around teeth (Lindhe et al., 1989; Berglundh et al., 1991 & 1992; Buser et al., 1992; Jovanovic et al., 1993).

A possible explanation for more severe peri-implant lesions is that the lack of a cemental surface with inserting collagen fibres enabled a more rapid down-growth of plaque. The parallel fibre orientation in the peri-implant tissue may favour a more rapid spread of the lesion and the progression of the lesion into the bone marrow may reflect the inability of the implant tissue to heal after infection. From various studies in animal models, and after consideration of the differences between the periodontal

connective tissue attachment and the peri-implant connective tissue cuff-like barrier, it is currently thought that the peri-implant tissues are more susceptible to plaque-associated disease (Bauman et al., 1993).

Newman and Flemming (1988), emphasised that the relationship between traditional clinical periodontal indices (bleeding on probing, pocket depths, attachment levels and plaque indices) and the susceptibility to, and pathogenesis of peri-implantitis is not well understood. There is a need for specific implant associated clinical parameters to be standardised so that potentially failing implants can be detected at an early stage, specific treatment regimens can be instituted and monitored, and the prognosis can be more effectively determined. Many clinical signs of failure emerge only when an irreversible and incurable state has already been reached. The parameters selected should be easy to measure and yield reliable and reproducible information (Mombelli & Lang, 1994).

Mombelli et al. (1987) and Pontoriero et al. (1994) suggested that peri-implantitis be regarded as a site specific infection which has many features in common with chronic adult periodontitis.

There are, however, no specific periodontal indices applicable to the features of tissues encountered around implant fixtures.

Kwan & Zablotsky (1991) raise the question of what failure means when discussing peri-implantitis? They classified failures as those implants which exhibited clinical mobility and were refractory to any peri-implant therapy. There is little that can be

done to improve the prognosis or to manage the situation effectively. An ailing implant is not mobile, and the peri-implantitis should be able to be managed effectively with a resultant improvement in prognosis (Meffert, 1991).

Newman & Flemming (1988) classified failures after osseointegration as resulting from two major aetiological factors. These are bacterial infection and occlusal overloading.

A model for the pathogenesis of peri-implantitis was proposed:

Decreased host response. Plaque. Occlusal stresses.

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Gingival inflammation and hyperplasia.

|

Progressive deepening of pockets, attachment loss and bone loss.

Change in subgingival microflora.

|

Osseo-disintegration with mobility and peri-implant radiolucency.

|

Exfoliation.

Kwan & Zablotsky (1991), in discussing the cause of peri-implantitis agreed with the above 'traditional' pathway, but stated that it can also occur via a retrograde occlusal pathway. This pathway extends from the bone because of microfractures from overloading or lateral forces, to cause a loss of the perimucosal seal, ingress of bacteria

and further bone loss. They also stated that combinations of both mechanisms should be considered.

2.1.3.b Periodontal Parameters to Assess Peri-implant Health and Disease.

A prerequisite for a successful implant should be to obtain a perimucosal seal of soft tissue against the implant surface. Failure to achieve or maintain this seal results in apical migration of the epithelium into the bone/implant surface, and possible encapsulation of the endosseous portion of the implant system. If the seal breaks down or is not present, a 'pocket' exists and the area is subject to periodontal-type disease (Meffert et al., 1992).

To assess peri-implant health the following methods have been employed:

1. Pocket probing depths.

The periodontal pocket depth is commonly used to monitor peri-implantitis by using a plastic periodontal probe in much the same as it is used in patients with periodontal disease around natural teeth (Lang et al., 1994). Pocket depth is the linear distance from the free gingival margin to the base of the pocket (Fiorellini & Weber, 1994).

There are many sources of variation which prevent a standardised approach and the collection of reproducible data. For example, different operators using differently designed probes and probing pressures, or gingival shrinkage changes that can occur during the healing phase resulting in a reduced pocket depth. The mucoperiosteal flap thickness at surgery will influence the pocket depth measurement (Haanaes, 1990). Also, some implant designs of superstructures prevent the accurate placement of the probe to the apex of the pocket, thereby resulting in an underestimation of the

depth since the probe is not parallel to the long axis of the implant (Van Steenberghe & Quirynen, 1993). To assist in standardisation, the length of the implant abutment head should be known to assess pocket depth accurately.

Newman & Flemming (1988) stated that stable implants should have an ideal pocket depth of 1.3 - 3.8 mm and that the pocket depth will increase if there is , or there has been, any inflammation. Mombelli et al. (1987) reported a mean probing depth of 8.5 mm for unsuccessful implants and 3.9 mm for successful implants. Becker et al. (1990), however, stated that a mean probing depth of greater than 5 mm MAY be related to implant failure, and that probing depth alone could not be used as a criterion for assessing implant failure.

The periodontal probe therefore, is probably only an easy and quick method for assessing any deleterious changes, with an increase in depth perhaps indicating that treatment is required.

2. Attachment levels.

While the attachment level is a good indicator of marginal bone height, there is a definite need for fixed reference points (for eg, restoration abutments) and standardised methods. Attachment levels can be measured as the distance from a defined implant landmark to the pocket base, measured with a plastic periodontal probe. The presence of peri-implant pocket progression along with loss of attachment signify resorption of the alveolar bone (Fiorellini & Weber, 1994).

3. Bleeding on probing, tissue tone and flaccidity.

These parameters are routinely used to assess periodontal health and are an important sign of disease. Their use should be of value when assessing peri-implantitis.

Haffajee et al.(1983) state, however, that the clinical parameters commonly used in diagnosing chronic periodontal disease do NOT correlate well with the progression of this disease. Parameters such as plaque accumulation, redness, bleeding on probing and suppuration are of marginal use in assessing the progression of periodontal disease, and may be equally ineffective for the evaluation of dental implant success.

In summary, increased pocket depths are usually associated with failing implants and seem to correlate well with inflammation of the peri-implant mucosa. The two parameters of mobility and radiographic radiolucencies seem to have a high specificity in the detection of a failing implant, ie, one that is progressively losing bony support.

2.1.4 USE OF RADIOGRAPHS TO ASSESS IMPLANT FAILURE.

One of the most reliable methods to evaluate current implant status is radiographic examination, including the evaluation of bone height and detection of any peri-implant radiolucency (Bränemark et al., 1977).

Radiographic evaluation should be made with serial radiographs using a standardised technique. This involves using a positioning device so that the radiographs are made with the x-ray beam at right angles to the long axis of the implant. Measurements of crestal bone loss can then be made and peri-implant radiolucency detected. The use of serial radiographs makes it much easier to identify progressive bone loss (Smith & Zarb, 1989).

Other methods of measuring the amount of bone loss adjacent to dental implants include digital imaging and subtraction radiography which allow the detection of more subtle changes in alveolar bone height.

2.1.5 MICROBIOLOGICAL CONSIDERATIONS OF IMPLANTS.

The microbiota around stable compared with failing implants seems to parallel the patterns observed around healthy teeth and those suffering from chronic adult periodontitis (Mombelli et al., 1987; Becker et al., 1990). In failing implant sites there is a higher proportion of those microorganisms usually associated with periodontal disease, and there is a possible role for pathogenic bacteria in the aetiology of implant failure (Newman & Flemming, 1988).

It is known that the microbial composition in healthy and diseased periodontal sites. Healthy sites have a predominance of coccoid cells and non-motile rods, with a low proportion of motile rods, spirochaetes and fusiform bacteria. The supragingival plaque around healthy subperiosteal, titanium and aluminium oxide implants, and healthy control teeth in partially edentulous patients, reveals a similar composition (Mombelli et al., 1987 & 1993; Newman & Flemming, 1988).

In peri-implant sites in patients with 'successful' implants which had been maintained for long periods, Mombelli et al. (1987) found that the microbiota was similar to that found at healthy periodontal sites. From studies reviewed by Mombelli & Lang (1994), irrespective of implant type and material, the normal microbial flora of oral implants was dominated by cocci, which are facultatively anaerobic and Gram positive.

Mombelli et al. (1987) compared clinical and microbiological findings related to healthy and failing titanium implants. Unsuccessful implant sites were characterised by probing depths of 6.0 mm or greater, suppuration, bone loss and microbiota consisting primarily of Gram negative anaerobic rods. *Prevotella intermedia* (formerly called *Bacteroides intermedius*) and *Fusobacterium* species were regularly found. Spirochaetes, fusiform bacteria and motile and curved rods were a common feature seen in darkfield microscopic specimens.

Becker et al. (1990) used a DNA probe to evaluate the microbiota around failing implants and found a high proportion of Actinobacillus actinomycetemcomitans, Bacteroides gingivalis and Bacteroides intermedius.

Rosenberg et al. (1991) stated that pathogens from natural teeth may 'seed' to newly inserted implants and result in tissue breakdown, since a greater proportion of infectious failures were found in partially edentulous patients. This might indicate a higher susceptibility for peri-implantitis in the partially edentulous mouth as the microbiota of remaining teeth are probably the primary source of putative pathogens to colonise adjacent implants (Mombelli, 1993; Papaioannou et al.,1995).

Mombelli (1993) in a summary of all the available data, concludes that there is a clear microbiological distinction between clinically stable implants and implants with peri-implant pathology. Gram-negative anaerobic bacteria are involved in the pathological developments in the peri-implant region, and spirochaetes can be perceived as indicators of a flora with anaerobic characteristics, which are definitely not a feature of the physiological flora associated with successful implants. Longitudinal, prospective studies are needed to determine whether microbiological parameters can indicate a risk of peri-implant tissue destruction or allow early disease states to be detected.

2.1.6 MAINTENANCE AND MANAGEMENT OF THE AILING AND FAILING IMPLANT.

The ultimate goal in restoring the ailing implant to a healthy state is to arrest the progression of the disease and to achieve a maintainable site for the patient. The ailing implant exhibits bone loss with pocketing with no progression of the lesions between maintenance checks. The failing implant exhibits bone loss, pocketing, bleeding on probing, purulence and evidence of rapid ongoing bone loss irrespective of therapy. There is also mobility, a dull sound when percussed and a peri-implant radiolucency radiographically. The failing implant must be removed since it is nonfunctional and bone loss will continue (Meffert, 1992).

The objectives of regular maintenance visits are to reduce the bacterial load, to remove excessive occlusal stresses and to monitor the peri-implant situation for early detection of the signs of implant failure (Newman & Flemming, 1988). Since it has

been found that the aetiology of peri-implantitis closely resembles that of advanced periodontitis, the treatment regimens proposed for the ailing implant after osseointegration are similar to those applied in cases of periodontal disease.

When a clinical and radiographic examination has been carried out (ie, evaluation of tissue health, superstructure fit, occlusion and oral hygiene procedures) and a diagnosis of peri-implantitis is made, Kwan & Zablotsky (1991) have divided the management into pre-surgical and surgical stages.

2.1.6.a Pre-surgical Management.

The main aim of the presurgical management should be to re-establish a healthy peri-mucosal seal, ie, decreased probing depths, absence of bleeding on probing and exudate.

2.1.6.b Surgical Management.

The surgical management phase occurs if the presurgical management has not produced a healthy peri-mucosal seal and the peri-implant tissues have continued to deteriorate. This may involve the elimination of deep pockets or attempts to regenerate bone around the implant.

The surgical techniques used are modified from techniques used to treat bone defects around teeth. The implant surface is contaminated with soft tissue cells, bacteria and bacterial by-products (Quirynen et al., 1990). Bacterial adherence is enhanced by micro-irregularities of the implant surfaces and, as long as the contamination is present, wound healing is compromised (Jovanovic et al., 1993).

When considering open debridement, there are many methods used to clean the fixture surface including air abrasive polishers, 'plastic' sonic and ultrasonic scalers, chlorhexidine, tetracycline, citric acid or a combination of these. These antimicrobials and antibiotics would aim to kill the periodontopathic microbiota and remove endotoxin from the implant surface (Meffert, 1992).

Meffert (1992), however, stated the importance of a smooth implant surface for plaque control and tissue adaptation, and suggests probable removal of any implant threads with a diamond bur and copious irrigation, once they become involved in any bone regeneration procedure.

After the implant surface is decontaminated, a type of osseous regeneration procedure can be performed. 'Re-osseointegration' can be defined as growth of new bone in direct contact to the previously contaminated implant surface without an intervening band of 'organised' connective tissue (Jovanovic et al., 1993).

There have been many case reports on the usefulness of conventional periodontal regeneration techniques in the treatment of ailing implants. Although they appear to be clinically successful, there has been only minimum follow-up and no histology available to support these methods for the treatment of peri-implantitis (O'Neal et al., 1992). What needs to be determined is whether treatment results in reattachment, or arrests the process of peri-implantitis or has no effect at all on progressive implant failure.

2.3 ACTISITE® (TETRACYCLINE HYDROCHLORIDE) PERIODONTAL FIBRE THERAPY

Tetracycline is one of the most common antibiotics used in the treatment of periodontitis. Actisite® (tetracycline hydrochloride) periodontal fibre therapy is indicated as an adjunct to mechanical debridement in patients with chronic adult periodontitis. It was first reported in the literature by Goodson et al. in 1979. Several clinical studies (Listgarten et al., 1978; Baker et al., 1985; Walker et al., 1985; Silverstein et al., 1988) have shown its effectiveness against many of the anaerobic microbes associated with various periodontal diseases. A 6-month multi-centre clinical trial by Newman et al. (1994) on periodontal maintenance patients, reported a significant clinical benefit in the clinical parameters of bleeding on probing, probing depth and attachment level with local delivery tetracycline fibre therapy.

The periodontal fibre is a monofilament of ethylene vinyl acetate (EVA), a biocompatible, non-irritating copolymer with enough elasticity to mould into the periodontal pocket. The fiber is 23cm in length and 0.5 mm in diameter, containing 25% (12.7mg) evenly dispersed tetracycline hydrochloride. When placed in a periodontal pocket, tetracycline is continuously released over a 10-day treatment period, achieving a per site mean gingival crevicular fluid (GCF) concentration of 1590μg/mL. This is about 100 times the peak concentration achievable with a 250mg oral dose of tetracycline. It has a zero-order release profile, with an exponential washout upon removal (Tonetti et al., 1990).

Despite high GCF levels, the concentration of tetracycline in the plasma is quite low. In a study by Rapley et al. (1992), mean tetracycline concentrations following local delivery placement were below the lower limit of assay detection (<0.1μg/mL). Actisite fibres thus achieve high GCF concentrations of tetracycline directly at the infection site while minimising serum concentrations and avoiding any adverse effects associated with systemic administration.

A study by Ciancio et al. (1992) evaluating tetracycline tissue concentration and location, and histologic effects following fibre use, found no difference between placebo and tetracycline fibres for tissue injury. Also, tetracycline was found to localise in the pocket epithelium and adjacent connective tissue with an average tissue concentration of 43μg/mL , which is at the uppermost end of the bacteriostatic range for suspected periodontal pathogens. Goodson & Tanner (1992) reported no significant increase in resistance to tetracycline after local fibre delivery treatment among the suggested periodontal pathogens including *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteriodes forsythus* and *Wollinella recta.*

2.4 CONCLUSIONS.

Actisite® (tetracycline hydrochloride) Periodontal Fibre was initially developed for periodontal pocket placement, as an adjunct to conventional scaling and root planing. It consists of a 23cm (9 inch) monofilament of ethylene/vinyl acetate copolymer, 0.5 mm in diameter, containing 12.7 mg of evenly dispersed tetracycline hydrochloride. Actisite fibre provides continuous release of a high local titer of tetracycline for ten days, and has been shown to be effective against probable periodontal pathogens *Porphyromonas gingivalis, Prevotella intermedia, Eikenella corrodens* etc. These same microorganisms have been found in studies around implants which show signs of peri-implantitis, and there have been no studies to date evaluating the effectiveness of Actisite® around these implants.

CHAPTER THREE.

3. MATERIALS AND METHODS

3.1 INTRODUCTION

The duration of this clinical study was between the periods of March to August, 1995, and data collected during this time is evaluated in this Research Report. Development of peri-implantitis around osseointegrated dental implants very often results in attempts at either surgical repair or even implant removal. A concentrated local drug delivery system (Acitsite®,tetracycline HCl containing fibres) has been previously used around natural teeth with chronic periodontitis and its usefulness may be extended to treat peri-implantitis situations. There have been no studies to date evaluating the effectiveness of Actisite® as an initial treatment regimen for peri-implantitis.

3.2 METHODOLOGY

3.2.1 PATIENT SELECTION

In order to obtain a sample population for this clinical study, the names of patients currently reviewed at the Implant Maintenance Clinic, School of Dentistry, Louisiana State University were obtained. These patients had received implant therapy at the Dental School within the last five years.

To supplement the patient source, written notices were sent to private General Dental Practitioners, Specialist Periodontists and Oral Surgeons within the Greater Metropolitan New Orleans Area, requesting them to inform the School of Dentistry of any patients with implant (peri-implantitis) problems.

3.2.2 PATIENT CONSENT FORM (Appendix II).

The selected patients were informed about the nature of the study and consent was obtained at the first appointment, using an Institutional Review Board approved consent form. The consent form explained the purpose of the clinical study with a detailed description of patient involvement, explaining the nature, purpose and duration of the study. In addition, subject inclusion and exclusion criteria were outlined, with risks to subjects and alternative treatment methods should the patients not wish to participate further in the study.

Patients referred from the private practice sector in New Orleans were required to sign an additional form **(Appendix III)** outlining that treatment procedures provided would only be those specified in the Consent Form for the study.

Intra-oral photographs were taken which are depicted in the following pages.

3.2.3 THE DATA RECORD SHEET (Appendix IV).

PATIENT DETAILS.

The patient's name, sex, casenote number and birthdate were recorded in this section.

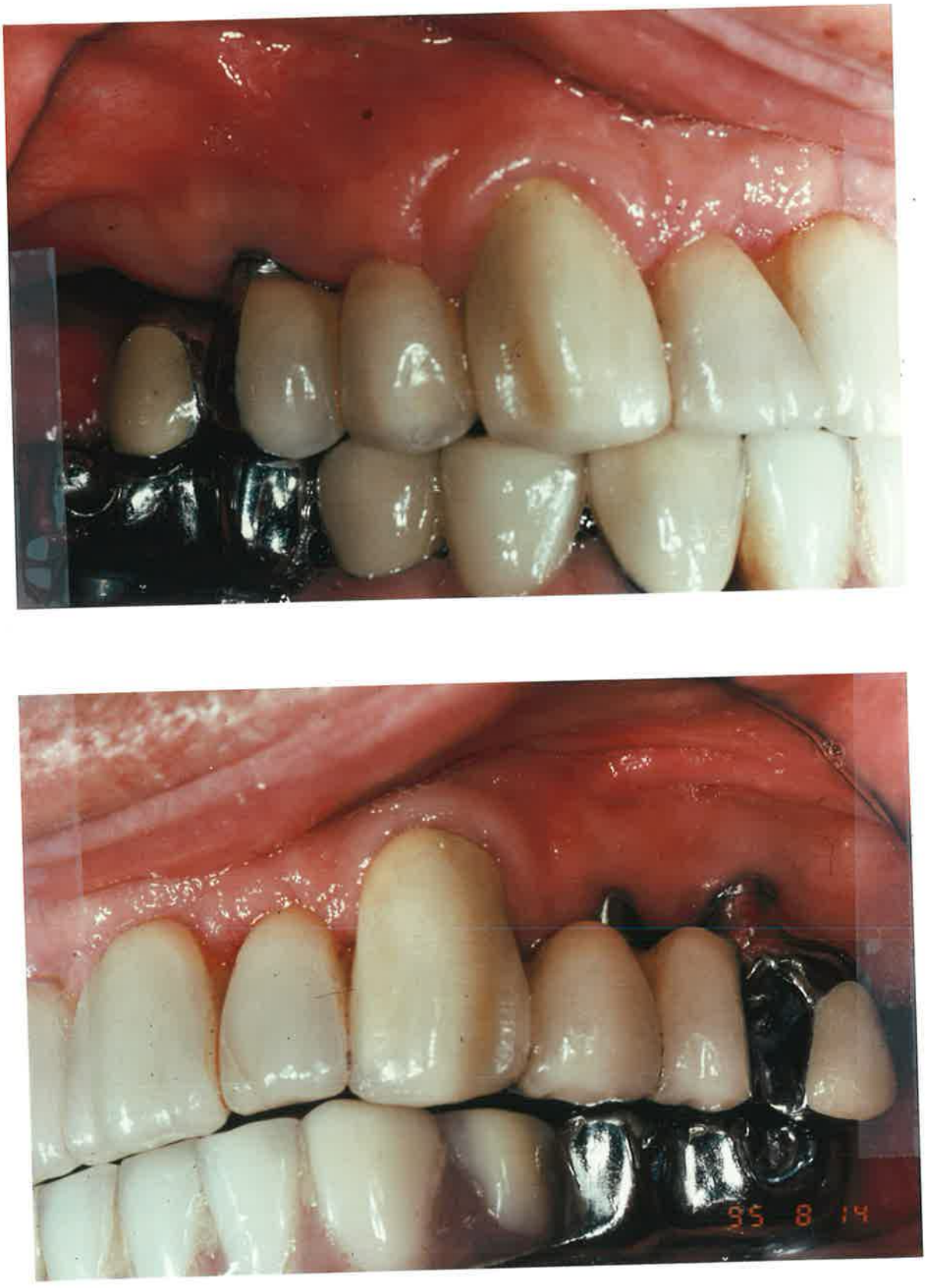


FIGURE 1 Intra-oral left and right buccal views of maxillary and mandibular implant prostheses. The implants used for Actisite® placement were in the maxillary first and second premolar positions. Control implants for use in the study were in the maxillary right and left lateral incisor positions.

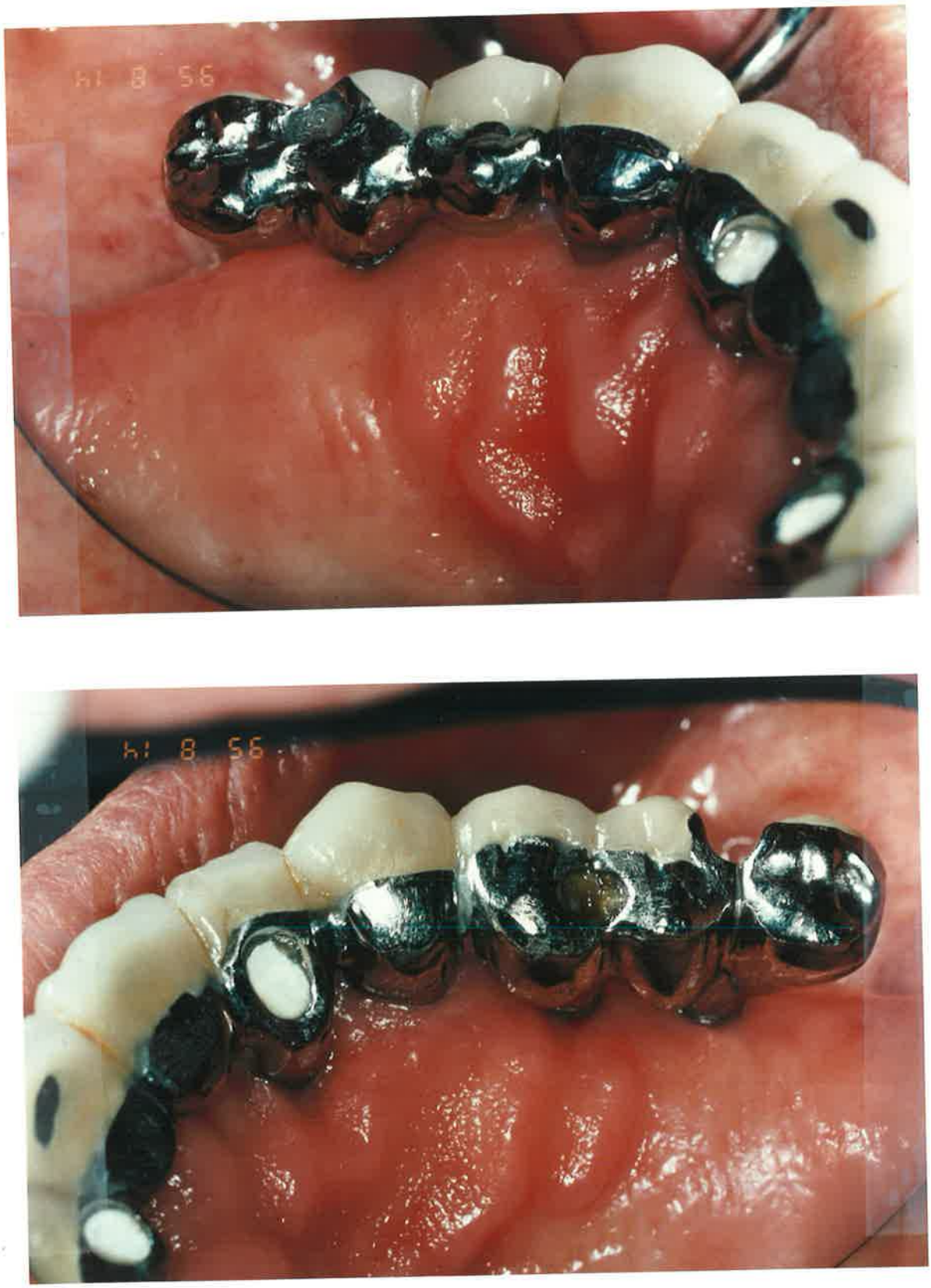


FIGURE 2 **Intra-oral left and right palatal views of the same patient as depicted and described in Figure 1.**

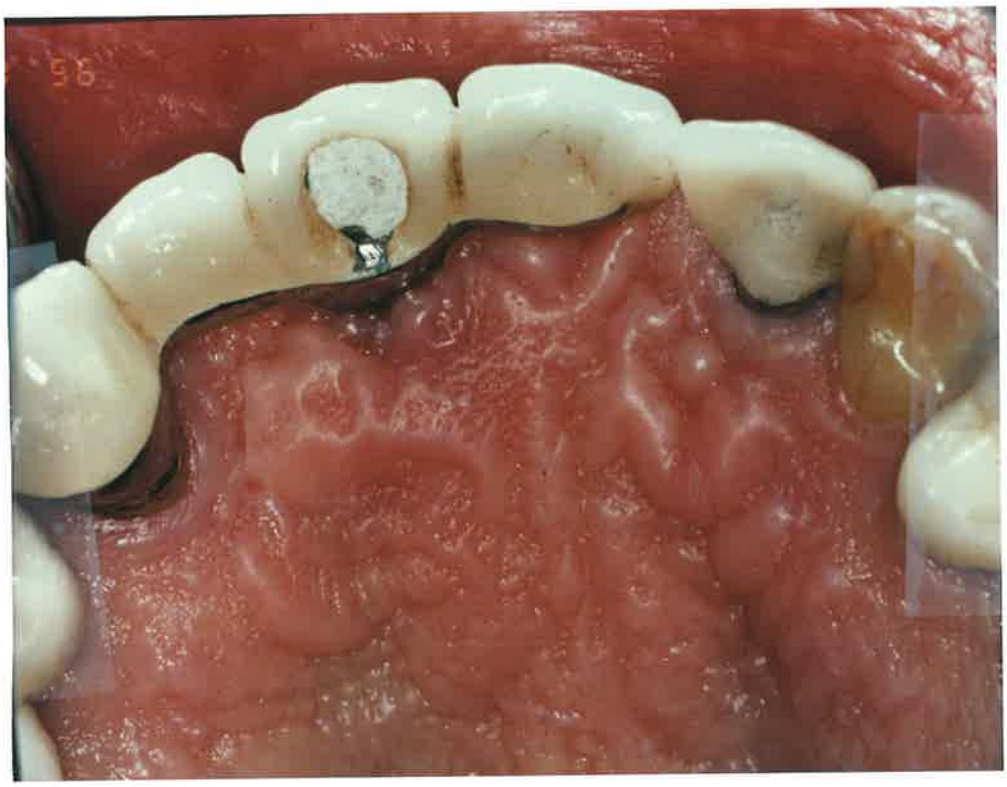


FIGURE 3 **Intra-oral palatal implant view in the position of the maxillary left central incisor, used for Actisite® placement.**

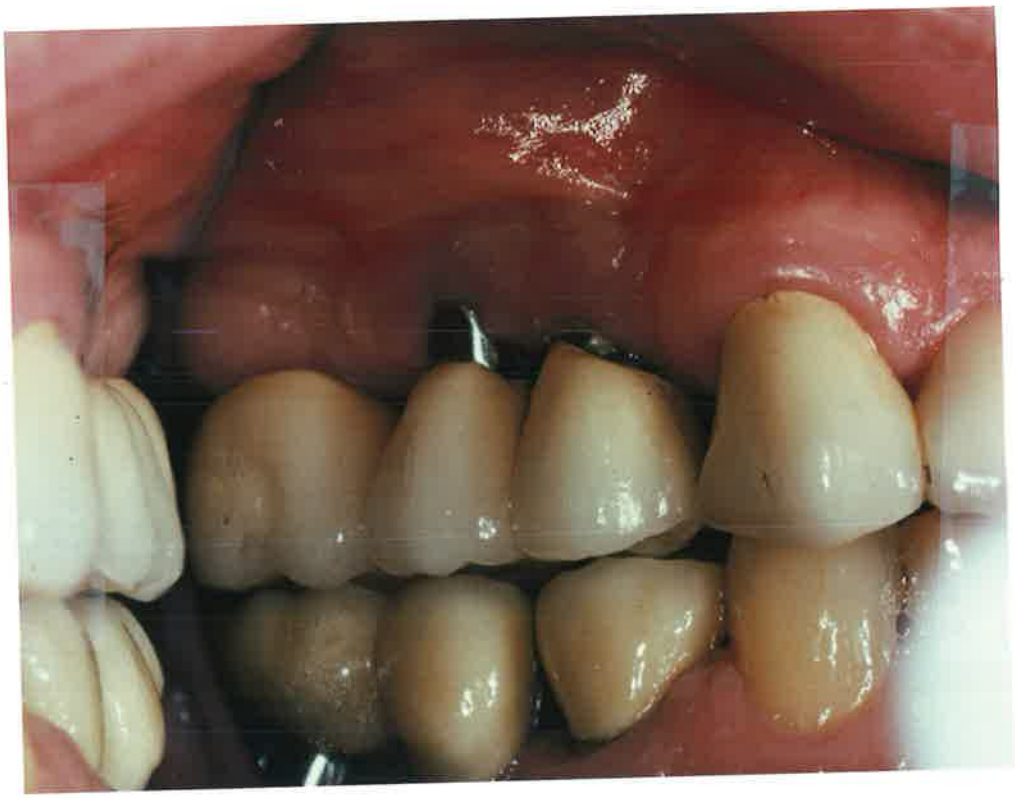
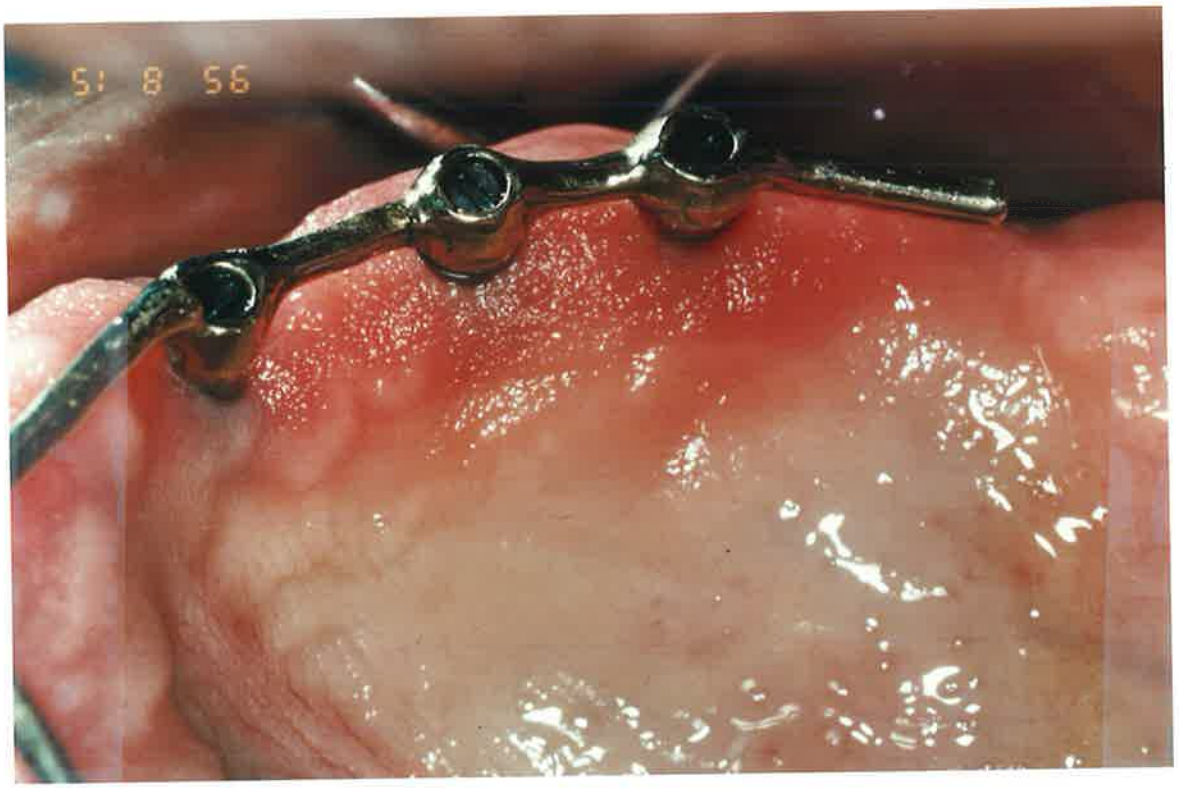


FIGURE 4 **Intra-oral left beuccal view of maxillary and mandibular fixed porcelain implant bridges. Control implants for used in the study were in the maxillary left premolar positions.**



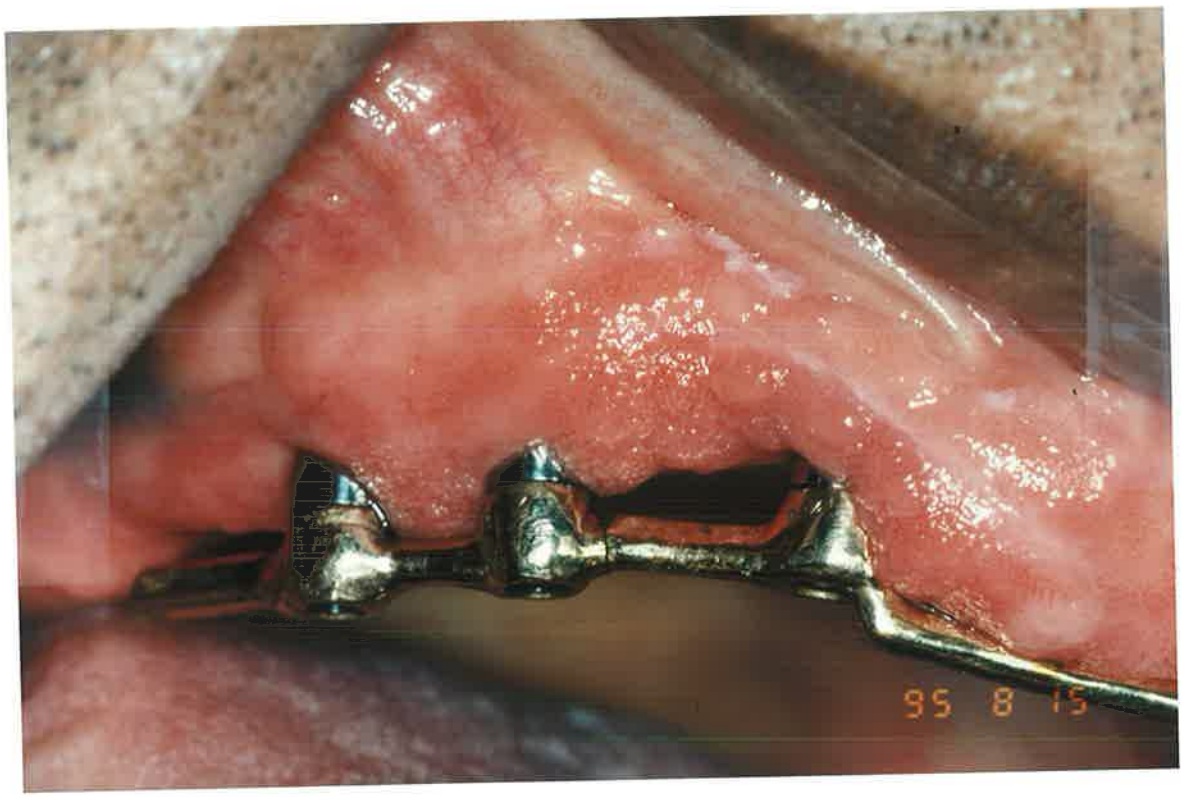


FIGURE 5 **Intra-oral palatal and labial views of maxillary bar retained implant suprastructure. The implant used for Actisite® placement was in the maxillary right second premolar position. The control implant for use in the study was in the maxillary right first premolar position.**

3.2.4 STUDY DESIGN.

The implant type selected for this clinical study were hydroxyapatite-coated root form implants (Integral*) placed within the previous five years. Patients with signs of slight-moderate peri-implantitis (bleeding on probing, probing depths 5-7 mm), and slight to moderate bone loss (no mobility) were enrolled in the study. Thirteen patients were enrolled at baseline, with a total of 20 test and 8 control implants.

Each implant was probed to detect which of four surfaces would fulfill the criteria for the study. Once this was established, the *surface* with the deepest implant pocket depth was chosen for data collection and Actisite® placement.

Controls were included in the study wherever possible. Control implants were selected from the study patients, with each control implant probed to detect which of four surfaces would fulfill the criteria for the study. Once this was established, the *surface* with the deepest implant pocket depth was chosen as the control. Oral hygiene instruction was the only treatment regimen provided at the control implant sites.

All data were recorded on the Data Record Sheet (Dental Implant Clinic Maintenance Record), which also included the implant positions (denoted by a reference number used for tooth positions) **(Appendix IV)**.

***Calcitek Inc., Carlsbad, California**

Each patient was examined at each stage of the study by the same examiner (myself) who was blinded to whether treatment was being provided or not. The examiner technique was calibrated prior to the start of the study. A Data Record Sheet was completed at each subsequent patient visit, without knowledge of prior findings. Data were collected, compared and analysed at each separate patient visit. Trainee dental hygienists assisted in the data collection. Instruction on plaque control methods around the implants were provided to all patients at each visit.

Placement and removal (after 10 days) of the Actisite® fibre and all oral hygiene instruction was provided by Resident Periodontics students at the School of Dentistry, Louisiana State University. Patients were recalled at 1 month for general evaluation and oral hygiene review. The baseline clinical and bacterial examination was repeated at 2 months. This examination was repeated again at 3 months with the addition of the radiographic examination.

3.2.5 BASELINE EXAMINATION.

Whenever possible, superstructures were removed in order to assess:

Gingival margin position (FGM)

Probing depths (PD)

Clinical probing attachment level (CPAL)

Bleeding on probing (BOP)

DNA probe (Affirm®): for detection of *Prevotella intermedia, Porphyromonas gingivalis* and *Bacteroides forsythus.*

Neutral protease levels (Periochek®).

3.2.5.a Clinical Examination:

1. Probing depths and clinical probing attachment levels:

The implant supra-structure was removed to facilitate accurate probing depth assessment and attachment level measurements. Four surfaces (mesial, distal, buccal and lingual) were scored around each implant, to the nearest millimeter, with a manual pressure sensititive plastic probe.

The probing depth was the linear distance from the free gingival margin to the base of the pocket. Care was taken to ensure that the probe remained parallel to the long axis of the implants.

The clinical probing attachment level was measured from the pocket base to the fixed reference point of the abutment head attached to the implant fixture.

The position of the free gingival margin was measured to the nearest millimeter as measured from the abutment head attached to the implant fixture.

2. Bleeding on probing:

Presence or absence of bleeding within 30 seconds after gentle probing with light standardized pressure. Bleeding was scored as present or absent.

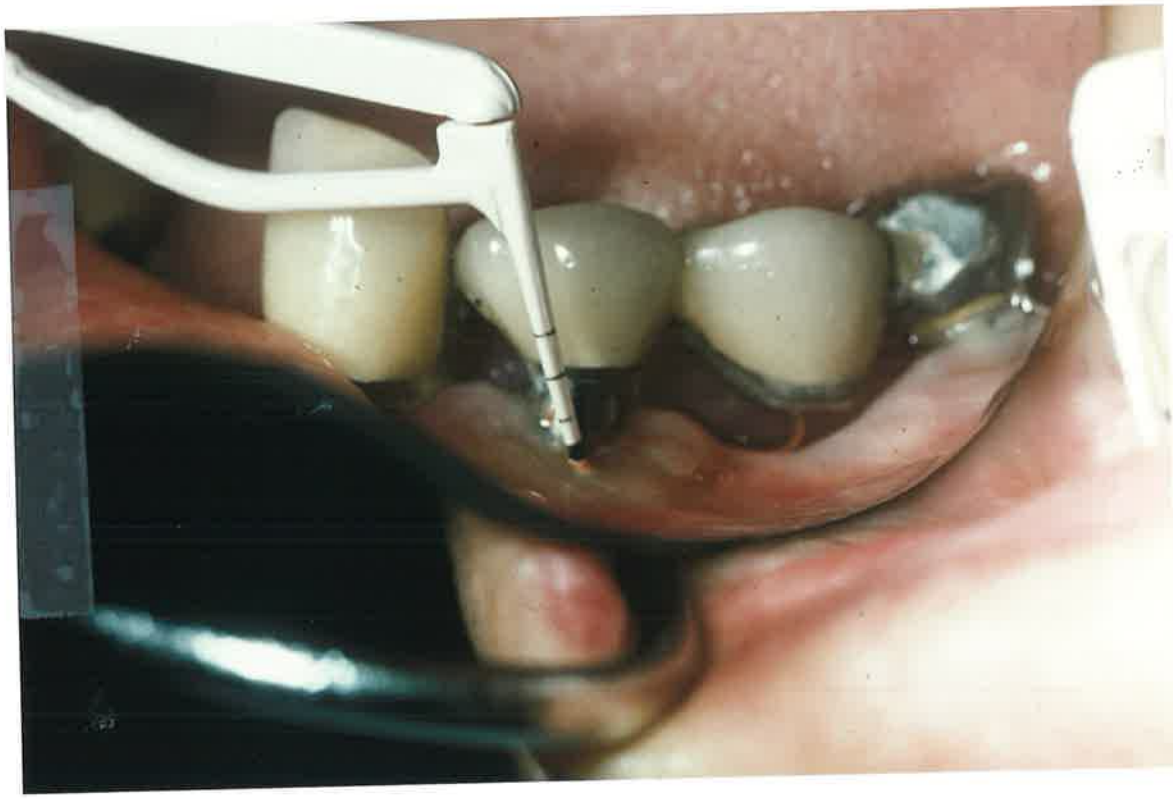


FIGURE 6 **Plastic periodontal probe for measurement of peri-implant sulcus.**

3.2.5.b Bacterial Examination:

1. DNA probe (Affirm®).

Detailed microbiological analyses were provided by a DNA probe (MicroProbe Corporation, Bothell, WA) **(Appendix V)**. The analysis could not be performed if the patient had been treated with antibiotics or any mechanical debridement within the last 4-6 weeks, or within 12 hours of using a chemotherapeutic mouthrinse.

A paper point was inserted to the base of the pocket and held in place for 10 seconds. The deepest probing depth that bled around each implant was selected for bacterial sampling. The paper point was removed and placed in a specimen collection vial and prepared for microbial identification. A probe analysis card (PAC) comprising three beads containing microorganism specific probes, and that also included negative control and positive control beads, provides the analysis.

The procedure involves three stages:

1. Sample preparation
2. Automated processing with small desk top Affirm® Processor
3. Results interpretation

The results are read visually, with a blue colour on the bead indicative of a positive result, while negative results showed no colour. Test results were available approximately 40 minutes after sample collection.

2. Neutral protease levels (Periochek®).

Neutral protease levels were provided by the Periochek® Periodontal Monitoring System (Professional Dental Technologies, Inc., Batesville, AR) **(Appendix VI)**.
An assay for these enzymes was conducted at the chairside. These enzymes, (particularly collagenase) are recognised as one indicator of active periodontal disease and can be used in peri-implantitis situations.

A paper strip was inserted 1-2 mm into the peri-implant sulcus and left for five seconds. The paper strips were placed on a tray covered with a collagen-based gel substrate. The tray was then placed in a dry bath incubator for twelve minutes, after which the strips were lifted onto a permanent mounting card for analysis. A blue strip indicated active disease.

3.2.5.c Radiographic examination:

Custom intraoral radiology stents were fabricated from Reprosil® (Dentsply Int Inc., Milford, DE) and an Up Rad® (UpRad Corporation, Upgrading Radiodontics, Chewsville, MD) film holder to allow repeatability of x-ray angulation and orientation. Radiographs were taken utilizing a superimposed grid attached to the individualized holder. Periapical radiographs were taken at baseline and at 3 months.

3.3 MATERIALS.

3.3.1 ACTISITE® (tetracycline hydrochloride) Periodontal Fibre.

The Actisite® Periodontal Fibre was available in boxes of 10 fibres, with each yellow fibre individually packaged. Each fibre was 23cm (9 inches) long and contained 12.7mg of tetracycline hydrochloride. It was inserted into the peri-implant pocket, under local anaesthesia, until the pocket is filled, with the length of the fibre used varying with the pocket depth and contour. The fibre was placed to closely approximate the pocket anatomy and should be in contact with the base of the pocket. A cyanoacrylate adhesive (Octyldent®) was placed around the gingival margin to help secure the fibre within the pocket.

When placed within the peri-implant pocket, Actisite fibre provided continuous release of tetracycline for 10 days (Goodson, 1989; Tonetti et al., 1990). At the end of 10 days of treatment, all fibres were removed. Any fibres lost before 7 days were immediately replaced.

® Procter & Gamble and ALZA Corporation.

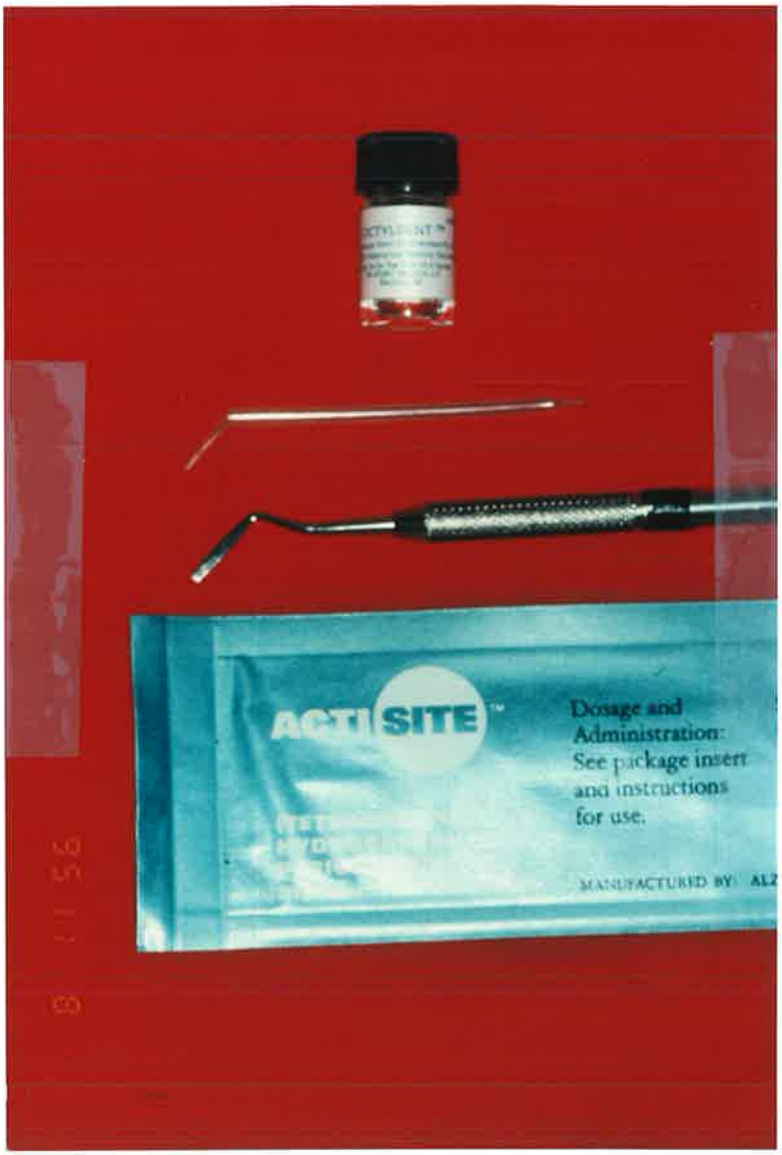


FIGURE 7 **Actisite® armantarium. Each individually packaged, yellow fibre is 23cm long and contains 12.7mg of tetracycline hydrochloride. Also included ia a packaging instrument and cyanoacrylate adhesive (Octyldent).**

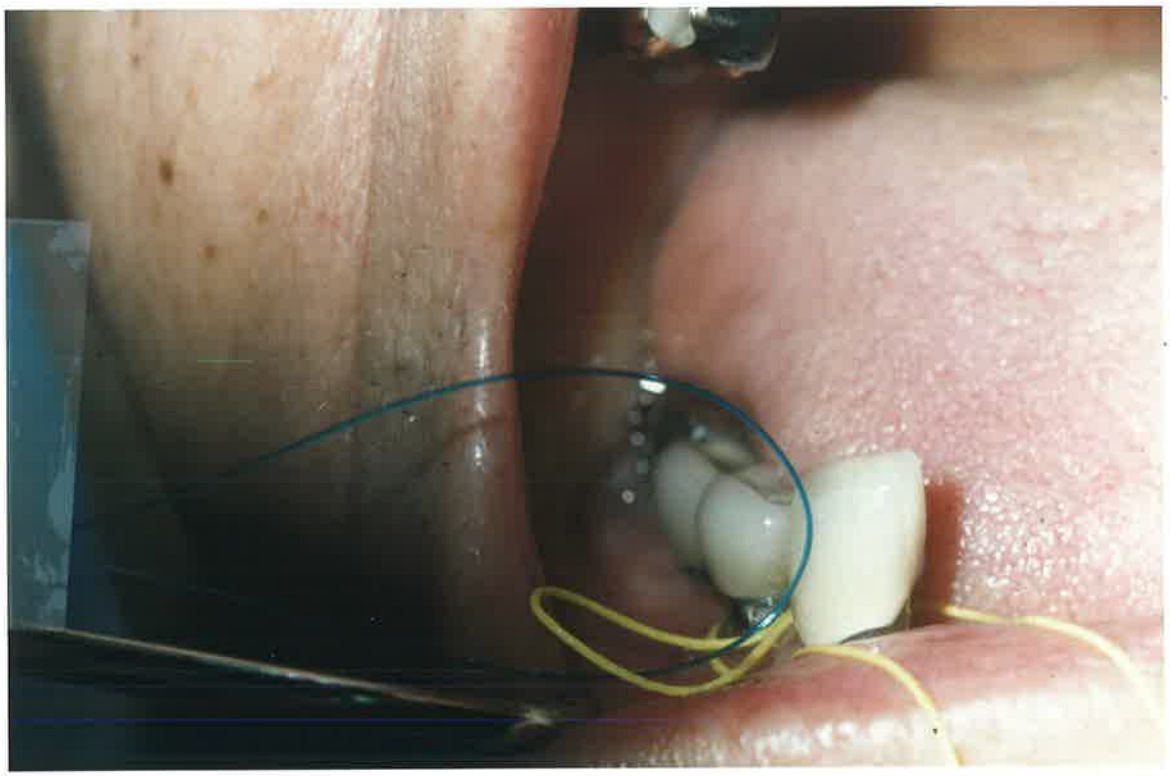


FIGURE 8 **Initial placement of Actisite® fibre underneath the contact area prior to placement within the peri-implant sulcus.**

3.4 DATA ANALYSIS.

Average indices (means) were determined from data collected at baseline, 2 months and 3 months for free gingival margin, probing depths, clinical probing attachment levels and bleeding on probing. Data were analysed to assess changes from baseline by t- tests and Analysis of Variance (SPSS Release 4.0 for Macintosh). The graphs were formulated using Cricket Graph (Macintosh). Significance was set at $\alpha = 0.05$.

3.4.1 OUTCOMES ASSESSMENT

The outcome was considered positive for Actisite treatment if probing depths, bleeding on probing, the level of periodontal pathogens and neutral protease levels were significantly reduced compared to baseline, and to controls, if appropriate. Radiographic changes may not be as definitive in this time frame, but would show at least no further bone loss at 3 months as a positive outcome.

CHAPTER FOUR.

4. RESULTS

During the study period from March to July, 1995, a total of 13 patients provided 20 Actisite® treated implants (69 surfaces), and 8 control implants (18 surfaces). There were no reports of any adverse effects attributable to Actisite® fibre therapy. One patient returned five days after fibre placement due to protrusion of the fibre from the peri-implant socket. The fibre was repositioned and secured into the pocket and secured with cyanocrylate (Octyldent®) adhesive.

Table 1 shows the number of implants used in the study with respect to the sample population age, with ten out of the thirteen patients within the 50 - 70 year old age group.

TABLE 1

Distribution of implants selected in relation to patient age.

Patient Age (Years)	Number of implants
30 -40	1
40 - 50	1
50 - 60	5
60 -70	5
70 +	1
Total	13

Table 2 shows the distribution of implants used for Actisite® treatment with 80% of mandibular implants.

TABLE 2

Location of implants used for Actisite treatment.

	Anterior	Posterior	Total
Maxilla	**2**	**2**	**4**
Mandible	**8**	**8**	**16**
Total	**10**	**10**	**20**

Table 3 shows the distribution of implants used for controls, with relatively equal numbers between the posterior maxilla and mandible, with only one control implant in the anterior maxilla.

TABLE 3

Location of implants used for Controls.

	Anterior	Posterior	Total
Maxilla	2	3	5
Mandible	-	3	3
Total	2	6	8

Table 4 shows the distribution of implant surfaces used for Actisite® placement with 27.5% (facial), 24.6% (distal), 24.6% (mesial) and 23% (lingual) surfaces used.

TABLE 4

Distribution of implant surfaces used.

	Actisite	Control	Total
Implant surface			
Facial	**19**	**3**	**22**
Distal	**17**	**5**	**22**
Mesial	**17**	**6**	**23**
Lingual	**16**	**4**	**20**
Total	**69**	**18**	**87**

Periapical radiographs taken at 3 months showed no further bone loss. There were essentially no changes or differences in neutral protease or bacterial levels between treatments or between time periods.

The t-tests **(Tables 5 - 8)** compared the means of the treated and control groups at the commencement of the study. The variables of free gingival margin levels, probing depths and clinical probing attachment levels **(Tables 5 - 7)** showed significant differences ($P < 0.05$) between the two groups. The differences in bleeding on probing data **(Table 8)** were not significant .

T-tests.

TABLE 5

Variable: **Free gingival margin**

Score	Number of cases	Mean	Standard deviation	Standard error
Actisite	69	-.0435	2.025	.244
Control	18	-1.2222	1.263	.298

		Separate Variance Estimate		
F value	2-tail Prob	t value	Degrees of Freedom	2-tail Prob
2.57	.033	3.06	42.66	.004

T-tests.

TABLE 6

Variable:	Probing Depths			
Score	Number of cases	Mean	Standard deviation	Standard error
Actisite	69	6.2754	1.662	.200
Control	18	4.6667	.686	.162

		Separate Variance Estimate		
F value	2-tail Prob	t value	Degrees of Freedom	2-tail Prob
5.87	.00	6.25	68.66	.00

T-tests.

TABLE 7

Variable: Clinical Probing Attachment Lengths.

Score	Number of cases	Mean	Standard deviation	Standard error
Actisite	69	6.1739	3.092	.372
Control	18	3.4444	1.617	.381

		Separate Variance Estimate		
F value	2-tail Prob	t value	Degrees of Freedom	2-tail Prob
3.66	.004	5.12	52.87	.00

T-tests.

TABLE 8

Variable: Bleeding on Probing.

Score	Number of cases	Mean	Standard deviation	Standard error
Actisite	69	.8551	.355	.043
Control	18	.9444	.236	.056

Separate Variance Estimate

F value	2-tail Prob	t value	Degrees of Freedom	2-tail Prob
2.26	.062	-1.28	39.55	.210

Having described the systematic differences between the Actisite® and control groups at the commencement of the study, the data obtained were scaled with the initial (baseline) values to start at zero, to enable easier comparisons between the treated and control implant sites over the twelve week period. This does not influence the statistical significance of the differences at later stages, but makes the assessment of the subsequet trends easier to understand.

The results for the Analysis of Variance tests which compare the differences between the Actisite® and control groups over time are shown in **(Tables 9 - 12)** and portrayed in **Graphs 1 - 4.**

The change in height of the free gingival margin **(Table 9 & Graph 1)**, did not differ significantly between the Actisite® treated and control implant sites (P= 0.348), and did not differ significantly with time (P= 0.992).

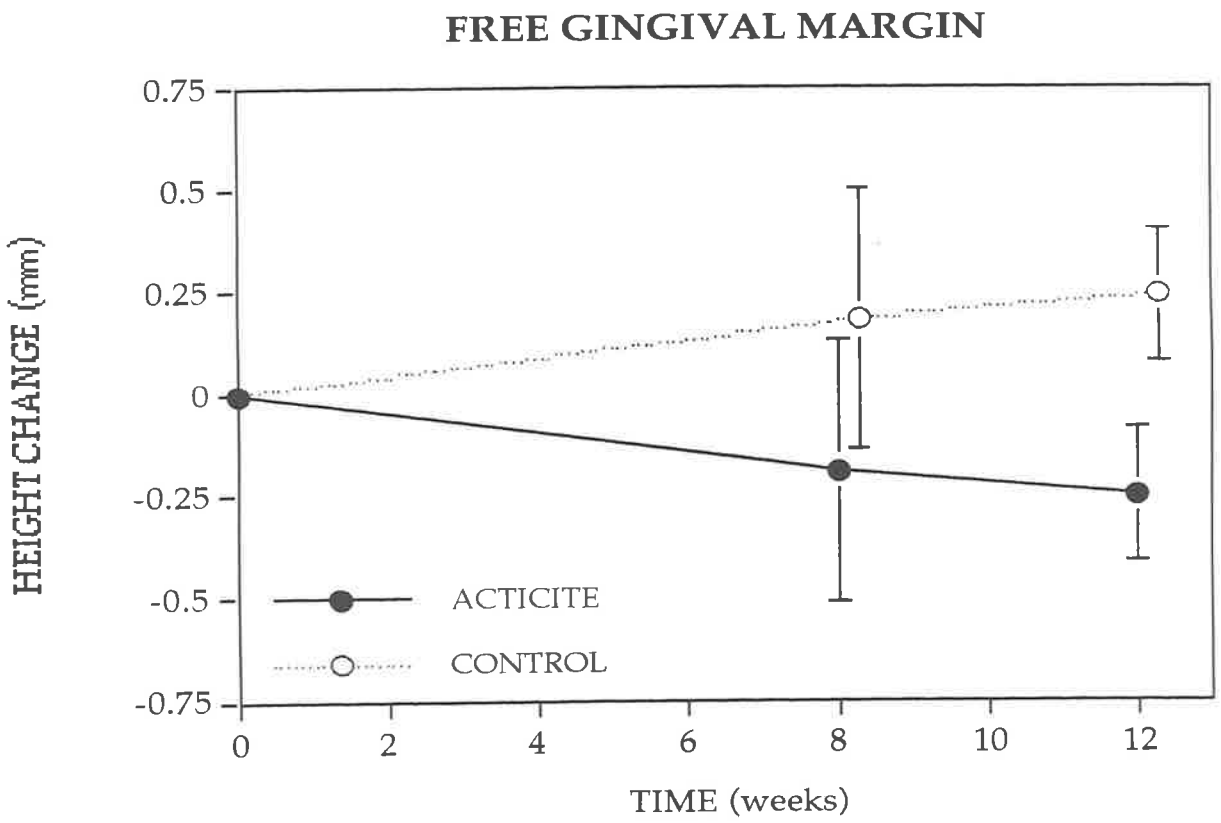
TABLE 9

ANALYSIS OF VARIANCE (ANOVA)

FREE GINGIVAL MARGIN DATA

		Mean	Std. Dev.	N
GROUP	ACTISITE			
Time	Baseline	.000	2.025	69
Time	8 weeks	-.189	1.926	69
Time	12 weeks	-.247	1.716	69
GROUP	CONTROL			
Time	Baseline	.000	1.263	18
Time	8 weeks	.1666	1.392	18
Time	12 weeks	.1666	1.110	18
For entire sample		-.092	1.774	261

	SS	DF	MS	F	Sig of F
Within Cells	812.36	255	3.19		
Group	2.81	1	2.81	.88	.348
Time	.05	2	.02	.01	.992
Group by Time	1.43	2	.71	.22	.799



GRAPH 1 : CHANGES IN HEIGHT OF FREE GINGIVAL MARGIN OF ACTISITE AND CONTROL IMPLANT SITES OVER THE TWELVE WEEK PERIOD.

In **Graph 2,** a significant improvement in probing depths was evident between baseline and 3 months (PD: 0.0 ± 1.7 mm vs. -1.6 ± 2.4 mm) for Actisite® treated surfaces compared to the control implant surfaces (0.0 ± 0.7 vs. -0.9 ± 1.5).

The results of the Analysis of Variance **(Table 10)** suggest that probing depths reduced significantly with time (P= 0.001), and differed significantly between the Actisite® and control groups (P= 0.025).

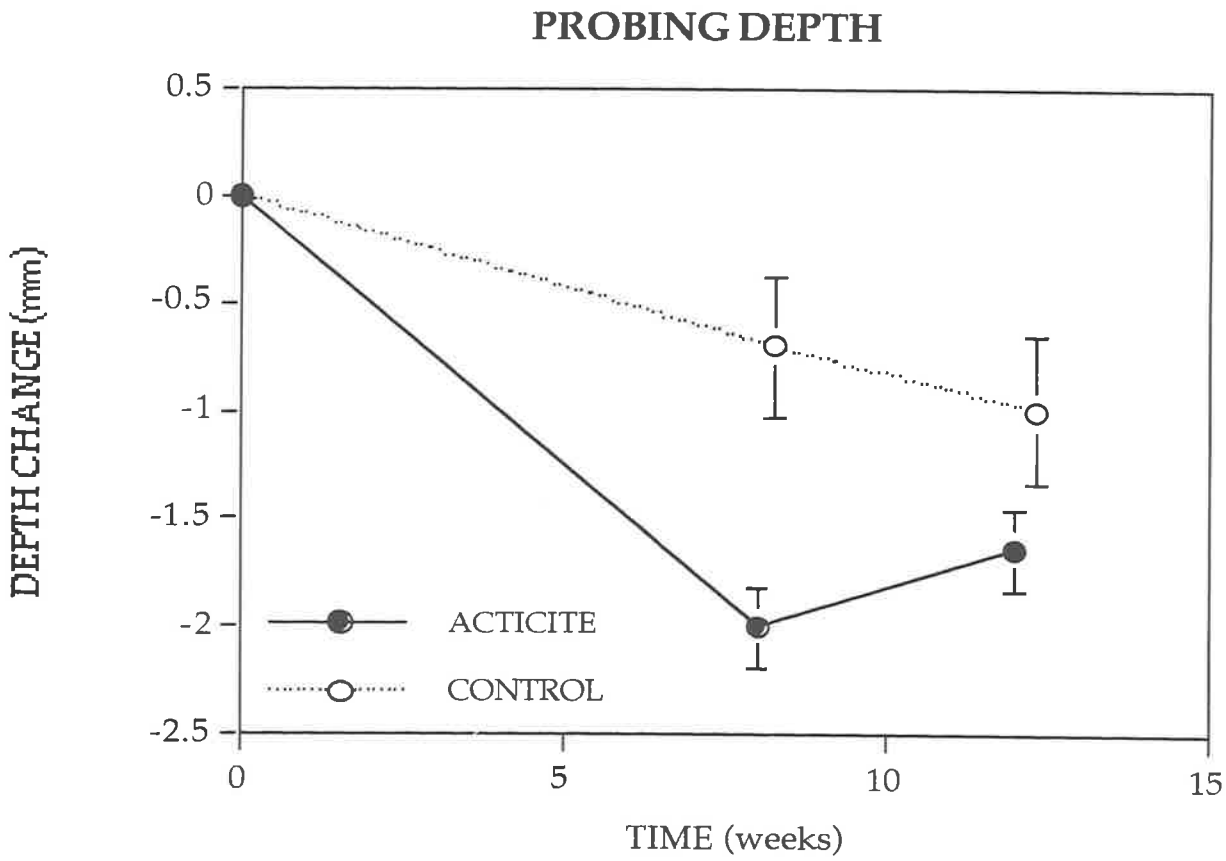
TABLE 10

ANALYSIS OF VARIANCE (ANOVA)

PROBING DEPTH DATA

		Mean	Std. Dev.	N
GROUP	ACTISITE			
Time	Baseline	.000	1.662	69
Time	8 weeks	-2.014	2.343	69
Time	12 weeks	-1.646	2.397	69
GROUP	CONTROL			
Time	Baseline	.000	.686	18
Time	8 weeks	-.611	1.862	18
Time	12 weeks	-.945	1.487	18
For entire sample		-1.077	2.189	262

	SS	DF	MS	F	Sig of F
Within Cells	1061.97	256	4.15		
Group	21.08	1	21.08	5.08	.025
Time	64.79	2	32.40	7.81	.001
Group by Time	14.06	2	7.03	1.69	.186



GRAPH 2: CHANGES IN PROBING DEPTH OF ACTISITE AND CONTROL IMPLANT SITES OVER THE TWELVE WEEK PERIOD.

As with probing depths, there was also a significant improvement in clinical probing attachment levels **(Graph 3)** between baseline and 3 months (0.0 ±3.0 mm vs. -1.8 ± 3.3 mm) for Actisite® treated surfaces compared to controls (0.0 ± 1.6 vs. -0.7 ± 1.6).

The results of the Analysis of Variance **(Table 11)** suggest that clinical probing attachment levels reduced significantly with time (P= 0.034), with an apparent difference between the Actisite® and control groups (P= 0.053).

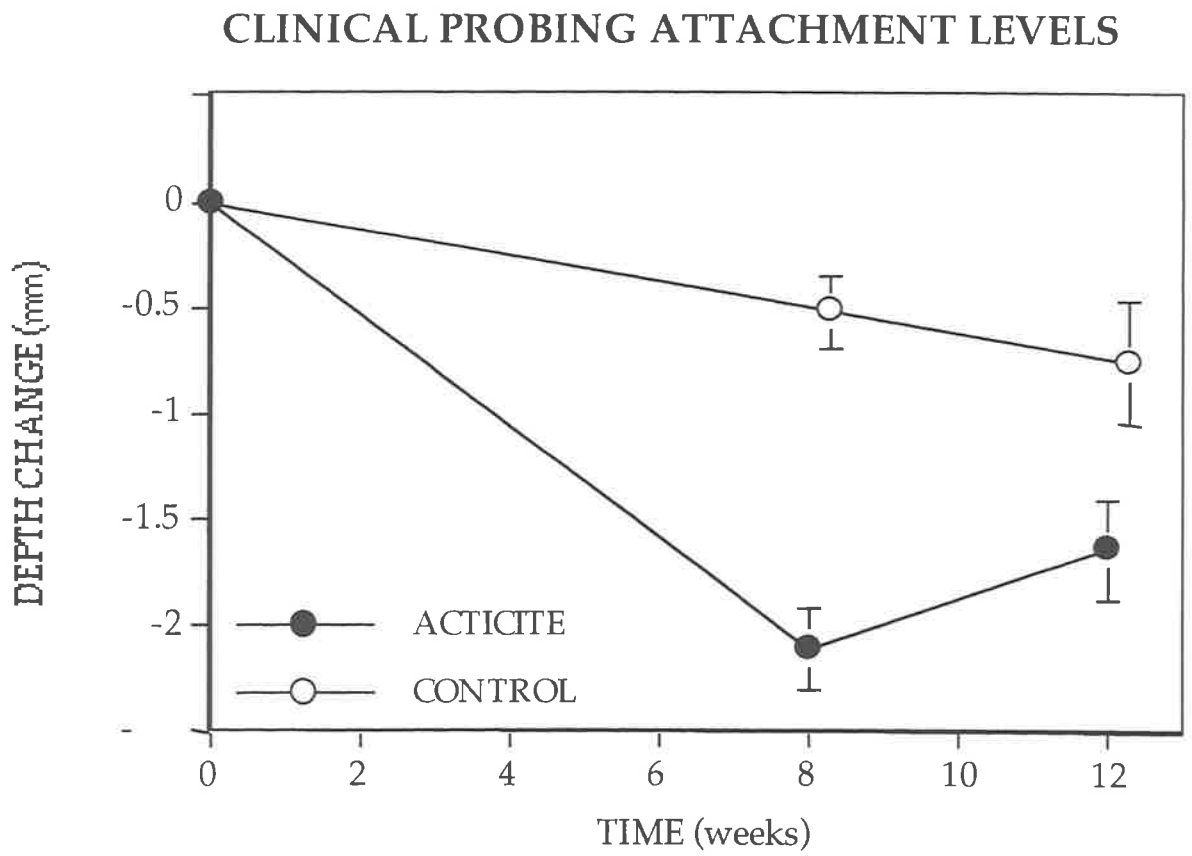
TABLE 11

ANALYSIS OF VARIANCE (ANOVA)

CLINICAL PROBING ATTACHMENT LEVEL DATA

		Mean	Std. Dev.	N
GROUP	ACTISITE			
Time	Baseline	.000	3.092	69
Time	8 weeks	-2.116	3.386	69
Time	12 weeks	-1.821	3.358	69
GROUP	CONTROL			
Time	Baseline	.000	1.617	18
Time	8 weeks	-.444	1.910	18
Time	12 weeks	-.777	1.879	18
For entire sample		-1.122	3.152	260

	SS	DF	MS	F	Sig of F
Within Cells	2351.66	254	9.26		
Group	35.07	1	35.07	3.79	.053
Time	63.31	2	31.65	3.42	.034
Group by Time	20.35	2	10.18	1.10	.335



GRAPH 3: CHANGES IN CLINICAL PROBING ATTACHMENT LEVELS (CPAL) OF ACTISITE AND CONTROL IMPLANTS OVER THE TWELVE WEEK PERIOD.

Bleeding on probing **(Graph 4)** was reduced (though not significantly) by both treatments between baseline and 3 months (Actisite® treated surfaces: 0.0 ± 0.3 vs -0.3 ± 0.6; Controls: 0.0 ± 0.2 vs. -0.6 ± 0.5). There was no statistically significant difference in bleeding reduction among treatments.

The results of the Analysis of Variance **(Table 12)** suggest that bleeding on probing reduced significantly with time (P= 0.00), and differed significantly between the Actisite® and control groups (P= 0.021).

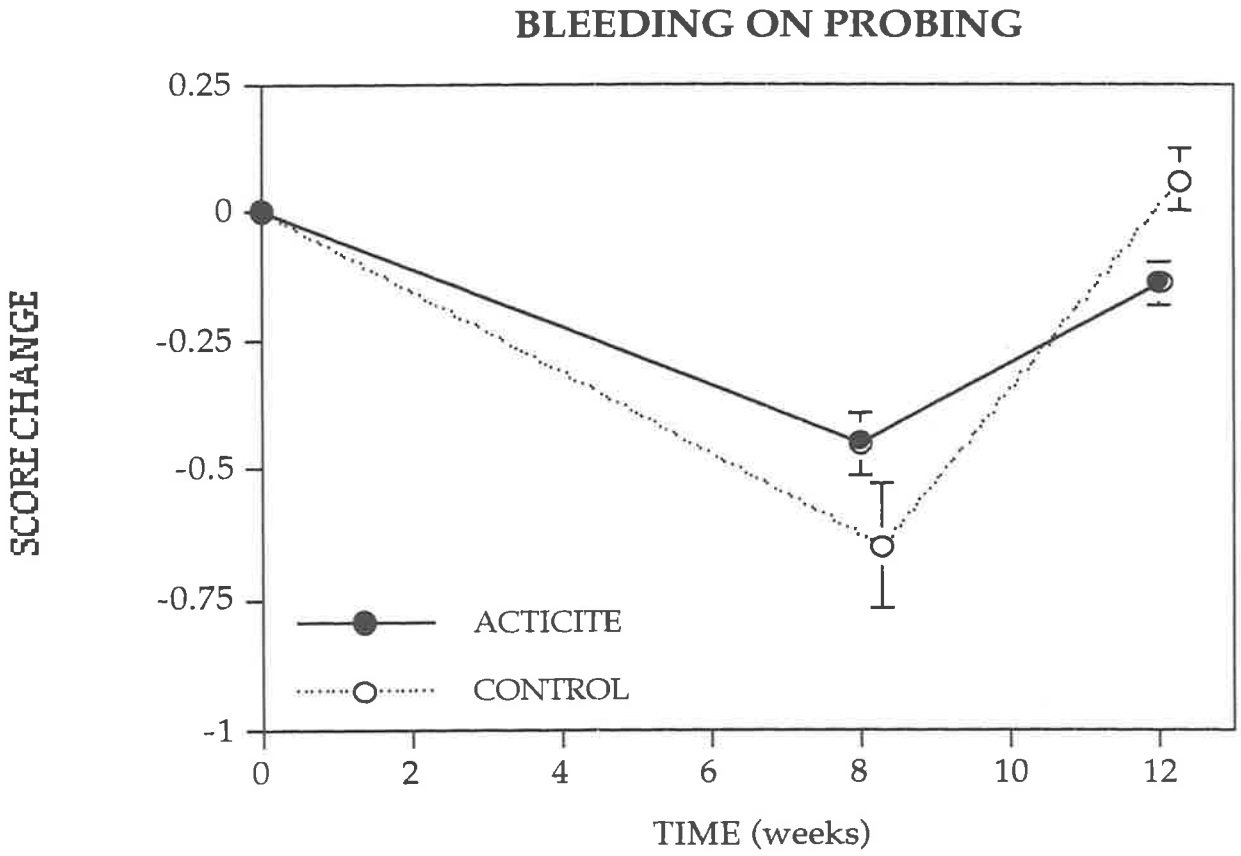
TABLE 12

ANALYSIS OF VARIANCE (ANOVA)

BLEEDING ON PROBING DATA

		Mean	Std. Dev.	N
GROUP	ACTISITE			
Time	Baseline	.000	.355	69
Time	8 weeks	-.435	.526	69
Time	12 weeks	-.275	.579	69
GROUP	CONTROL			
Time	Baseline	.000	.236	18
Time	8 weeks	-.611	.485	18
Time	12 weeks	-.611	.485	18
For entire sample		-.272	.524	261

	SS	DF	MS	F	Sig of F
Within Cells	59.12	255	.23		
Group	1.24	1	1.24	5.36	.021
Time	9.07	2	4.53	19.55	.000
Group by Time	.81	2	.40	1.74	.178



GRAPH 4: BLEEDING ON PROBING SCORE CHANGES OF ACTISITE AND CONTROL IMPLANTS OVER THE TWELVE WEEK PERIOD.

CHAPTER FIVE.

5. DISCUSSION.

This clinical study compared two treatments for implants with slight-moderate peri-implantitis: Actisite® (tetracycline hydrochloride) fibre therapy and treatment with oral hygiene only. Patients were treated once with Actisite® with continued oral hygiene instruction, and monitored over 3 months. Previously, there have been no published reports detailing the effect of a concentrated local tetracycline delivery regimen around implants with peri-implantitis. This preliminary study was therefore undertaken to assess the suitability of local drug delivery treatment for the ailing implant.

Due to the small sample size in this study, all implant surfaces used for both the Actisite® fibre treated and control implants were grouped together. This was due to preliminary analysis of variance (ANOVA) results between maxillary and mandibular, and anterior and posterior implants which showed no significant differences between the samples.

Each implant surface was probed to detect which would fulfill the criteria for the study (ie, exhibiting slight to moderate peri-implantitis: probing depths 5-7 mm, bleeding on probing with slight-moderate bone loss). Once this was established, the *surface* with the deepest implant pocket depth was chosen for data collection and Actisite® placement.

Similarly, if there were other implants within the same patient that fulfilled the above criteria, the surface with the deepest implant pocket depth was selected as a control. Of the two implants chosen, that with the deepest pocket depth was selected for Actisite® treatment, which is in accordance with the study protocol. This accounts for the significant differences between the Actisite® and control groups at the commencement of the study and was required on ethical grounds. Ideally, control implants would have been selected in a contralateral position to the test implant and with similar clinical findings, but this was not possible with the patients selected for the study.

Control fibres have been used in previous studies (Goodson et al., 1991 & Maiden et al., 1991), to compare the efficiacy of tetracycline fiber therapy. These fibres were composed of the ethylene vinyl acetate copolymer (EVA) without the tetracyline. In both studies, the bacterial composition was not found to differ between the control fibre and untreated sites, but there was a decrease in the number of sites infected with the monitored species when treated with tetracycline fibres, and scaling and root planing. There were no control fibers used in this study (untreated sites only were used) due to the similar outcome of previously reported results.

Due to the split-mouth design of this study, the potential existed for tetracycline released into the saliva to have had a beneficial 'antibacterial mouthwash' effect on the control implant sites treated with oral hygiene instruction only (Drisko et al., 1995). Studies with natural teeth (Pitcher et al., 1980; Wunderlich et al., 1984) involving dyes rinsed in the mouth have indicated, however, that the level of penetration into pockets (retrograde perfusion) is rarely more than 3 mm. There was

also no significant association between the *number* of teeth treated with tetracycline therapy and the clinical response at sites treated with scaling and root planing only. The possibility of such an effect cannot be dismissed, however, since cross-over effects are potential problems in split-mouth design.

There are no specific clinical and radiographic indices to monitor the peri-implant tissues at present, and no specific clinical criteria that indicate the failure or success of implants. Current periodontal parameters (probing depths, clinical probing attachment levels, bleeding on probing, changes in bone mass by radiographic techniques etc.) are used for assessing natural teeth are also generally used for evaluating peri-implant tissues, and have accordingly been used in this preliminary study. Individually or in combination, however, these measures are relatively poor predictors of future disease (Haffajee et al., 1983). Jepsen et al. (1996) recomend attachment level recordings with a controlled force electronic probe in conjunction with enzymatic diagnostic tests of the host response as parameters of the future.

Studies have shown (Lindhe et al., 1989; Badersten et al., 1990; Claffey et al., 1990; Michalowicz et al., 1995), however, that periodontal sites losing clinical attachment during maintenance periods were, on average, initially deeper than sites which did not lose clinical attachment. Badersten et al. (1990) reported that in patients monitored for five years after non-surgical treatment, that diagnostic predictability for attachment loss improved with increasing probing depths. In addition, some of the parameters used for assessing the natural periodontium may be inadequate for evaluating implants because of the differences between implants and natural teeth (Bauman et al, 1993).

There is a need for better identification of peri-implantitis lesions and, a need to evaluate the effectiveness of specific indices used for the surrounding soft and hard tissues. At present, there is no consensus regarding the rate of progression of peri-implant destruction, as it is not known whether it progressess continuously or in bursts, and whether remissions are possible.

As with patients with periodontal problems, a maintenance programme is essential to monitor oral hygiene procedures and the health of the peri-implant tissues for long-term implant success (Koutsonikos et al., 1996). Jepsen et al. (1996) emphasise the importance of consecutive recordings of peri-implant attachment levels for the detection of changes, and the limited value of single probings. This is even more important in patients with implants, due to a higher susceptibility for peri-implantitis in the partially edentulous mouth, where by the microbiota of remaining teeth are probably the primary source of putative pathogens to colonise adjacent implants (Mombelli, 1993; Papaioannou et al., 1995).

In the present study, probing depth was significantly reduced and there was a significant gain in clinical attachment levels for the fibre treated surfaces for the three month period, when compared with controls. Probing measurements appear to be the most useful method to assess the longitudinal progression of peri-implant lesions (Mombelli & Lang, 1994). A peri-implant attachment loss of 1 mm or more within a short observation period of six months should be regarded as critical when monitoring implants (Jepsen et al., 1996), especially when an annual vertical bone loss of less than 0.2 mm following an implants first year of service is considered acceptable (Albrektsson et al., 1988).

In other studies around natural teeth, Michalowicz et al. (1995) reported in an evaluation of periodontal treatments, that scaling and root planing in conjunction with tetracycline therapy for ten days can significantly reduce disease recurrence 3-12 months following treatment with no futher supportive care, when compared to scaling and root planing alone, and tetracycline fibre therapy alone. It is important to note that with natural teeth, tetracylcine fibre therapy in chronic periodontitis patients has the additional benefit of tetracylcine crystals remaining bound to the root surface after fibre removal (Morrison et al., 1992), and following absorption, tetracycline HCl is released at bacteriostatic concentrations (Baker et al., 1983; Christersson et al., 1993).

Both the control and treated implant sites benefited from oral hygiene instruction in this study, with a reduction in bleeding on probing values. This periodontal parameter is at best a weak predictor of disease activity, and it has been suggested that the lack of bleeding on probing should be a criterion for stability rather than an indicator of active disease (Lang et al., 1990). However, in an animal study by Ericsson & Lindhe (1993), bleeding on probing was found in a large number of healthy peri-implant sites. Jepsen et al. (1996) found no differences between patients with peri-implantitis and stable implants with regard to bleeding on probing scores. Some patients exhibited a peri-implant mucositis with stable implants which bled on probing, and they state that peri-implant probing may provoke a non-specific bleeding that in unrelated to the amount of inflammation in the peri-implant tissues.

Until recently, there have only been six month studies (Newman et al., 1994) available evaluating the performance of controlled-release tetracycline fibres around natural teeth, with follow-up evaluations now available up to twelve months (Drisko et al.,

1995; Lowenguth, et al., 1995; Michalowicz et al., 1995). Drisko et al., (1995) evaluated the clinical response between four different treatment types (scaling and root planing, scaling and root planing plus tetracycline fibre for ten days, fibre therapy alone for ten days, and two ten-day serial fibre applications) in adult periodontitis patients. *All* treatments resulted in similar improvements in clinical parameters as measured by probing depth reduction, clinical attachment level gain and reduction of bleeding on probing. There was no difference in results between a single (10 day) application of tetracycline fibre (as used in the present study) and two 10-day serial fibre applications.

Clinical studies (Listgarten et al., 1978; Baker et al., 1985; Silverstein et al., 1988; Walker et al., 1985; Goodson et al., 1991; Lowenguth et al., 1995) have shown that controlled-release tetracycline fibres are clinically effective in the reduction of putative periodontal pathogens in patients with chronic adult periodontitis. In conjunction with anti-microbial effects, the tetracycline fibre may also effect the local periodontal environment. A series of *in vivo* studies (Morrison et al., 1992; Ciancio et al., 1992; Kazakos et al., 1993) have reported absorption of tetracycline to both root surfaces and pocket epithelium. The root surfaces exhibited a mild etching effect and plaque adhering to both root and pocket epithelium appeared to be non-vital. Topically applied, tetracycline displays considerable substantivity (Baker et al., 1983), and is detectable in crevicular fluid several weeks following a single application (Christersson et al., 1993).

The three species *Prevotella intermedia, Porphyromonas gingivalis and Bacteriodes forsythus,* were selected for monitoring in this study because of previous published reports linking these putative pathogens with peri-implantitis, and the availability of

DNA probes to detect their presence (Mombelli et at., 1987; Becker et al., 1990). The use of DNA probes have previously provided more uniform assays, specific identification and quantification of microorganisms in multiple samples. In this study, however, there were essentially no changes in bacterial levels for the duration of the study, to provide any data for meaningful analysis. This may have been due to the decreased prevalence of pathogens within the peri-implant site which were below the detection limit of the assay system, or a number of other pathogens present which were not detected by the particular DNA probe system used. In addition, it has been reported that culture methods are more sensitive than DNA probe methods, where low numbers of organisms are present (Maiden et al., 1991).

A twelve-month study reported by Lowenguth et al. (1995) evaluated six putative periodontal pathogens as monitored by DNA probe methods. Periodontal sites treated with tetracycline fibre therapy resulted in lower percentages of detectable pathogens when compared to scaling and root planing alone. The only substantial (but not statistically significant) difference in microbial profiles was that *Campylobacter rectus* was detected more frequently in progressing sites. However, only 21% of progressing sites were positive for *C. rectus,* other factors, including bacterial species not assessed in this particular study, could have been responsible for this type of treatment failure.

Socransky et al. (1987) have reported on the difficulties encountered in the search for these putative pathogens with respect to periodontal diseases, which may have contributed to the lack of useful data in this study. These include technical problems such as acquiring an appropriate microbial sample, in addition to the difficulties in dispersion, cultivation and identification of microbial isoltates within that sample.

Other conceptual problems include the difficulty in distinguishing between different types of periodontal diseases, and determining the state of activity of the periodontal lesion (ideally, a plaque sample should be taken at the peak of disease activity). Also, the progress of the lesion may involve complexes of organisms and different sequences of species. A further problem when attempting to distinguish overgrowths of opportunistic species from increases in proportions of the true pathogens. It also appears that different infections can occur at the same time in the oral cavity.

Tetracyclines have also been shown to inhibit most mammalian collagenases and other matrix degrading metalloproteinases (Golub et al., 1983, 1984 & 1985a). The authors proposed that this property could be useful in reducing the collagenase activity in periodontal pockets. These enzymes play an important role in inflammatory tissue reaction and destruction (Havemann & Janoff, 1978). The anti-collagenase activity of tetracycline fibres was not measured *in vivo*; however, *in vitro*, the fibres inhibited tissue and bacterial collagenase activity, and decreased the severity of gingival inflammation (Golub et al., 1985b).

A chairside assay has been developed for the non-specific assessment of neutral protease activity in crevicular fluid (Dankers & Zahradnik, 1986; Zahradnik et al.,1986; Zahradnik & Dankers, 1988), by using a colorimetric technique (Rinderknecht et al., 1968). There was no change in neutral proteolytic enzymes (NPE) as assayed by Periocheck® in the peri-implant sites up to the three months of this study, and so further evaluations are required. Jepsen et al. (1996) evaluated the effectiveness of the NPE-test and found it produced high negative predictive values, with negative scores indicating a stable peri-implant condition.

A study by Apse et al. (1989) reported cross-sectional associations between elevated activites of proteolytic enzymes in the peri-implant sulcus and inflammatory signs of peri-implant tissues, however, there are limited longitudinal data available indicating the usefulness of monitoring these enzyme levels for the prediction of peri-implant disease activity.

One of the most reliable methods of evaluating implant status is by periapical radiographs for detection of bone height and any peri-implant radiolucency (Bränemark et al., 1977). Bone resorption is indicated by apical migration of the alveolar crest and therefore, it is important to establish a radiographic baseline (Fiorellini & Weber, 1994). Radiographic changes were not definitive during the time frame of the study, but there was no further bone loss which may be regarded as a positive outcome. Longer evaluations (six to twelve months) may be required to more definitively evaluate any loss in alveolar crest height.

The results from this preliminary study suggest a possible role for local antibiotic delivery as an effective early therapy regime, in combination with mechanical debridement and oral hygiene measures. However, longer evaluations are required to investigate the maintenance response.

CHAPTER SIX.

6. CONCLUSIONS.

This study evaluated the effectiveness of Actisite® (tetracycline hydrochloride) Periodontal Fiber around implants with slight-moderate peri-implantitis. The implant sites were monitored at baseline, two months and three months using specific outlined clinical criteria and microbiological sampling techniques. Significant improvements ($p<0.05$) in probing depths and clinical probing attachment levels were found between baseline and three months.

While there were improvements in all parameters with both treatments, other changes were not statistically significant. There were essentially no changes or differences in neutral protease or bacterial levels between treatments or between time periods.

The results of this study suggest that local delivery tetracycline fibres would indicate that they are useful in the initial treatment for slight-moderate peri-implantitis for up to three months. There is a need for further long term studies with longer evaluations (six months) of local delivery tetracycline fibre therapy.

Appendix I

Research Protocol (Submitted to the Louisiana State University Medical Centre in New Orleans Institutional Review Board).

RESEARCH PROTOCOL: EVALUATION OF THE EFFECTIVENESS OF ACTISITE® (TETRACYCLINE HYDROCHLORIDE) PERIODONTAL FIBER AROUND AILING IMPLANTS.

PRINCIPAL INVESTIGATOR: Anna Koutsonikos, B.D.S., Grad. Dip. Clin. Dent., FRACDS. Periodontics Dept, School of Dentistry.

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Hisham Nasr, B.D.S., M.Sc.
Periodontics Dept, School of Dentistry

INTRODUCTION

The use of dental implants has increased within the profession over the last 5-10 years. Most of the literature has concentrated upon implant placement techniques and patient selection, with accompanying high success rates. There have been fewer studies, however, concerned with the ailing and failing implant. Specifically, the effectiveness of specific indices used to evaluate implants at maintenance, and the efficiacy of various non-surgical and surgical treatment procedures, has not been extensively studied to date.

The ailing and failing implant situation closely resembles that of chronic adult periodontitis clinically, radiographically and microbiologically. The term 'periimplantitis' is used to describe the inflammatory reaction of the supporting hard and soft tissues around the implant. The ailing implant exhibits progressive pocketing, bleeding on probing, and bone loss, but should be responsive to treatment. The implant has failed when the implant becomes mobile, can no longer function, is symptomatic, is no longer responsive to treatment, and must be removed.

Due to the lack of specific clinical and radiographic indices, most implant problems are not detected until the later stages. Then, extensive remedial surgical therapy is performed to attempt to arrest the disease process, to rebuild lost bone and reestablish osseointegration, and hopefully retain the implant in service for a longer period of time. Substantial need exists for effective treatment of mild-moderate periimplantitis so that corrective therapy can be instituted at earlier stages of the problem. This would improve the prognosis for implants

that have developed periodontal-like problems and allow effective management of initial implant problems.

A data collection form has been developed to better document and track the clinical status of dental implants. This should result in better identification of early periimplantitis lesions. Concommitant with improved documentation is the opportunity to provide effective early therapy. A local antibiotic delivery technique involving Actisite® will be used in this study around periimplant sites which exhibit bleeding on probing and periodontal pockets from 5-7mm deep. Its effectiveness will be evaluated in treating the ailing implant and ultimately preventing disease progression and implant loss.

Actisite® (tetracycline hydrochloride) Periodontal Fiber@ was initially developed for periodontal pocket placement, as an adjunct to conventional scaling and root planing. It consists of a 23cm (9 inch) monofilament of ethylene/vinyl acetate copolymer, 0.5mm in diameter, containing 12.7 mg of evenly dispersed tetracycline hydrochloride. Actisite fiber provides continuous release of a high local titer of tetracycline for ten days, and has been shown to be effective against probable periodontal pathogens *Porphyromonas gingivalis, Prevotella intermedia , Eikenella corrodens* etc. These same microorganisms have been found in studies around implants which show signs of periimplantitis, and there have been no studies to date evaluating the effectiveness of Actisite® around these implants.

OBJECTIVE

The purpose of this study is to evaluate the effectiveness of Actisite® (tetracycline hydrochloride) Periodontal Fiber around implants with slight-moderate periimplantitis. The implant sites will be monitored at baseline, two months and three months using specific outlined clinical criteria and microbiological sampling techniques.

@Procter & Gamble and ALZA Corporation

MATERIALS AND METHODS

STUDY DESIGN

The study population will consist of at least 30 patients obtained from the Implant Maintenance Clinic, School of Dentistry, Louisiana State University. The patients will be informed and consent obtained via signature on an IRB approved consent form.

The implant type selected for this study will be a hydroxyapatite coated root form cylindrical implant (Integral *). The patients will have obvious clinical signs of periimplantitis (bleeding on probing, probing depths 5-7 mm), slight-moderate bone loss on radiographs and evidence of peri-implant pathogens as determined by bacterial sampling.

A baseline examination (methods detailed under Examinations) for bleeding on probing, probing depths, radiographs, and bacterial analyses will be performed. Superstructures and/or removable prostheses may need to be removed to help obtain the necessary data, since bulky or overcontoured prosthetic designs may inhibit accurate probing depths.

The Actisite will be placed in selected sites in a given segment, quadrant, or arch and retained with Octyldent- dental cyanoacrylate. The Actisite will be removed after 10 days. Instruction on plaque control methods around the implants will be provided to all patients. The clinical and bacterial examination will be repeated at 2 and 3 months.

It may be possible to include controls during this study, depending on the availability of other implants (ie contralaterally placed implants) present in the patients selected. These implants will be monitored clinically and radiographically, and they will be exited from the study and be treated in an appropriate manner if probing depths become deeper by > 2mm.

EXAMINATIONS

Each subject will be examined throughout the study by the same examiner who will be blinded to whether treatment was provided or not. The examiner will be calibrated prior to the start of the study, and a LSUSD Dental Implant Clinic Maintenance Record will be completed at each visit, without knowledge of prior findings. Data will be collated, compared and analyzed separate from each patient visit.

* Calcitek Inc, Carlsbad, California

Clinical Examination:

Probing depths:

The implant supra-structure will be removed to facilitate accurate probing depth measurements. Four surfaces (Mesial, Distal, Buccal and Lingual) will be scored around each implant, to the nearest millimeter, with a pressure sensititive plastic probe.

Bleeding on probing:

Presence or absence of bleeding within 30 seconds after gentle probing with light standardized pressure. Scoring will be noted as present or absent.

Bacterial Examination:

Detailed microbiological analyses will be provided by a DNA probe (OmniGene®, Inc.). The analysis cannot be performed if the patient has been treated with antibiotics or any mechanical debridement within the last 4-6 weeks, or within 12 hours of using a chemotherapeutic mouthrinse.

A paper point is inserted to the base of the pocket and held in place for 10 seconds. The paper point is removed and placed in a Specimen Collection Vial and sent for multi-site, 6 pathogen detailed analysis (DMDx® Plus). The deepest probing depth that bleeds around each implant will be selected for bacterial sampling.

Radiographs:

Custom intraoral radiology stents will be fabricated from Reprosil and an Up Rad film holder to allow repeatability of x-ray angulation and orientation. Radiographs will be taken utilizing a superimposed grid attached to the individualized holder. Radiographs will be taken at baseline and at 3 months.

EVALUATION

Average indices will be determined at baseline, 2 months and 3 months. They will be analysed by appropriate statistical tests for changes in findings from baseline by Repeated Measures ANOVA. Comparisons between treated and control implants will be made with the Wilcoxson Signed Rank test. Significance wil be set at $\alpha = 0.05$.
The data and results will be submitted as part fulfilment for the Masters Degree of Dental Surgery (Prosthodontics).

OUTCOMES ASSESSMENT

The outcome will be considered positive for Actisite treatment if probing depths, bleeding on probing, and the level of periodontal pathogens are significantly reduced compared to baseline, and to controls, if appropriate. Radiographic changes may not be as definitive in this time frame, but would show at least no further bone loss at 3 months as a positive outcome.

Appendix II

Louisiana State University Medical Centre in New Orleans Consent Form.

LSUMC in NO IRB # 2742
Actisite Implant Periodontal Study
Periodontics Department
School of Dentistry

LOUISIANA STATE UNIVERSITY MEDICAL CENTER IN NEW ORLEANS CONSENT FORM

1. **STUDY TITLE - Evaluation of the Effectiveness of Actisite™ (tetracycline hydrochloride) Periodontal Fiber Around Ailing Implants.**

2. **PERFORMANCE SITE** - School of Dentistry, Departments of Periodontics and Prosthodontics

3. **INVESTIGATORS -**

   a.) Anna Koutsonikos, B.D.S., Grad. Dip. Clin., FRACDS., Periodontics Dept., School of Dentistry, 948-8570. Evenings/weekends - 833-4068.
   b.) Raymond A. Yukna, D.M.D., M.S., Periodontics Dept., School of Dentistry, 948-8570. Evenings/weekends - 482-1383. Beeper - 568-7747, #4306
   c.) Israel M. Finger, M.S., D.D.S. Prosthodontics Dept., School of Dentistry, 948-8528. Evenings/weekends - 456-1398. Beeper- 833-2337, #851288 FD1.
   d.) Hisham Nasr, B.D.S., M.Sc., Periodontics Dept., School of Dentistry, 948-8570. Evenings/weekends - 283-6662.
   e.) Luis R. Guerra, D.D.S., M.S., Prosthodontics Dept., School of Dentistry, 948-8687. Evenings/weekends - 833-4300 or 454-0816

Telephone answering machine, beeper numbers, and home telephone numbers are available for 24 hour access.

4. **PURPOSE OF STUDY** - Subjects are being asked to participate in a three month long research study to evaluate whether Actisite tetracycline-containing local drug delivery fibers are useful as a treatment for periimplant (gum) pockets around dental implants. Actisite is a commercially available material sold predominantly for professional treatment of gum pockets around natural teeth.

5. **SUBJECT INCLUSION CRITERIA.** To be included, subjects:

- may be either male or female
- must be between 25 and 75 years old
- must be of sufficiently good health to undergo routine dental treatment
- must not have received scaling and root planing (deep cleaning), or treatment with antibiotics within the last 2 months; or used a mouthrinse within the last 12 hours.
- must have slight to moderate periimplant disease in at least one quadrant of the mouth, which contains at least two pockets on at least one implant which measure 5-7 mm that bleed on gentle probing.

Initials _____ Date _____

6. **SUBJECT EXCLUSION CRITERIA.** Subjects may **NOT** participate in this study if they:

- have any requirements for antibiotic premedication for heart murmurs, artificial joints, or any other condition
- have a history of significant heart, stomach, liver, kidney, blood, immune system or other organ impairment or systemic disease that would preclude their undergoing the proposed treatment
- have a true allergy to tetracycline type antibiotics
- have taken systemic antibiotics or any investigational drugs on a regular basis anytime in the previous month
- have or are susceptible to candidiasis (thrush)
- have dental conditions likely to require treatment, necessitating exit from the study
- have had periimplant surgery within the last 6 months
- cannot comply with the extra treatment visits and follow-up visits out to 3 months

Female subjects must NOT be pregnant or nursing; must be using an acceptable method of birth control, sterile, or have undergone menopause; and must be aware that tetracycline antibiotics have been shown to interfere with the effectiveness of birth control pills. Female subjects 21 - 55 years old will be required to have a home pregnancy test performed at no charge immediately prior to the start of the study.

7. **DESCRIPTION OF STUDY.** Subjects who agree to participate will receive specific home care devices and instructions in oral hygiene, and will receive local gum treatment in problem pockets around some of their implants with Actisite (tetracycline hydrochloride antibiotic) fibers for about 7 - 10 days at the start of the study. The material will be held in place with standard periodontal dressing or a special weak dental superglue. The Actisite fiber will be removed by the dentist at about 7 - 10 days. Other implants may be left as untreated controls for the duration of the study. The results that are obtained with treatment will be evaluated and followed closely. At baseline and at the 1 month, 2 month and 3 month recall appointments, personal oral hygiene will be reinforced and practiced. Certain measurements of the gum condition around the implant will be made at each visit. Bridge work on the implants may need to be removed at these visits to facilitate the taking of these gum measurements. Total treatment and evaluation will require 5 visits, and all visits may be one to two hours long. Photographs of the gums and implants may be taken to follow the progress of treatment. About 30 subjects will be included in this pilot study at LSU.

X-rays will be taken to follow the progress of the healing at the initial appointment, and at the three months evaluation. This will involve 2 additional dental x-rays per area treated. These additional dental x-rays constitute about 1-2% of the total head and neck radiation felt to be safe by the Food and Drug Administration. There is virtually no risk of scatter radiation affecting other parts of subjects' body because of the use of lead aprons, high speed dental film, and specially collimated (restricted) x-ray beams. The more radiation that subjects receive over the course of their life, the more is the risk of having concerns for tumors or of inducing changes in genes. The changes in genes possibly could cause abnormalities or disease in subjects future offspring. The radiation in this study is not expected to greatly increase these risks, but the extent increase in such risks is not known.

Initials _____ Date _____

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Actisite Implant Periodontal Study
Periodontics Department
School of Dentistry

Subjects agree to comply with the study schedule of visits for Actisite placement; Actisite removal at about 7 - 10 days; and evaluations at 1, 2, and 3 months. Subjects understand that no deep cleanings will be done at any of these appointments, nor can they be done in any dental office except at the completion of the 3 month evaluation. The gum condition will be monitored closely to detect any adverse changes. If such changes occur to any worrisome degree, then those implants will be treated differently by usual means to try to resolve the problem. This may also necessitate that the subject be dropped from the study.

8. **BENEFITS TO SUBJECT.** There are no known benefits to this study since any clinical benefit received from treatment with the test article around dental implants has not been confirmed at this time. Alternative methods of deep cleaning and other pocket treatments will be available to subjects if they desire. However, it is hoped that this particular new type of treatment for problem implants may improve tissue conditions and implant health. Subjects will be compensated when they complete the study in the form of a professional dental cleaning at no charge. Subjects will also receive periodontal examinations and oral hygiene supplies during the study. The Actisite placement and removal will be performed at no charge to the subjects.

9. **RISKS TO SUBJECT.** There is a possibility that this product may cause the gums to become irritated and swollen, mild to moderate gum pain, irritation of the tongue and/or cheek from the dressing or "superglue", or a strong taste from the tetracycline. There is also the possibility of dislodging and/or swallowing the Actisite fiber. In rare instances, the Actisite treatments may be associated with abscess formation, tissue damage, severe inflammation, severe pain, or possibly loss of the implant. Subjects may also develop a condition called oral candidiasis (thrush) in which the gums become red and develop white patches. Depending upon the complication, the dentist may decide to remove the product before the 7 - 10 days of treatment are complete. If subjects have any side effects or complications associated with the treatments in this study, they will be treated in an appropriate manner. None of these are considered serious and should resolve with simple local treatments.

There is a risk of subjects' gum problems becoming worse, in which case immediate remedial treatment will be performed at no cost to the subject. Such a situation may also cause the subject to be dropped from the study. There may be other unforeseen risks to participation in this study which may be evident only after it is underway. Other possible, lesser risks can be discussed later if the subject desires.

10. **ALTERNATIVES TO PARTICIPATION IN THE STUDY.** The usual alternative treatments for gum problems around implants are repeated deep cleanings, gum surgery, and/or systemic antibiotics, and these are available to subjects through normal channels should subjects choose not to participate in this research.

nitials _____ Date _____

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Periodontics Department
School of Dentistry

11. **SUBJECT REMOVAL.** Subjects may be removed from the study if their gum problems worsen to an unacceptable degree (for health). Subjects may also be dropped from the study if they do not keep any or all of the appointments (5 appointments, each of one or two hours in duration, over a 3 month period); begin to take antibiotics for any condition; become too ill to undergo routine dental procedures; receive cleanings of any type or other treatment that alters the local condition of the implant being evaluated in any dental office; or otherwise compromise the progress and validity of the study (for cause).

12. **SUBJECT'S RIGHT TO REFUSE TO PARTICIPATE OR TO WITHDRAW.** Subjects may refuse to participate or withdraw from the study at any time without jeopardizing, in any way, their dental treatment at the Louisiana State University School of Dentistry in the present or future. Subjects will be informed if significant new findings develop during the course of the research which may relate to their willingness to continue participation.

13. **SUBJECT'S RIGHT TO PRIVACY.** The results of the study may be published. Subjects privacy will be protected, their records will be confidential, and they will not be identified in any manner.

14. **RELEASE OF INFORMATION.** The medical records related to the study are available to the Food and Drug Administration.

15. **FINANCIAL INFORMATION.** The usual fees for the examinations, x-rays, enzyme tests, bacterial tests, and the final cleaning appointment will be paid by a special grant. The additional fees normally charged for the Actisite placement (and its removal) will also be paid by a special grant. All other dental care (such as additional cleanings, bite adjustments, bite appliances, temporary bridges, temporary fixed or removable splints, small fillings); periimplant surgery; prescription or in-office medications and sedatives; the cost of any definitive, permanent and/or replacement fillings or tooth replacements; or further periodontal or implant treatment following subject's participation in this study will be the subject's financial responsibility.

In the event subjects' participation in this research directly results in physical injury, medical treatment will be available to them, but will be payable through the subject's own usual means. No compensation will be available for any medical complications other than the provision of actual medical treatment.

16. **SIGNATURES.** The study has been discussed with me and all questions have been answered. I understand that additional questions regarding the study should be directed to the investigators listed on page 1 of this consent form. I understand that if I have questions about subjects rights or other concerns, I can contact the Chancellor of the LSU Medical Center at (504)568-4801.

Initials _____ Date _____

LSUMC in NO IRB # 2742
Actisite Implant Periodontal Study
Periodontics Department
School of Dentistry

I agree with the terms above and acknowledge I have been given a copy of the consent form.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

"The study subject has indicated to me that the subject is unable to read. I certify that I have read this consent form to the subject and explained that by completing the signature line above, the subject has agreed to participate."

_____ _____

Signature of Reader

Appendix III

Louisiana State University School of Dentistry Patient Acceptance Form.

Louisiana State University
School of Dentistry

Periodontics Department Box 138
1100 Florida Avenue
New Orleans, LA 70119
(504) 948-8570

To: Oral Diagnosis Department

Please accept _____ as a patient for possible participation in a clinical research project in the Periodontics Department.

He/She understands that they are being accepted for participation in the research project only, and not for any other dental care at the School at this time. The only treatment procedures to be provided for this patient are specified in the Consent Form for the study.

As part of the screening process, the patient agrees to pay for the necessary initial Dental School evaluation procedures that include registration as a **Limited Care - Research** patient, laboratory blood tests, and a panoramic x-ray (Approximate cost = $35.00).

_____ _____

Raymond A. Yukna, D.M.D., M.S. Witness

Professor and Head

Patient Agreement:

I understand and agree to the above statements, especially the restricted acceptance to the Dental School **ONLY** as a possible patient for the **research project using Actisite around dental implants.** I realize that only some of the patients will receive the new treatment, and some the other treatments or no treatment. I realize that I may be in the control group(s), but that I will be followed closely and will receive a thorough cleaning at the end of the study as outlined in the Consent Form.
I am not being accepted for any other care at the Dental School at this time.

_____ _____

Patient's Signature SSN

Appendix IV

Dental Implant Clinic Maintenance Record.

LSUSD
Dental Implant Clinic Maintenance Record

Patient _____ Date: _____
Last *First* *MI*

DOB: _____ Sex ___ Race _____ Chart No. _____

Location						
Placement Date						
Brand						
Type: B Sub RF - cyl? or screw?						
MGI (0-3)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Calculus (L,M,H)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Plaque Index (+/0)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Plaque Amount (L,M,H)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Stain (L,M,H)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
FGM Recession (mm from AH)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Probing Depth (mm)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
KG (mm)	F L	F L	F L	F L	F L	F L
BOP (+/0)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Pus (+/0)	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L
Tenderness/Pain (Y/N)						
Mobility (0-3)						
Bacteria Test	F D M L	F D M L	F D M L	F D M L	F D M L	F D M L

OS160/15

Patient Home Care Devices Used

Brush

Manual (texture) _____

Powered (type) _____

Proximal

- ☐ Floss
- ☐ Superfloss
- ☐ Yarn
- ☐ Proxibrush
- ☐ Other _____

Chemical

- ☐ Rinse (type) _____
- ☐ Irrigation
- ☐ Other _____

Prosthetic Evaluation

DIs involved

Type _____

☐ Looseness

☐ Broken screws/parts

Occlusion check:

- ☐ Light
- ☐ Medium
- ☐ Heavy

Superstructure removed? ☐ Yes ☐ No

Office Procedures

☐ Photos

☐ Radiographs: ☐ Panorex ☐ Periapicals _____

☐ Sonic/US

- ☐ Nylon tip
- ☐ Plastic tip

☐ Hand

- ☐ Plastic
- ☐ Graphite
- ☐ Other

☐ Prophyjet

☐ Polish with _____

☐ Irrigation

Faculty Evaluation _____

Clinical Evaluation _____

Radiographic Evaluation _____

Need for Additional Tx

- ☐ Hygiene
- ☐ Periodontics
- ☐ Prosthetics
- ☐ Oral surgery

NV

Recall _____ months

X-rays _____ months

Signed: _____ Date: _____

Appendix V

DNA Probe Test -Microprobe® Corporation.

Affirm® DP
Microbial Identification Test

DNA Probe test for use in the direct qualitative detection and identification of *Bacteroides forsythus* and *Porphyromonas gingivalis* nucleic acids in subgingival plaque specimens from patients with symptoms of periodontitis.

Catalog Number 803226
24 Test Kit

INSTRUCTIONS FOR USE

INTENDED USE

FOR IN VITRO DIAGNOSTIC USE

MicroProbe Corporation's Affirm® DP Microbial Identification Test is a DNA probe test for the qualitative detection and identification of *Bacteroides forsythus* and *Porphyromonas gingivalis* nucleic acids in subgingival plaque specimens from patients with symptoms of periodontitis.

EXPLANATION OF THE TEST

Periodontitis is a disease of the periodontium characterized by inflammation of the gingiva, resorption of the alveolar bone, degeneration of the periodontal membrane (ligament), migration of the epithelial attachment apically, and formation of periodontal pockets[1,2].

Several lines of evidence support the conclusion that specific bacteria are the etiologic agents of periodontal disease. This evidence includes inducibility studies of gingivitis and periodontitis in animals, disease transmissibility observations in animals, and response of the disease with antibiotics[3,4,5,6]. While over 300 different species of bacteria have been isolated from the oral cavity, only a limited number of species have been strongly associated with periodontal disease and can be detected in subgingival plaque[7].

Historically, the determination of periodontal disease has been based on clinical measurements including subgingival pocket depth, bleeding on probing, attachment loss and alveolar bone loss[8,9,10]. Periodontal disease can be episodic in nature, including periods of active infection and quiescence. It is important to distinguish active periodontal sites from inactive sites that may not exhibit symptoms of periodontal disease as a result of previous infectious episodes. It is possible to identify the presence of activity in a suspected site by culturing the microbiota. However, culture determination is technique dependent, expensive and time consuming.

The Affirm® DP Test is a DNA probe test for the direct detection of specific nucleic acids from *Porphyromonas gingivalis* and *Bacteroides forsythus* in subgingival plaque specimens. The Affirm® DP Test is designed to be used by dental practitioners as an adjunct to clinical evaluation for differentiating potential periodontal disease microorganisms. The Affirm® DP Test applies DNA probe technology to detect and identify two microorganisms from a single subgingival plaque specimen, using organism specific DNA probes on beads. Two beads containing microorganism specific probes are embedded in a Probe Analysis Card (PAC). The PAC also includes a Negative Control bead and a Positive Control bead. Results are read visually, with blue color on the bead indicative of a positive result, while negative results show no color. Sample preparation is simple, requiring just over 5 minutes. The sample and reagent processing steps are completed automatically by the small desk top Affirm® Processor, leaving the user free to do other tasks. Test results are available approximately 40 minutes after sample collection.

PRINCIPLES OF THE TEST

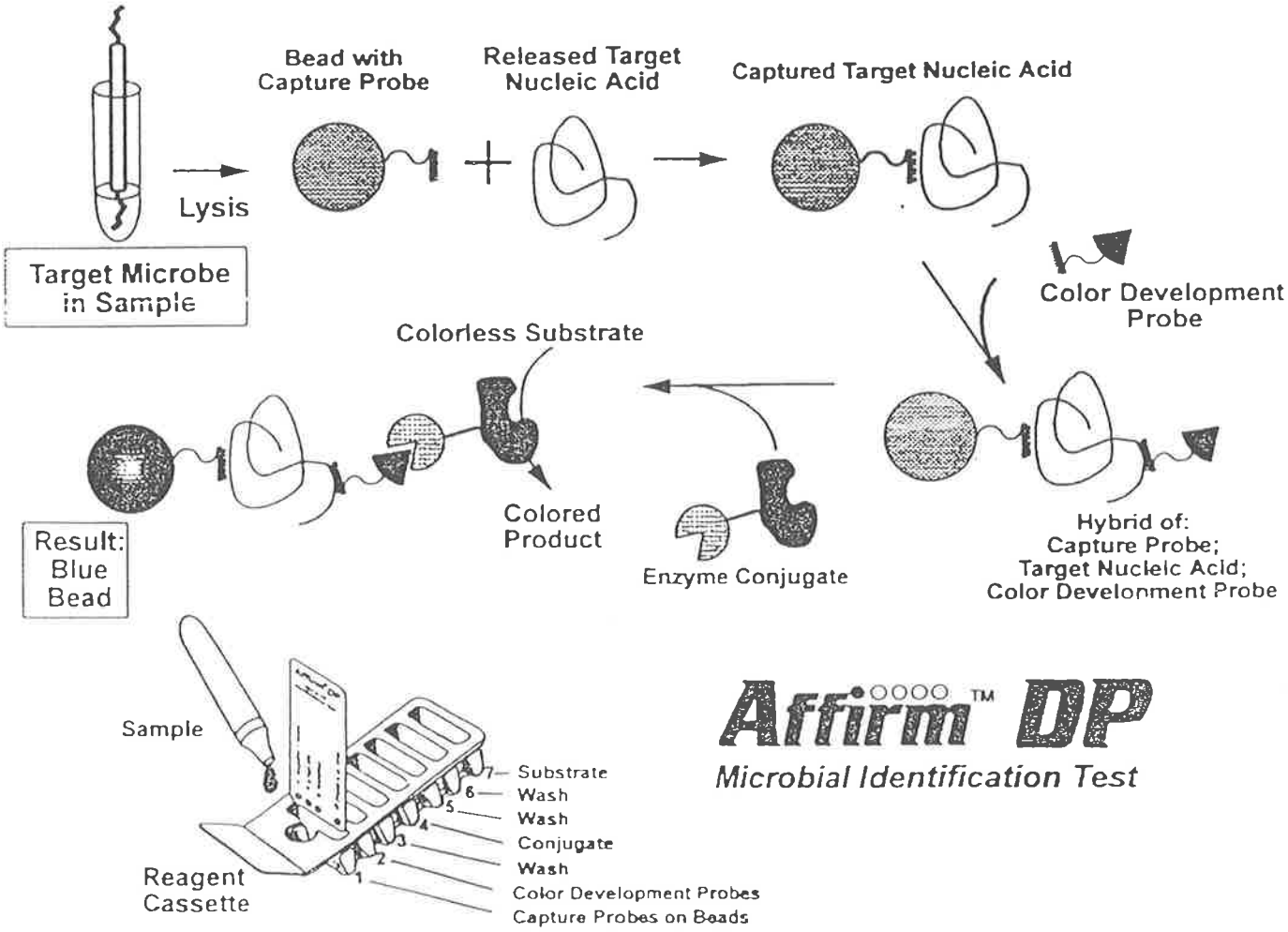
The Affirm® DP Test is based on the principles of nucleic acid hybridization. Nucleic acid hybridization tests, also known as DNA probe tests, depend on the ability of complementary nucleic acid strands to align and form specific, double-stranded complexes called hybrids. The formation of hybrids between the test probes and target microorganism nucleic acid, but not with other nucleic acids, is responsible for the high specificity possible with DNA probe tests.

The Affirm® DP Test uses two single-stranded nucleic acid probes, a capture and a color-development probe. The

capture probes are immobilized on beads that are embedded in the PAC. The PAC contains a separate bead for each target microorganism. The color development probes are contained in a multi-well Reagent Cassette.

The procedure is outlined in three parts: 1) Sample Preparation, 2) Automated Processing, and 3) Results Interpretation. In Sample Preparation, a properly collected sample of subgingival plaque is suspended in Diluent Solution followed by treatment with Buffer Solution and heating. This process ruptures the cell walls of the microorganisms, releasing the target nucleic acids. At this point, the prepared sample is added to the first well of the Reagent Cassette, along with the PAC, and Automated Processing begins. The Affirm® Processor moves the PAC from one well of the Reagent Cassette to another (see Figure 1). Hybridization occurs when the PAC enters the first and second wells of the Reagent Cassette. Hybridization of the target nucleic acid to the probe on the bead occurs in well 1, and the hybridization of the color-development probe occurs in well 2. All unbound sample components are washed away in well 3. Enzyme conjugate binds to the captured color-development probe in well 4. Unbound conjugate and probes are washed away in wells 5 and 6. In well 7, the enzyme substrate is converted to a blue-colored product if bound enzyme is present on the bead. The final step is reading the color development on the bead.

Test Principles



Affirm™ DP

Microbial Identification Test

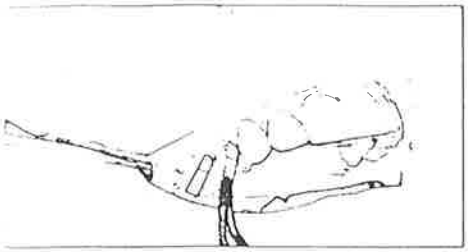
Appendix VI

Neutral Protease Levels - Periochek®.

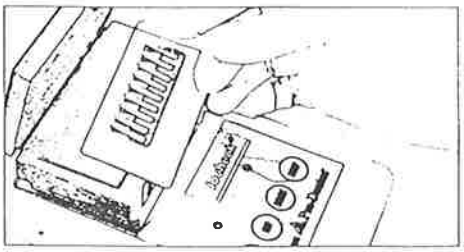
✓Periocheck®

Periodontal Monitoring System

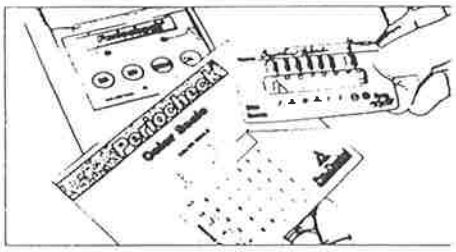
The Procedure is as Simple as . . .



1. Paper strip inserted 1-2mm under gum margin



2. Paper strip put in incubator for 12 minutes



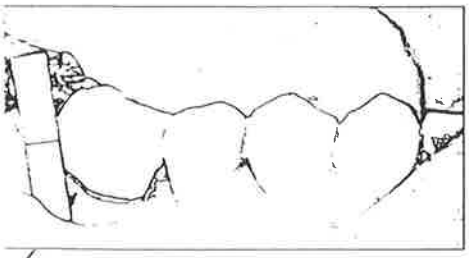
3. Blue paper strip indicates activ disease

Which of your Patients would benefit from Periocheck!

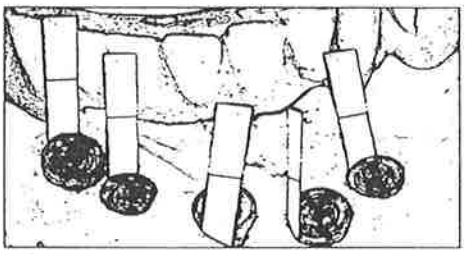
Use Periocheck at the **evaluation appointment** following active periodontal therapy, **before** scheduling them into a maintenance program, and at **maintenance appointments.**

In your **recall base** there may be **restorative – cosmetic patients** with perio sites of concern (see examples below). Or use Periocheck anytime you need **additional information** to determine the best course of treatment or monitoring.

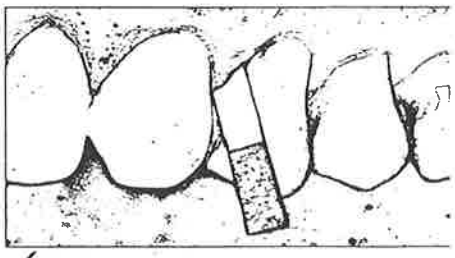
Typical Situations



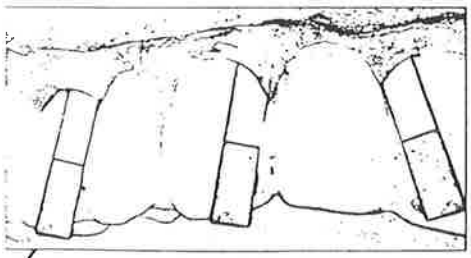
✓ Teeth with **furcation** involvement



✓ **Implants** especially at each evaluation appointment during first year

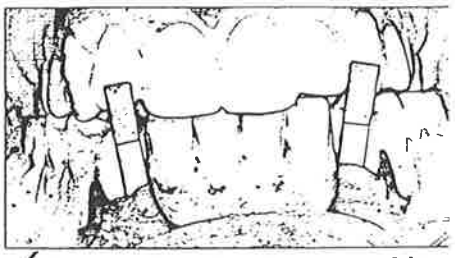


✓ Pocket associated with **proximal groove,** maxillary first premolar



✓ **Crowns,** with subgingival margins

✓ Abutment teeth with **fixed bridge**



✓ Abutment teeth with **removable partial**

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Appendix VII

Actisite® (tetracycline hydrochloride)
Periodontal Fibre Product Sheet - Procter & Gamble
and ALZA Corporation.

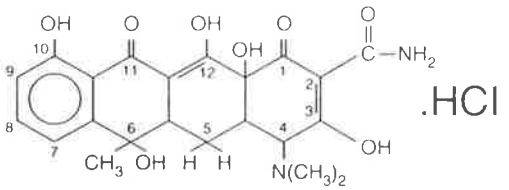
ACTISITE® (tetracycline hydrochloride) Periodontal Fiber

DESCRIPTION

Actisite® (tetracycline hydrochloride) periodontal fiber for periodontal pocket placement consists of a 23 cm (9 inch) monofilament of ethylene/vinyl acetate copolymer, 0.5 mm in diameter, containing 12.7 mg of evenly dispersed tetracycline hydrochloride, USP. Actisite fiber provides continuous release of tetracycline for 10 days.

Tetracycline hydrochloride is an antibiotic originally isolated from *Streptomyces aureofaciens*. Chemically it is the monohydrochloride of [4S-(4α,4aα,5aα,6β,12aα)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.

The chemical structure of tetracycline hydrochloride is shown at right:



Empirical Formula: $C_{22}H_{24}N_2O_8.HCl$

CLINICAL PHARMACOLOGY

Microbiology—The clinical significance of the microbiological findings with Actisite is not known. The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by inhibiting protein synthesis. In vitro testing has shown that probable periodontal pathogens, including *Fusobacterium nucleatum, Porphyromonas (Bacteroides) gingivalis, Prevotella intermedia (Bacteroides intermedius), Eikenella corrodens, Campylobacter rectus (Wolinella recta),* and *Actinobacillus actinomycetemcomitans,* are susceptible to local 32 μg/mL tetracycline concentrations achieved in the periodontal pocket with the use of Actisite® (tetracycline hydrochloride) periodontal fiber.

Pharmacokinetics—Actisite fiber releases tetracycline in vitro at a rate of approximately 2 μg/cm-h. In the periodontal pocket, the system provides for a per site mean gingival fluid concentration of 1590 μg/mL tetracycline throughout the 10-day treatment period.

Concentration in saliva immediately after fiber placement (9 teeth) was 50.7 μg/mL and declined to 7.6 μg/mL at the end of 10 days.

During fiber treatment of up to 11 teeth per patient (average tetracycline dose of 105 mg) mean tetracycline concentrations in plasma were below the lower limit of assay detection (<0.1 μg/mL). This lower assay limit is 20- to 25-fold lower than that expected during a regimen of 250 mg by oral capsule every 6 hours.

Clinical Studies—In a controlled 60-day clinical trial, 113 adult patients with periodontitis (56 men and 57 women; age range 25-88; 95 Caucasian, 11 Black, 3 Hispanic and 4 Asian) entered with a mean pocket depth of 7.2 mm (98% of pocket depths were within the range of 4 mm to 11 mm). Subjects received supragingival cleaning followed by one of four treatments, randomized to a single tooth per quadrant. These treatments were: 1) Actisite fiber for 10 ± 2 days, 2) control fiber for 10 ± 2 days, 3) scaling and root planing under local anesthesia, or 4) no treatment. Teeth treated with Actisite fiber were later found to have significantly reduced probing depth and bleeding on controlled force probing.

Probing depth reductions were greater in deep (≥ 7 mm) than in moderate (< 6 mm) sites.

In a randomized, single-blind 6-month study of 113 adult periodontal maintenance patients (57 men and 56 women; age range 32-75; 111 Caucasian, 2 Black), the effects of scaling and root planing alone, and scaling and root planing followed by Actisite fiber treatment, were compared. Subjects entered with a baseline pocket depth mean of 6.4 mm (97% of the pockets were within a range of 4 mm to 11 mm). Two non-adjacent sites with pockets with bleeding on probing were selected for treatment and follow-up at 1, 3, and 6 months. A longitudinal multi-variate analysis showed that adjunctive fiber therapy with scaling and root planing provided significantly greater reductions in probing depth and bleeding on probing than scaling and root planing alone at follow-up visits. The results are summarized in the following table.

	Probing Depth Reduction (mm)		Bleeding on Probing (%)	
Time (mo.)	S/RP[a]	S/RP + Fiber	S/RP	S/RP + Fiber
0	0.00	0.00	90	87
1	0.82	1.20*	48	30**
3	0.98	1.27*	48	34*
6	1.05	1.72**	51	38*

* Significant difference between treatment groups ($p<0.05$)
** Significant difference between treatment groups ($p<0.01$)
[a]S/RP = scaling and root planing

Microbiology—In the 60-day study, immediately following therapy, both Actisite fiber and scaling and root planing produced significant reductions in the number of sites infected with probable periodontal pathogens compared to untreated controls. The clinical significance of these findings is not known.

INDICATIONS AND USAGE

Actisite (tetracycline hydrochloride) periodontal fiber is indicated as an adjunct to scaling and root planing for reduction of pocket depth and bleeding on probing in patients with adult periodontitis.

Treatment with Actisite is a component of an intervention program which includes good oral hygiene and scaling and root planing.

Effectiveness of repeated fiber applications in a site has not been studied.

The effects of Actisite on bone loss, tooth mobility, or tooth loss from periodontal disease has not been established.

CONTRAINDICATIONS

Actisite® fiber should not be used in patients who are hypersensitive to any tetracycline.

WARNINGS

The use of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to age of 8 years) may cause permanent discoloration of the teeth. Tetracycline drugs should not be used in this age group unless other treatment is not likely to be effective or if alternative therapy is contraindicated.

Tetracyclines as a class are associated with photosensitivity. Treatment should be discontinued at the first sign of cutaneous erythema.

Accumulations of tetracycline associated with renal failure can lead to liver toxicity. These effects have not been studied in the plasma concentration range associated with Actisite.

PRECAUTIONS

General: Actisite fibers must be removed after 10 days. Packing fibers tightly into a draining abscess without allowance for drainage might result in the formation of a lateral fistula. Fibers should not be used in an acutely abscessed periodontal pocket. Their use in chronic abscesses has not been evaluated.

As with other antibiotic preparations, Actisite (tetracycline hydrochloride) periodontal fiber therapy may result in overgrowth of nonsusceptible organisms, including fungi. Actisite should be used with caution in patients with a history of or predisposition to oral candidiasis.

The safety and effectiveness of Actisite fiber have not been established for the treatment of periodontitis in patients with coexistent oral candidiasis.

Use of antibiotic preparations may result in the development of resistant bacteria. Resistance has not been observed during 10 days of Actisite fiber therapy. The effects of prolonged treatment have not been studied.

Management of patients with periodontal disease should include a consideration of potentially contributing medical disorders.

Information for Patients: When Actisite fiber is in place, patients should avoid actions that may dislodge the fiber. Patients should receive the following instructions:

1. Do not chew hard, crusty, or sticky foods.
2. Do not brush or floss near any treated areas. (Continue to clean other teeth.)
3. Do not engage in any other hygienic practices that could potentially dislodge the fibers.
4. Do not probe at the treated area with tongue or fingers.
5. Notify the dentist promptly if the fiber is dislodged or falls out before the scheduled recall visit, or if pain or swelling or other problems occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal studies with Actisite fiber have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy Category C: Administration of tetracycline during pregnancy may cause permanent discoloration of teeth of offspring. Animal studies indicate that tetracyclines can cause retardation of fetal skeletal development. Actisite fiber should be administered to a pregnant woman only if clearly needed. Animal reproduction studies have not been conducted with Actisite fiber. It is also not known whether Actisite fiber can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

Nursing Mothers

Tetracycline appears in breast milk following oral administration. It is not known whether tetracycline is excreted in human milk following use of Actisite® (tetracycline hydrochloride) periodontal fiber. Because of the potential for serious adverse reactions from tetracycline HCl in nursing infants, Actisite fiber should be used in a nursing woman only if clearly needed.

Pediatrics

The safety and effectiveness of Actisite fiber in children have not been established. Oral doses of tetracycline in children up to 8 years of age have caused permanent discoloration of teeth.

ADVERSE REACTIONS

Actisite fiber has been studied in 1437 patients distributed as follows over pivotal, controlled, and open-label studies.

	Study Type			
Demographics	Pivotal	Controlled	Uncontrolled	TOTAL
Gender:				
Male	113	70	455	638
Female	113	55	631	799
Age Range	25-88	25-73	13-87	13-88
Race:				
Black	13	12	41	66
Asian	4	1	10	15
Hispanic	3	3	11	17
Caucasian	206	105	964	1275
Native American	0	2	56	58
Other	0	2	5	7

The most frequently reported adverse reactions in the 226 patients in the pivotal clinical trials were discomfort on fiber placement (10%) and local erythema following removal (11%).

In controlled and open-label trials patients, the following adverse reactions have been reported in less than 1% of patients:
oral candidiasis, glossitis, possible allergic response, staining of the tongue, severe gingival inflammation, throbbing pain, pain following placement in an abscessed area, and minor throat irritation.

DOSAGE AND ADMINISTRATION

Actisite (tetracycline hydrochloride) periodontal fiber for 10 days is indicated as an adjunct to scaling and root planing. Repeated fiber applications have not been studied. Actisite fiber should be inserted into the periodontal pocket until the pocket is filled. The length of fiber used will vary with pocket depth and contour. The fiber should be placed to closely approximate the pocket anatomy and should be in contact with the base of the pocket. An appropriate cyanoacrylate adhesive should be used to help secure the fiber in the pocket.

When placed within a periodontal pocket, Actisite fiber provides continuous release of tetracycline for 10 days. At the end of 10 days of treatment, all fibers must be removed. Fibers lost before 7 days should be replaced.

HOW SUPPLIED

Actisite® (tetracycline hydrochloride) periodontal fiber is available in boxes of 10 fibers. Each individually packaged, yellow fiber is 23 cm (9 inches) long and contains 12.7 mg of tetracycline hydrochloride.

NDC 17314-4800-1

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

For product information call: 1-800-ACTISITE

To place an order call: 1-800-543-2577

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