Emerging Trends in Oral Care

In February 2005 the Philips Oral Healthcare Company organized an outstanding international symposium entitled 'Emerging trends in oral care', which was held at the Grand Hotel Schloss Bensberg in Cologne, Germany. In contrast to other symposia organized by industrial partners, this meeting focused very much on research and clinical science rather than product marketing. Since the presentations given by internationally well-known experts in the field of periodontology are of fundamental importance, it was decided by the editorial board to include short versions of the keynote lectures in the form of an extended congress report in Perio. Thus not only the participants of this outstanding symposium, but also the readers and the subscribers of Perio, can benefit from the excellence of these presentations.

Prof. Dr. Joerg Meyle

INTRODUCTION

Introducing 'Emerging Trends in Oral Healthcare', Dr Jörg Strate, Philips Oral Healthcare's European Director of Professional Relations and Clinical Affairs, commented:

"We all share a vision – the vision of improving consumer oral healthcare."

The fact that we share this vision gives us a lot of strength and will help us to continue on the way to further improvements and to eventually implement these improvements into better products, which will successfully help consumers and patients to achieve oral healthcare benefits."

Philips Oral Healthcare's Dr Arthur Hefti, Global Vice President of Clinical and Scientific Affairs, opened the symposium: "We have put together a programme for you that will cover various aspects of clinical research. Clinical research can be defined as a process that investigates concepts of human health and disease. Such research is typically executed in a clinic: we sometimes take specimens from research subjects, take them to the lab, and explore connections between the biological sample and the underlying disease; still, these studies always have a relationship to clinical practice. Similarly, all presentations today have a connection to clinical practice."

EVIDENCE-BASED DENTISTRY – T. Van Dyke, Boston

The first speaker, Professor Dr Thomas Van Dyke, professor of periodontology at Boston University, Director of the Clinical Research Center and Graduate Periodontology in the School of Dental Medicine, and associate director of the General Clinical Research Center in the Medical Center , continued: "I've been asked to talk about evidence-based dentistry in the context of clinical practice, and in order to do so I thought I would use the American Dental Association as an example. The American Dental Association is one of many national dental associations, and it has undertaken to try to involve evidence-based dentistry in its policy statements and in dental education. I take my information from their guidelines.

We are going to talk about the how and why of evidence-based dentistry. We can go from no ev-

idence, being completely empirical in the decisions that we make in the clinic (the art), to making decisions that are based on well-documented evidence (the science). What is the difference between the two? Empirical decisions are usually based on expert opinions or case reports presented in the literature. Evidence, by definition, is based on systematic review of randomized, controlled clinical trials that test a hypothesis. In a recent editorial in the Journal of the American Dental Association it was said that today we are armed with more research funds and fortified with better information and new concepts and treatment of dental diseases, so the busy dentist faces the problem of keeping abreast of the latest scientific developments in order to provide his or her patients with the latest and best scientific treatment and dental health information.

Why do we want to use evidence-based dentistry? First, one of the biggest reasons is that patients have access to evidence from a variety of sources such as the internet, and this is continually increasing. Patients are no longer content to simply accept the treatments they are offered or advised to take from the dentist and now ask whether the proposed treatment will work, whether it is necessary for them to have it and whether there is an alternative treatment.

The internet has changed our lives in many ways, but it is also available to your patients, and they routinely use this as one of their primary healthcare information sources. The internet, however, is not refereed – which is one of its major problems – so the information has no quality control. The information they may come to you with could be from an internationally respected expert, but it could also be from a quack. So a dentist should, therefore, be in a position to respond with good-quality information that is supported by appropriate references.

There is an ever-increasing amount of information, treatment options and an enormous proliferation of journals, so one of the problems we have as practitioners is just keeping up with the voluminous information that is being provided to us on a daily basis.

So what is evidence-based healthcare? It is the process of systematically finding, appraising and using contemporaneous research findings as the basis for clinical decisions.

It is also the conscientious and judicious use of the current best evidence in making decisions about care of individual patients. One of the issues we have in dentistry is that clinical trials make statements about populations, and the issue is how you treat an individual based upon the findings of population studies? In other words, what is the clinical significance and what is going to happen to my patient if I use this data? It is something that is very, very difficult for us to answer.

In the first annual Nordic workshop on how to critically appraise and use evidence and decisions about healthcare, it was said that current best evidence is up-to-date information from relevant valid research about the effects of different forms of healthcare, potential for harm from exposure to particular agents, the accuracy of diagnostic tests and the predictive power of diagnostic factors. Now that is a sentence filled with catchwords – 'relevant', 'valid', 'predictive power' etc – the keys of evidence-based dentistry.

Where did this all start? We are going to be looking at this from the framework of the American Dental Association and its definition of evidence-based dentistry, which is

'Evidence-based dentistry is an approach to oral healthcare that requires the judicious integration of systematic assessments of clinically relevant scientific evidence relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences'.

This is also often used as a definition for clinical significance in clinical trials – this idea that you take the best scientific evidence and you relate it to the dentist's clinical experience and the patient's treatment needs and preferences.

Evidence-based healthcare integrates individual clinical experience, proficiency and expertise from clinical experience and it also embodies patient choice and characteristics, and the best available external clinical evidence; that is, clinically relevant research. The idea is that good clinicians will use both.

Dentistry is the science and art of healing of dental and maxillo-facial diseases and conditions. Dentists play an important role in promoting oral health, which is an integral part of systemic health. Dentists are distinct specialists among a category

of healthcare providers, and dentists are decision-makers. Furthermore, dentists strive to provide the best care for their patients, and this leads to a series of questions that must be asked. What is the best care? How do we define best care? Who should define it? And whose values should be used to define best care? And can the patients and the dentists afford the best care that is available?

Further assumptions are that the scientific basis of dental practice, like medicine, varies from weak to strong. Dentists, like all healthcare providers, face challenges in dealing with the large volume of evidence presented by different groups, experts, journals and meetings, and the translation of best scientific evidence in the clinical practice is a major challenge.

What separates the theory and practice of evidence based dentistry? Theoretically; evidence-based dentistry is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. In application, evidence-based dental clinical practice means integrating individual clinical experience with the best available external clinical evidence from systematic research. It includes the experience of the dentist. This is a very important concept in evidence-based dentistry because it is very often misunderstood that evidence-based dentistry is simply following a written prescription for treatment. It is not practice guidelines, it is not standards of care, it is not parameters of care, it is not 'cookbook' practice.

Quality oral healthcare comprises doing the right thing based upon the scientific evidence, doing it at the right time, using patient preferences and professional experience. It encompasses doing it the right way, with the technical skills and experience of the practitioner, for the right person. Decision-making principles and scientific evidence; in other words providing the right treatment for the right disease and the right patient, getting best possible results, which encompasses quality assurance and outcomes assessment.

What is the process of evidence-based dentistry? You have heard a lot about what it is and how we are supposed to use it, but how do we go about getting the evidence? This has been laid out in great detail by Sackett and his co-workers, and I would like to go through these quickly. Of course, the first thing you have to do is define a clinically relevant question, and then you need to conduct systematic reviews of the available scientific evidence. Well-built clinical questions contain four elements. The ADA has adopted this procedure for building clinical questions, and they call it

PICO – P stands for patient or problem. You start with your patient and ask: 'How would I describe a group of patients similar to mine?' The I stands for intervention, a cause or a prognostic factor or a treatment. You ask: 'Which main intervention am I considering in this investigation?' C is the comparison intervention, that is, 'what is the main alternative to compare with intervention?' A classic discussion in periodontology would be surgical versus non-surgical, so the intervention is periodontal surgery, the comparator is scaling and root planning without periodontal surgery, and lastly, O is for the outcome.

Ask 'What can I hope to accomplish?'

There is a difference between narrative and systematic reviews. Narrative reviews, by definition, ask general questions: 'What is the effect of oral hygiene on healthcare?' They search for the evidence – the search method is not described and not linked to the question. What that means is the person writing the review is choosing the literature that is being discussed, and there is no explicit description of what evidence was included or excluded or why.

In a systematic review you have to answer a specific clinically relevant question. The search methods are explicit and developed to answer the question. You have to report the search methods and exactly what was found. When you undertake an experiment you have to describe your experimental methodology so that the paper can be reproduced by someone else. This is inherent in the systematic review. Someone else using your method should come up with the same literature, and the exclusion and inclusion criteria have to be defined.

Narrative reviews make no attempt to include all the evidence. The reviewers use their own preference in summarising the evidence, and no checks on accuracy or reliability of the reviewers are generally made.

In a systematic review all evidence is included. This is a very important point. Hand searches of

journals, unpublished studies, and reports are also included. The attempt is to get absolutely all of the evidence on the subject. The reviewers critically appraise and summarise all of the studies in evidence tables. Excluded studies are listed and there is a detailed explanation of why they are excluded, and accuracy and reliability are checked and documented.
In narrative reviews the quality of the studies may or may not be evaluated, meta-analysis may not be conducted, traditional pre-review is used for the evaluation of the studies – in other words, if it is published in a journal it is considered to be valid. Pre-reviews are conducted by experts in the methodology and the topic. Meta-analysis of trials is conducted. What do we know about experience- versus evidence-based dentistry? In experience-based decisions, clinical observations are used for building up a knowledge base for diagnosis, decision-making and treatment and, of course, commonsense is used. This is what we generally do in our practice. New treatments and diagnoses can be evaluated by a combination of traditional dental education – and again commonsense – and problems can be answered by asking colleagues and local experts, reading textbooks, attending CE or reading journals.
In evidence-based dentistry, clinical observation or clinical experience is important, but the observations must be validated by systematic reviews of the evidence without bias. Regular reference must be made to original literature, and the results of all studies must be critically examined using all the rules of evidence. This changes the playing field. We all use experience-based decision-making in our practice, but the shift is to use documented evidence and try to eliminate bias.
Meta-analysis is a statistical method that is a systematic approach to identifying, appraising, synthesising and, if appropriate, combining the research results of relevant studies to arrive at a conclusion about a body of research. It is applied with increasing frequency these days to randomised controlled clinical trials, which are considered to provide the strongest evidence regarding an intervention. The point is to summarise the results of several studies into a single estimate, giving more weight to the results from larger studies.
What is good evidence?

The gold standard for strong evidence is at least one published systematic review of multiple, well-designed randomised controlled trials.

It is the randomised controlled trial that is considered the highest form of evidence, and then the systematic review of several of those provides the gold standard.
How do you go about finding evidence? Probably the easiest thing is to ask somebody, as a colleague or an expert. You can consult a textbook; you can find a relevant article in a personal reference file. You can use a bibliographical database such as Medline.
If you ask somebody for references for evidence, you are really asking for expert opinion. Experts often disagree. Experts may not be up to date in that particular subject area, or they may disagree with the latest evidence. The best method of using an expert, therefore, is to ask them for specific references so you can appraise the evidence for yourself, which they are often not willing to provide, lest you disagree with them.
Consulting a textbook is useful more for historical information. Textbooks are only as current as their most recent reference. If you take the latest textbook on any subject and look at the most recent reference, it is often three or four years old. The authors also may not accept the latest evidence in the writing of their textbook. Personal reference files are unlikely to be extensive enough to cover the wide variety of problems and questions encountered in everyday practice.
How do you find the evidence? There are bibliographical databases such as Medline and Ovid, and these are the quickest and easiest ways of accessing information as they are accessible from your home or from your office by the internet. The sources of evidence for decision-making in clinical practice have a hierarchy. The **double-blind randomised controlled clinical trial** is considered the most unbiased and highest form of clinical evidence. If you go to the dental literature and look for these kinds of trials you will be hard pressed to find more than one or two on any subject, if at all.
Cohort studies, which are usually what we find, compare one pre-selected group with another. There are **case-controlled studies**, **case series** and the ever-present **case report** Case series and case reports have no controls. There are **ideas**,

editorials and opinions of experts, which are also published. There are animal studies where one tests the concept in animals before moving to humans, and then of course there are in vitro laboratory studies, which are generally the precursor to the animal studies.

So where is the evidence? Where do we find the evidence? Coming up empty on a finding of appropriate studies when conducting a systematic review to answer a clinical question is, in fact, itself a significant finding. It means we do not have the evidence.

In the USA, probably the single most relevant thing is the need to direct funds to clinical research – we really do not have very much to go on when making clinical decisions. The outcome will be to build a scientific foundation from clinically relevant research, to integrate evidence into clinical experience, to promote the self-questioning in clinical practice and education. There is a definite need for objective and scientifically critiqued systematic reviews and a strategic redirection of research funding to address the questions of interested dentists that have direct impact on patient care and dental education.

If the dentists of today and tomorrow ask clinically relevant and focused questions, find objective and scientific critiques, systematic reviews, include findings in their practice, are lifelong learners, and clinical problems and clinically focused questions flow into systematic reviews of best evidence, then these findings can be translated into practice, policy and education, which, to complete the circle, have to be evaluated using established outcomes assessment systems. Sometimes evidence-based dentistry works well. It is thorough, it is critical, there is examination of the information, and there is emergence of clinical and practical research and approved appropriateness of care. Results of studies showing new effective interventions will be communicated faster. It is easier to communicate with informed patients. If there is an 80% chance that the patient will benefit from the treatment, you can tell the patient that they may be one of the eight who will benefit or you could be the two who will not benefit, and then the patient can make the decision on the data available on the benefits and harms.

There are concerns as well. Like all human endeavours, bias and political agendas can influence the process. One of the reasons that the ADA is so concerned that all data be included is in an attempt to eliminate bias.

CLINICAL TRIALS – C. Scully, London

Crispian Scully, Professor and Dean of the Eastman Dental Institute, University College in London, began by outlining his subject matter as follows: "I have been asked to talk about clinical trials – an approved protocol selection of investigators, an approval process equivalent of patients, data collection and analysis, presentation and publication and then the firework display when everything is sorted. Clinical trials come in various kinds: pre-clinical studying for testing for toxicology in the laboratory, phase one, phase two and phase three trials, phase one testing for absorption and distribution in healthy volunteers, and then the ones that test on small numbers of patients for the dose and duration, and testing on larger numbers of patients for efficacy and safety. For some years now we have become aware of the need for good clinical practice, and this consists of four important principles.

Has anyone heard of Willowbrook It is really a good example of why we probably need good clinical practice. Willowbrook was a US mental institution for mentally challenged patients in New York State, run by a physician called Blumberg who fathomed out that a lot of the patients with Down syndrome seemed to be yellow on the odd occasion – they had jaundice. He was aware there was a connection between Down syndrome and jaundice and couldn't understand why.

He worked out that there was something being transmitted between these patients with Down syndrome by their close contact, so he took blood from patients with jaundice and he injected it into patients with Down syndrome. You can see the need for protection of clinical trial subjects. It was a terrible thing to do. On the other hand, without someone going down that route, how would we have ended up with a vaccine against hepatitis B at some point in the future? So there is a balance to be thought about and, unless there is some risk-taking at some point, we are not going to get anywhere.

Before a clinical trial is initiated this is what good clinical practice involves: foreseeable risks and inconveniences should be weighed against antici-

pated benefit for the individual trial subject and society. The trials should be initiated and continued only if anticipated benefits justify risks, and trials are abandoned if there are significant risks identified.
The safety and the well-being of trial subjects are the most important considerations and prevail over the interest of science and society.
Good clinical practice demands that true informed consent is obtained from every subject prior to clinical trial participation.
The available non-clinical and clinical information on the product should be adequate to support the proposed clinical trial. All the information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.
Confidentiality of records that could identify a subject should be protected. That is a real challenge sometimes, particularly if you anonymise studies. For example, what do you do if you come up with two people who are carrying a disease that they did not know about and the study is anonymised? This raises some serious ethical and moral issues.
The medical care given to and the medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist. All the products should be handled, stored in accordance with good manufacturing practice and used in the way that they were designed to be used. Systems with the procedures that assure the quality of every aspect of the trial should be implemented.
In Europe we now have the new European Clinical Trials Directive – which was raised in 2001 and implemented last year. It is a legal requirement across Europe that clinical research will be subjected to the same rigorous standards that currently exist in the pharmaceutical industry. It protects the rights, safety and well-being of clinical trial subjects and places particular emphasis on vulnerable groups, including children and incapacitated adults, and it applies to all clinical research, including phase one studies as well as post-marketing studies.
The new Clinical Directive is designed around the clinical trial authorisation application. It provides a legal framework for ethical committees – all legally binding. In the UK the Central Office for Research Ethics Committees (COREC) controls ethics committees and all ethics approvals.
There is a European database, European Drug Regulatory Agencies Clinical Trial (EUDRACT), which captures all the data and, in theory, allows exchange of information between the European Agency for Evaluation of Medicinal Products, which is EMEA, and the various authorities and different member states.
The various investigational medicinal products including placebo and comparative products have to be manufactured according to good manufacturing practice standards. There are obligations on both the investigator and the sponsor to record adverse effects and reactions and to report those adverse reactions.
Why all the fuss? Do you remember thalidomide? It was introduced as a sedative for pregnant women who couldn't sleep yet ended up proving to be teratogenic. You cannot tell with some of these products what they are going to do. This does not usually apply to oral healthcare products, but with systemic products it certainly does.
So those are the key points: protection of clinical trial subjects, procedures for the ethics committee, exchange of information between the regulatory bodies and the EMEA, standards for good clinical practice and good manufacturing practice and reporting of single events. This is now the requirement in UK and other countries in Europe for phase one trials to be looked at."

EFFECT AND EFFECTIVENESS IN CLINICAL TRIALS – J. Suvan, London

The next speaker, Jean Suvan of the Eastman Dental Institute in London, addressed the topic 'From effect to effectiveness in clinical trials'. "Setting the context for this topic, it is first important to understand the goal of research and in particular, clinical trials. The underlying objective of all research is targeted at "finding the truth". In the context of clinical trials, some trials, for example pilot studies, may be hypothesis-generating and others may direct therapy, for example, the testing of specific interventions in large scale trials. Through the focus that evidence – based healthcare has brought on relating or applying clinical trial results to clinical practice, clearer definition of many study design criteria has evolved. Regardless of trial design or applicability, the focus is still to "find the truth". How is the truth discovered? Galileo has eloquently summarized the essence of research methodology in this quote; 'The aim of science is not to open the door to infinite wisdom but to set a limit to infinite error.' This is to say that truth is

discovered through attempts to minimise bias." Some examples from history followed by highlighting current important elements of clinical trial design that elucidate future directions needed in clinical trials.

"History reports some of the earliest attempts to minimise bias. In 167 BC one of the first documented examples of an experiment was done by the prophet Daniel when he compared, in a group of warriors, a vegetarian diet to the meat and wine diet recommended by King Nebuchadnezzar. After ten days of separating the men into two groups he observed which were healthier and confirmed, much to the king's disappointment, that the vegetarian diet without the wine was actually better. In 200 AD the "lemon experiment" was conducted by an Egyptian judge. A convict due to be killed through the use of insect bites and asp bites was offered a lemon on the way to his death and subsequently survived the bites The Egyptian judge then proceeded to divide convicts into two groups, noting who survived asp bites having eaten a lemon or not. In the 11th century, the scientist Avicenna proposed seven rules of research, highlighting the problems of a single variable versus multiple variables. He proposed it easiest to deal with a "simple" illness when trying to determine whether or not a remedy worked. He suggested comparison to those without the illness noting that there were differences appearing dependant upon degrees of illness. He suggested the importance of a definite protocol to define the manner to administer the remedy and felt the study of the remedy should be replicated numerous times. He stated animal studies were not suitable for evaluating remedies to be used in humans.

So where are we today in our attempts to minimise bias, to discover the truth? Focus on evidence-based healthcare has brought much attention to minimising bias. In 1979 David Sackett identified 35 types of bias. Since then the focus, particularly in systematic review methodology, has been on addressing some of these types of bias. This has brought discussion about "how" research results are produced, that is the methodology that contributes to generating the research results feeding into systematic reviews. Another trend facilitated by evidence based healthcare has been the closure of the gap between clinical research and clinical practice, resulting in increased interest in outcomes directly applicable to patients. The process of critical appraisal has brought significant awareness of the quality of research. Although the connotation of the word 'quality' has a judgemental inference, "quality" in clinical research is intended to refer to the degree to which the methods employed minimise bias, therefore, taking us closer to the truth.

The mentioned focus on trial design in evidence – based healthcare has facilitated the clarification of four study objectives or outcomes referred to as 'effect, efficacy, effectiveness and efficiency'. These terms are not new but have often been confused or inappropriately used interchangeably.

Definitions of these four "E"s are as follows;

'Effect' refers to the observed association between interventions and outcomes, or a statistic to summarise the strength of an observed association. This can be positive or negative, and it can generate further hypothesis.

'Efficacy' brings in the concept of benefit. This is the extent to which an intervention can produce a beneficial outcome under ideal circumstances.

'Effectiveness' focuses on the extent to which an intervention can be a preventive measure, a diagnostic tool, a screening tool, an educational intervention and so forth.

'Efficiency' includes cost-effectiveness – the extent to which the balance between input and output represent value for money or value for resources.

(Khan et al 2004)

Each of the four "E"s has an important role in the generation, interpretation and application of evidence. For example, once effect is established, and assuming it appears beneficial, the next step would include studies addressing efficacy, that is, to investigate the magnitude of effect (benefit) in a highly controlled environment and specific population group. After establishing efficacy, effectiveness can be studied by testing the intervention in a large multi-centre trial and less controlled conditions (a more "real world" setting). These trials can also incorporate assessment of resources and economic implications leading toward outcomes of efficiency. The relationship between these four aspects is not intended as a solely linear flow but each study category may feed back into a previous category as new research questions arise.

The implication of appropriate function of these categories is paramount to clinical trial design and to implementation of evidence in practice. To facilitate application of findings to clinical practice, the key

is to start with well defined, clearly reported trials with interpretation of results based on study design. It is important to define the focus (effect, efficacy, effectiveness, efficiency) of the study outcomes a priori and to build the design accordingly. The key is to begin with literature review, establish the hypothesis, then state a well defined question. Next choose the study design and define specific characteristics, for example, randomised controlled trial versus a cohort trial and population inclusion criteria. After collection and analysis of the data, interpretation should be based on the study protocol and design. Results should be protocol – defined rather than results – defined, as is often seen in published literature. Interpretation and application of results should be carried out in the context of the initially defined focus. For example, was it a study of efficacy or effectiveness? Ultimately, this highlights that clear study reporting is one of the key factors in facilitating the applicability of the evidence.

These categories have brought further attention to the discussion of the clinical significance of research findings, known to be a complex and controversial topic. A key element of confusion lies in understanding the meaning of p values. P value is a statistical assessment of effect. It does not relate to clinical significance. Therefore, no set rule exists for the relationship between these two – it can be meaningful but needs to be handled with care. For example, it should be noted that a higher level of statistical significance does not take the results closer to clinical significance.

A practical example of these concepts can be drawn from an article published in Perio 2000, January 2005. The article is a critical appraisal and summary of 12 systematic reviews containing synthesis of data pertaining to mechanical instrumentation in management of periodontal disease. To give an example in this context, an "effect" outcome relates to a situation if scaling and root planing is performed. What happens? Is there a change? Typically, studies would report surrogate outcomes such as changes in probing depth, attachment level, or gingival inflammation. As mentioned, efficacy refers to the benefits in a specific well defined population, with therapy delivered in a highly controlled environment, such as a trial done in a university setting with a hygienist of 25 years using only new manual sharp instruments compared to one particular power instrument. The next type of trial to facilitate clinical application would be the effectiveness trial. This might be a multi-centre study including a broad population, and numerous therapists. Moving toward understanding efficiency, patient feedback of the experience, elements of operator fatigue, and time spent together with costs would be included. Currently, there is substantial amount of effect and efficacy data published on scaling and root planing. A specific example might be the many underpowered trials published on the comparison between hand and ultrasonic instruments. Systematic reviews have served to add meaning and utility of this evidence. The data lacking lies in the effectiveness and efficiency trials. For example, the data from the systematic reviews shows that hand and ultrasonic instruments are equal in terms of clinical outcomes. However, in the context of effectiveness or efficiency, it is not known if the two are equal. Are they equal in terms of patient experience, operator harm and fatigue? What do we know about root sensitivity and mechanical instrumentation? Does one instrument or the other give more side-effects? These are the research results that are lacking and yet to be discovered.

What is the way forward? Taking history into consideration and where we are at today we have come a long way. We have advanced dramatically in our scientific approach and our application of research to clinical practice. However, we have many pressures from ethical, legal and social bodies, from government and policy-makers, and more recently from the informed patient. These pressures highlight the need for us, as clinicians and academics to focus on effectiveness and efficiency studies, therefore, further influencing appropriate implementation of research findings into practice. Continuation of research methods identified centuries ago and advanced in more recent years, applied together with patient centred outcomes in intricate study designs has the potential to provide substantial additional understanding of existing therapies.

As generators and consumers of clinical research findings, we should continue to be as precise as possible, never abandoning the quest for the truth. Over 100 years ago Louis Pasteur stated that 'Imagination should give wings to our thoughts, but we always need decisive experimental proof, and when the moment comes to draw conclusions and to interpret the gathered observations imagination must be checked and documented by the factual results of the experiment.'"

GINGIVITIS MARKERS –
P. Preshaw, Newcastle

Dr. Philip Preshaw, a researcher in periodontology, spoke on gingivitis markers and methodology: "We can all recognise the difference between healthy and inflamed gingival tissues when we examine a patient clinically. Our challenge as researchers is to be able to reproducibly quantify such differences in clinical trials. In the past there has been much emphasis on the plaque removal abilities of various oral hygiene products, and it is now very timely that we are starting to move away from looking just at plaque to also look at the inflammatory response in the tissues. However, it is hard to measure gingival inflammation accurately. When comparing the histology of healthy and inflamed gingival tissues, we can see in the healthy tissues the well organised collagen fibre bundles, the normal anatomy of the epithelial and connective tissues, and the knife edge of the free gingival margin. The inflamed tissues look very different histologically; the tissues are enlarged, swollen, with dilated blood vessels, and we can see a dense inflammatory cell infiltrate in the connective tissues, which may well account for as much as 50–70% of the volume of the tissues. The histological differences between healthy and inflamed tissues are easy to see, just like the clinical differences, but how are we going to measure gingival inflammation accurately, reproducibly, reliably, and objectively? That is the challenge.

Let us discuss first the clinical assessment of gingivitis. There are several indices for measuring gingivitis. The most famous is undoubtedly the Löe and Silness gingival index (GI) which has been used since 1963 and was originally designed as an epidemiological screening tool for measuring gingivitis in pregnant women. Another scoring system is the Lobene modification of the Löe and Silness gingival index (mGI). Having recently reviewed the periodontal literature, I know that in excess of 90% of researchers who clinically measure gingivitis use the Löe and Silness gingival index.

The ideal scoring system should follow a linear scale, so that, for example, a score of two means the tissues are twice as inflamed as a score of one, and so on. The scoring system should be reproducible, valid and objective. Problems arise, however, because scoring a clinical scenario can be quite subjective, since we all have a slightly different way of looking at, interpreting and assigning a score to the tissues. The scoring system should not alter the clinical status and it should not change what we are trying to measure. If it does, this will create significant problems in calibration. The scoring system should be sensitive, specific, quick and easy, and, ideally, it should be non-invasive.

The main problems with clinical assessment of gingival inflammation are those of subjectivity and calibration. When considering calibration, we are asking how repeatable the measurements are, either for one examiner on different occasions, or for different examiners. There are several ways to assess repeatability. We can look at site-based scores, thereby treating each site as a unit of statistical analysis and, for example, calculate Î (which is very frequently reported, and often misused, in the literature). Another method is to calculate percentage agreement, resulting in a statement that might say that the examiners had perfect agreement 60% of the time, were within ±1 for the next 20% of sites, within ±2 for the next 10%, and so on, to give some indication of how well the examiners are agreeing. We can also consider subject-based scores, for example, intraclass correlation coefficients (ICC), which take account of errors at the site level, the subject level, and also spontaneous error. I also find it very useful to graphically present the data, such as plotting differences between examiners versus their mean scores.

Recently, I have undertaken a systematic review of the literature with respect to examiner calibration when measuring gingivitis. 12 dental journals, including the main periodontal and dental research journals were reviewed for the years 1996–2003, together with hand searches of the literature and key word searches. 501 papers that reported using either the GI of Löe and Silness or Lobene's mGI were identified. About half of those papers gave no information at all on whether examiners were calibrated; 29% gave the statement that one examiner did all the assessments, thereby implying that there was good repeatability but without actually saying whether that examiner had been calibrated or not; and the remaining 23% did report that calibration was performed, but very frequently there was a mismatch between the units of analysis that were used in the calibration exercise compared with the actual study.

In a recent paper [McClanahan et al, Journal of Periodontology 2001], styles of using the GI were evaluated in different clinical examiners who were conducting gingivitis studies. Mean GI scores were calculated for each patient, and plotted against the total number of bleeding sites for the same patient. The data identified that the different examiners behaved very differently when scoring gingivitis. For example, all of one examiner's mean GI scores were around 0.5 and virtually no bleeding sites were recorded. A second examiner used primarily 0's and 1's when assigning GI scores. Another examiner used 0's and 2's, primarily. Despite the different scoring styles, however, all of the examiners identified reductions in gingivitis scores following a prophylaxis. The magnitude of the differences identified following the prophylaxis was different for each examiner, however, which could clearly create problems if a reduction in GI scores was used to support a claim for an oral hygiene product, for example.

Moving away from the clinical assessment of gingivitis, another method to quantify gingival inflammation could be to take a biopsy of the tissues. What are some of the advantages of a gingival biopsy? The method provides direct access to the tissues which then could be analysed histologically, perhaps involving immunohistochemistry, or assessment of the size or the composition of the inflammatory cell infiltrate, or monoclonal antibodies could be used to stain for cytokines, or mRNA expression could be assessed, and so on. A biopsy gives very good information about the histopathology and residual tissue can be retained, or may be homogenised and then assays performed for inflammatory mediators in the homogenates.

But there are many disadvantages. Would we (the researchers) be willing to have our gingival tissues biopsied? It is an invasive surgical procedure, it yields a small tissue sample, and it is difficult to reproducibly quantify changes in the tissues because the samples are small and patients vary. It can be expensive to analyse the samples, laboratory support is required, and it raises very important ethical considerations. In any case – will subjects volunteer for this procedure?

Another method for assessing gingival inflammation is to measure biochemical markers in collected gingival crevicular fluid (GCF), which is often sampled using filter paper strips that are inserted below the gingival margin. GCF sampling is a relatively simple technique that is essentially non-invasive and is quick, although it is very technique-sensitive. We know that GCF mediator levels approximate those in the inflamed gingival tissues, and samples can be stored at –70°C until analysed. The disadvantage with GCF is that sample volumes are very small, typically <1 µl, and very sensitive assays (which can be expensive) are therefore required. Variables to consider when sampling GCF include whether or not GCF volume should be measured (as this may introduce further errors), and whether flowing or pooled GCF should be collected (and, indeed, whether this impacts on outcomes). It may be necessary to define an acceptable volume range for the samples, for example 0.2–1.0 µl. Below this, and samples volumes are so small that there is a likelihood of being at the limit of sensitivity of the assay, and above this, GCF volume readings may be inaccurate. Studies that report GCF sampling frequently demonstrate very variable data, which is due to a combination of errors inherent in volume estimation and in the analytical procedures as a result of the very small volumes, as well as variations between patients.

Mediators that have been analysed in GCF include a variety of host-derived enzymes such as alkaline phosphatase or collagenases, inflammatory mediators such as cytokines, and tissue breakdown products. Studies have shown, for example, that GCF IL-1, levels rise as the tissues become more inflamed, in parallel with increases in GI scores [Liu et al, Cytokine 1996]. GCF IL-1, levels have also been extensively studied in experimental gingivitis protocols, with demonstrated increases in mediator content occurring in parallel with the development of gingivitis.

Subgingival temperature has also been proposed as a method for assessing gingival inflammation, though there has not been much research in this area. Early studies have shown that subgingival temperature is correlated with clinical inflammation, with consistent rises of gingival temperature as the tissues become more inflamed from health to gingivitis to periodontitis [Niederman et al, Journal of Clinical Periodontology 1995]. The temperature of the gingival tissues has also been found to be elevated in smokers [Dinsdale et al, Journal of Clinical Periodontology 1997]. There are minimal data on the effects of tooth, site, location in the arch, and maxilla versus mandible

with respect to subgingival temperature, however. Gingival blood flow has also been investigated as a marker for gingival inflammation, possibly using laser Doppler flowmetry. Studies have generated very mixed results, however. Baab [Archives of Oral Biology 1987] found no correlation between blood flow and resolution of gingival inflammation in dogs. Another study found an increased number of vessels and decreased blood flow in those vessels (presumably reflecting a degree of stasis in the vessels) in experimental gingivitis [Matheny, Journal of Clinical Periodontology 1993]. No significant effect of smoking on gingival laser Doppler flow measurements was reported in a study by Meekin et al [Journal of Clinical Periodontology 2000]. In another study [Morozumi, Journal of Clinical Periodontology 2004] there was increased gingival blood flow following quitting in smokers, however.

Subgingival pH has also been investigated as a means to distinguish inflamed and healthy tissues. One study found no correlation between crevicular pH and clinical status [Eggert, Archives of Oral Biology 1991]. Another study found no significant correlations between pH and gingivitis, with variations in pH between 2 and 9 within a single pocket [Galgut, Journal of the International Academy of Periodontology 2001]. Yet another study identified significant fluctuations of pH during experimental gingivitis, with positive correlations between pH and the gingival index [Kobayashi, 1998]. Increased alkalinity was observed with increasing gingival inflammation, presumably as a result of the release of substances such as NH3 by bacterial cells, or metabolism of organic acids.

Another major consideration when studying gingival inflammation is that there is wide variation in patient responses. A recent report by Trombelli et al [Journal of Clinical Periodontology 2004] looked at what were termed high and low responders. In an experimental gingivitis model, plaque levels tended to increase in a similar fashion for all subjects, but some individuals developed very mild gingival inflammation whereas others developed very pronounced gingivitis in response to the plaque accumulation. This raises the question 'Should the high responders be selected preferentially into a study, or should we try to make the study population representative of the wider population (including high and low responders)?', even though we know that it may well be harder to identify differences between treatment groups in the latter population. To further complicate matters, smokers and non-smokers behave differently in their inflammatory responses, and also stress may have an effect in exacerbating the inflammatory response, and these various factors are all difficult to account for.

Any study assessing gingivitis should ideally involve pilot testing of both the population and the assay and scoring systems first, and of course appropriate support facilities (both clinical and laboratory) need to be available. These factors tend to result in increased cost, as will the need for larger patient populations. The larger the population that is studied, the easier it may be to identify statistically significant differences between two groups, even if the actual differences are quite small. A danger then may be that if such data are used to support a claim for some kind of treatment, the clinical relevance of the differences between groups may be hard to justify.

When conducting research including both clinical scoring systems and biochemical assays, it is always reassuring if the clinical and laboratory data correlate. Currently available clinical scoring methods for gingivitis have limitations, and my recommendation would be that the clinical scoring system should be as simple as possible to reduce subjectivity. If biochemical methods are to be used, then GCF sampling is probably the most well established technique, as well as being the least invasive, though it is not without technical challenges. It would be important to choose a mediator (if not several mediators) for analysis in GCF samples which is measurable in healthy sites and shows a marked and consistent change (either increase or decrease) in diseased sites, so that change over time could be measured (for example IL-1,). The assay system requires good sensitivity and specificity, and one useful approach would be to use a multiplex system to assay several mediators in the same samples. This would allow us to identify which of a range of mediators might be important in gingival inflammation, and also to assess the importance of the balance between different mediators. For example, some cytokines are pro-inflammatory, whereas others are anti-inflammatory, and perhaps the balance between these is more important than the absolute values of any one given mediator."

CONCLUSIONS

Dr Hefti summed up the overview of what had been learnt from the session: "Today, we have learnt that a lot of what has been published under the topics 'critical review', 'meta analysis' or 'evidence-based information' actually must be looked at very critically too. Today's presentations have provided tools to evaluate evidence-based information much better. In addition, clinical research must be considered also in the context of appropriate ethical behaviour. We have seen that in the past the scale for implementing ethical behaviour – for example, how researchers inform study subjects on experimental risks and benefits, or how they design a clinical study – was completely different from today. The fact that the research community is now openly discussing the limits of clinical research means we are heading in the right direction."