From the Editor

Another new year is here and as always, there is a lot to anticipate. It is great to be in a program that gives you the flexibility to move from purely clinical experiences to the basic sciences with such ease. It just keeps getting better, thanks to the constant efforts by dedicated faculty and staff members.

Our current group of third year residents Drs. Renita Burrell, Samer Khoury, Chun-Han Chou and Jeffrey Wessel are working hard towards their graduation this year. It has been and is a great pleasure working with all of them. I wish them all the best of luck in their endeavors.

I hope you enjoy this issue of The Cutting Edge. I would like to thank my faculty advisor Dr. Claman and “cub-reporter”, first year resident Dr. Weiting Ho for all their help with putting it together.

The Ultimate Path
Angelo Mariotti, DDS, PhD, Chair

Two realms, the clinical sciences and the basic sciences, seem to be separate entities, a view that is widely held today. In fact, the divide between the two cultures has been amplified by the hubris of the clinical sciences. There is an implicit agreement within the dental community that one must be familiar with clinical techniques but it is tolerable to be uninformed about cellular processes. As a clinician and scientist, I’ve often encountered this attitude among clinicians. It’s rarely derogatory, and it’s frequently accompanied by embarrassment, sometimes feigned, that the otherwise intelligent and informed dentist has a modest understanding of science or mathematics.

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Important News

Please Join Us
For
VOLPE Research Competition
Friday, May 4, 2007
And
Periodontal Research Day
Friday June 8, 2007

See Page 31 for event information.
Hope to see you there!
Generally, the encounters end with a well-meaning chuckle that says “it’s really okay to know only fragments of math or science.”

But in the twenty-first century, such willful ignorance of science is not in our interest. We are living through a radical cultural shift, one in which science and technology play an increasingly pervasive role in everyday practice. From stem cells to nanotechnology, computer-enhanced perception to periodontal bioengineering, full participation in dental management of patients requires a familiarity with the major advances in science and technology as well as the scientific way of thought. The most far reaching choices will be made in the years ahead, whether through action or apathy, are ones that have a critical scientific component. Informed decision making requires dental professionals who are engaged with science, not someone that is looking in from the periphery and not someone that takes pride in their lack of knowledge.

Since a scientifically literate dentist is vital, how do we make headway toward this outcome? Why isn’t the hubris of clinical sciences overcome by the smugness of the basic sciences? Why isn’t it considered inappropriate to know little or nothing about probability and statistics, biochemistry and genetics, or molecular biology and cell biology? One can come up with many explanations: science requires a specialized language that few dentists have the inclination to master, science deals with esoteric questions that only experts can truly appreciate, science operates in the abstract; but I think all such propositions add up to this: to many dentists, science, unlike surgical revision of the periodontium, seems dry, cold and removed from clinical practice. Our interest in wiggling teeth, periodontal probings and surgical revision tell us about ourselves because they augment our understanding of the range and texture of clinical practice. Science, many feel, doesn’t do this and hence is dispensable, or more precisely can be left to the scientists. One culture is thus deemed profoundly relevant while the other profound but extremely distant. Although this line of thought is specious, I can see where it comes from and how aspects of our educational system foster it. But the conclusion is wrong and in the long run, dangerous.

Science needs to be recognized for what it is: the ultimate path for oral health improvement. Researchers worldwide are closing in at an exhilarating pace on unanswered questions that will prepare us for the next step in which we go from being inquirers about nature to becoming manipulators. In fact, today’s researchers routinely tinker with the molecular structure of life, so it’s clear that we have already taken the first steps on this latter journey. However, if the dental community can’t recognize what science can do to solve their clinical problems, if it can’t intelligently discuss and debate the data generated, and if it can’t determine the clinical relevance of basic science discoveries, then our profession will no longer be the stewards of dental health and the next steps for dental health and clinical practice will be dictated by others.
Dear Alumni and Friends,

It was a real pleasure seeing so many of you at the Buckeye reception during the annual AAP meeting in San Diego. It was a joy for me to have the opportunity to spend time with several of you during the meeting and to hear first-hand about all the exciting things going on in your professional and personal lives. Our current residents enjoyed not only attending several of the sessions of the meeting, but also having the chance to meet and interact with many of you.

Congratulations to Drs. Rupa Hamal ('99) and Swati Rawal ('04) for becoming Diplomates of the American Board of Periodontology after successfully participating in the November 2006 Oral examination!

Our current third year residents, Drs. Renita Burrell, Chun-Han Chou, Samer Khoury and Jeffrey Wessel are preparing to complete their research and clinical requirements to graduate on time. All four of them will be presenting results of their M.S. research at the upcoming College Research Day. Chun-Han, Samer and Jeff will also be presenting their research at the upcoming AADR/IADR meeting in New Orleans (March 21-24). It is a pleasure to inform you that Jeff Wessel is one of the three Research Forum finalists at the annual Midwest Society of Periodontology Meeting in Chicago (February 23-25), as well as a AADR Pfizer Hatton Awards finalist (Senior category). We will be celebrating the accomplishments of our third year residents during the annual graduation dinner, scheduled for June 1st 2007.

Our second year residents, Drs. Ling Chang, Pooja Maney, Jessica Stilley and Vlad Shapiro are steadily progressing in their clinical training and research pursuits. Before we know it, they will be “taking over” the Program after June 30, when Chun-Han, Jeff, Renita and Samer graduate.

Our first year residents, Drs. Weiting Ho, Patrick Kelsey, Stacey Papapostolou, and Mabel Salas are now integral members of the Program and strong contributors to all of our activities. All four of them have selected their M.S. thesis research projects and have started work on them.

The interview process for next year’s incoming class took place this past autumn. The program had a large number of highly qualified applicants and the two days of interviews were busy but very enjoyable. I am very pleased that we were able to recruit four first-rate candidates to join the program in July 2007. Many thanks go to our residents and our staff, as well as our faculty, for spending a lot of time and effort on the interviews and for making it possible to recruit these highly desirable candidates.

Along with all the other activities of the Program, residents and faculty had opportunities to attend lectures or presentations from a number of colleagues visiting OSU or to go and listen to various speakers. Among them were: Dr. Violet Haraszthy, Assistant Professor of Prosthodontics, SUNY at Buffalo, NY; Dr. Steven Lewis, Prosthodontist, Cincinnati, OH; Dr. Samuel Low, Professor of Periodontics, University of Florida, Gainesville, FL; Dr. Michael Pikos, Oral and Maxillofacial surgeon, Palm Harbor, FL; Dr. Philip Preshaw, Senior Lecturer in Periodontology, University of Newcastle, Newcastle upon Tyne, UK; Dr. Tomaso Vercellotti, Piezosurgery, at the University of Illinois at Chicago; Dr. Hom-Lay Wang, Professor of Periodontics, University of Michigan, Ann Arbor, MI.
An update on our Graduate Periodontal Clinic: the expansion/renovation of the clinic space has been completed. The third implant operating room has already seen significant use, as has our new developing room. Our new digital panoramic x-ray unit has been installed and we anticipate putting it to use soon. These facility improvements will help us not only maintain but also enhance the level of patient services and resident training we provide.

The residents and I greatly appreciate your continuing support of the program as we keep on receiving referrals for patients who represent specialized treatment challenges or who cannot afford periodontal treatment in a private practice setting. Should you need to contact the clinic for a patient referral or any other reason, please call 614-292-4927. You can always reach me at tatakis.1@osu.edu or at 614-292-0371.

I look forward to seeing many of you at the Periodontal Research Day meeting in June.

Best wishes,
Dimitris Tatakis
In the past several issues of The Cutting Edge, we have discussed our predoctoral program, both from the perspective of helping dental students understand the importance of periodontology in general practice and in helping them perform well National Board and Regional Board examinations. In this issue, we will highlight development of the Dent IV competency exam, administered during the Summer Quarter the 4th year.

Until 2005, the fourth-year Clinical Competency Examination in Periodontology has involved evaluation of periodontal exam and therapy performed on periodontal patients. Feedback from our full time faculty, part time faculty and graduate students as well as test results made it clear that the exam had problems. Some of the shortcomings were (a) students selected patients with varying degrees of periodontal disease severity with different clinical findings, (b) there was examiner subjectivity, resulting in inter-examiner assessment variations and (9) we were trying to test too many skills for the time allotted.

There are several critical periodontal examination skills that are essential for general dentists to be successful in providing the best optimal care. We therefore decided to drop the treatment section of the exam and focus on periodontal examination skills. Treatment evaluation is now deferred to the Mock Board Exam. Dr. Swati Rawal (now at the University of Tennessee) implemented a two-part exam intended to measure important basic skills in periodontal examination. This format for the exam was presented as a poster at the March 2006 American Dental Education Association Meeting in Orlando, Florida. The poster was entitled “Objective Structured Clinical Examination to Assess Competency in Periodontal Examination”

Clinical periodontal examination, including radiographic interpretation, is crucial in establishing accurate periodontal diagnosis. The purpose of developing a standardized exam (Objective Structured Clinical Exam) was to assess student competency in basic periodontal examination skills needed for general dental practice. The standardized portion of the exam was combined with a non-standardized patient based exam.

We designed the standardized exam to evaluate three skills we consider to be most critical for general dentists. The skills are correct probing technique, ability to detect calculus, and radiographic interpretation. Probing depth and calculus detection skills were evaluated by calibrated full-time periodontal faculty. Students demonstrated their ability to properly position and angle the periodontal probe for probing depth measurements and to correctly use the 11/12 explorer for calculus detection. Typodont models were used to observe the techniques. For radiographic interpretation, we made composite radiographs, and duplicated the series so that each examiner observed student performance on the same radiographic series. The radiographic component tested students' ability to identify signs of periodontal pathology (angular and/or horizontal bone loss, furcation radiolucencies) and etiologic factors (calculus, restorative overhangs and caries).

In the traditional clinical section, students made periodontal measurements (probing depth, gingival margin position, attachment loss, tooth mobility, keratinized/attached gingiva) on patients they provided. The purpose of this portion of the exam was to test students' measurement accuracy. Thirteen part-time faculty and graduate students were involved in this non-calibrated portion of the test.

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With the help of Dr. Pinar Emecen, a visiting periodontal faculty from Hacettepe University in Ankara, Turkey, we have continued this exam this past summer for the Class of 2007. In general, we have found student accuracy on probing techniques and assessing attachment loss to be accurate (+/-1 mm). Students were able to find obvious periodontal related changes in bone and showed good techniques in probe placement and angulation.

However, we have been disappointed that despite extensive preclinical and clinical educational experiences many students were deficient in techniques to explore for subgingival calculus and recognize etiologic factors on radiographs. Sixteen of 92 students showed deficiencies that required retesting. We hope to better test for competency in critical areas before students enter the clinical years. Additionally, the competency exam results have made us more aware that it is essential for our faculty to continually reinforce techniques throughout the four years of dental school.

Recent Awards to Faculty and Students

At the 2006 American Academy of Periodontology meeting in San Diego, Dr. Lewis Claman was the recipient of the Outstanding Periodontal Educator award.

At the 2007 Midwest Society of Periodontology meeting in Chicago, Dr. Jeffrey Wessel's abstract presentation ‘Revascularization of Gingival Grafts: a Laser Doppler Flowmetry Study’ won the first place prize.

Congratulations to Our New Diplomates

Dr. Rupa Hamal (class of 1999)

Dr. Swati Rawal (class of 2004)
ALAN HUDSON LIKES TO TELL A STORY about a soldier and his high school sweetheart. The young man returns from an overseas assignment for their wedding with a clean bill of health, having dutifully cleared up an infection of sexually transmitted chlamydia.

“Three weeks later, the wife has a screaming genital infection,” Hudson recounts, “and I get a call from the small-town doctor who’s trying to save their marriage.” The soldier, it seems, has decided his wife must have been seeing other men, which she denies.

Hudson pauses for effect, stretching back in his seat and propping his feet on an open file drawer in a crowded corner of his microbiology laboratory at Wayne State Medical School in Detroit. “The doctor is convinced she’s telling the truth,” he continues, folding his hands behind a sweep of white, collar-length hair. “So I tell him, ‘Send me a specimen from him and a cervical swab from her.’” This is done after the couple has completed a full course of antibiotic treatment and tested free of infection.

“I PCR ‘em both,” Hudson says, “and he is red hot.”

PCR stands for polymerase chain reaction - a technique developed about twenty years ago that allows many copies of a DNA sequence to be made. It is often used at crime scenes, where very little DNA may be available. Hudson's use of the technique allowed him to find traces of chlamydia DNA in the soldier and his wife that traditional tests miss because the amounts left after antibiotic treatment are small and asymptomatic. Nonetheless, if a small number of inactive chlamydia cells passed from groom to bride, the infection could have become active in its new host.

Hudson tells the tale to illustrate how microbes that scientists once thought were easily eliminated by antibiotics can still thrive in the body. His findings and those of other researchers raise disturbing questions about the behavior of microbes in the human body and how they should be treated.

For example, Hudson has found that quiescent varieties of chlamydia may play a role in chronic ailments not traditionally thought to be related to this infectious agent. In the early 1990s he found two types of chlamydia - *Chlamydia trachomatis* and *Chlamydia pneumonia* - in the joint tissue of patients with inflammatory arthritis. More famously, in 1996, he began fishing *C. pneumonia* out of the brain cells of Alzheimer's victims. Since then other researchers have made headlines after reporting the genetic fingerprints of *C. pneumonia*, as well as several kinds of common mouth bacteria, in the arterial plaque of heart attack patients. Hidden infections are now thought to be the basis of still other stubbornly elusive ills like chronic fatigue syndrome, Gulf War syndrome, multiple sclerosis, lupus, Parkinson's disease, and types of cancer.

To counteract these killers, some physicians have turned to lengthy or lifelong courses of antibiotics. At the same time, other researchers are counterintuitively finding that bacteria we think are bad for us also ward off other diseases and keep us healthy. Using antibiotics to tamper with this complicated and little-understood population could irrevocably alter the microbial ecology in an individual and accelerate the spread of drug-resistant genes to the public at large.

The two-faced puzzle regarding the role of bacteria is as old as the study of microbiology itself. Even as Louis Pasteur became the first to show that bacteria can cause disease, he assumed that bacteria normally found in the body are essential to life. Yet his protégé, Élie Metchnikoff, openly scoffed at the idea. Metchnikoff blamed indigenous bacteria for senility, atherosclerosis, and an altogether shortened life span - going even so far as to predict the day when surgeons would routinely remove the human colon simply to rid us of the "chronic poisoning" from its abundant flora.

Today we know that trillions of bacteria carpet not only our intestines but also our skin and much of our respiratory and urinary tracts. The vast majority of them seem to be innocuous, if not beneficial. And bacteria are everywhere, in abundance - they outnumber other cells in the human body by ten to one. David Relman and his team at Stanford University and the Veterans Administration Medical Center in Palo Alto, California, recently found the genetic fingerprints of several hundred new bacterial species in the mouths, stomachs, and intestines of healthy volunteers.

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"What I hope," Relman says, "is that by starting with specimens from healthy people, the assumption would be that these microbes have probably been with us for some time relative to our stay on this planet and may, in fact, be important to our health."

Meanwhile, the behavior of even well-known bacterial inhabitants is challenging the old, straightforward view of infectious disease. In the nineteenth century Robert Koch laid the foundation for medical microbiology, postulating that any microorganism that causes a disease should be found in every case of the disease and always cause the disease when introduced into a new host. That view prevailed until the middle of this past century. Now we are more confused than ever. Take Helicobacter pylori. In the 1980s infection by the bacterium, not stress, was found to be the cause of most ulcers. Overnight, antibiotics became the standard treatment. Yet in the undeveloped world ulcers are rare, and H. pylori is pervasive.

"This stuff drives the old-time microbiologists mad," says Hudson, "because Koch's postulates simply don't apply." With new technologies like PCR, researchers are turning up stealth infections everywhere, yet they cause problems only in some people sometimes, often many years after the infection.

These mysteries have nonetheless not stopped a free flow of prescriptions. Many rheumatologists, for example, now prescribe long-term - even lifelong - courses of antibiotics for inflammatory arthritis, even though it isn't known if the antibiotics actually clear away bacteria or reduce inflammatory arthritis in some other unknown manner.

Even more far-reaching is the use of antibiotics to treat heart disease, a trend that began in the early 1990s after studies associated C. pneumonia with the accumulation of plaque in arteries. In April two large-scale studies reported that use of antibiotics does not reduce the incidence of heart attacks or eliminate C. pneumonia. But researchers left antibiotic-dosing cardiologists a strange option by admitting that they do not know if stronger, longer courses of antibiotics or combined therapies would succeed.

Meanwhile, many researchers are alarmed. Curtis Donskey, an infectious-diseases specialist at Case Western Reserve University in Cleveland, says, "Unfortunately, far too many physicians are still thinking of antibiotics as benign. We're just now beginning to understand how our normal microflora does such a good job of preventing our colonization by disease-causing microbes. And from an ecological point of view, we're just starting to understand the medical consequences of disturbing that with antibiotics."

Donskey has seen the problem firsthand at the Cleveland's VA Medical Center, where he heads infection control. "Hospital patients get the broadest spectrum, most powerful antibiotics," he says, but they are also "in an environment where they get exposed to some of the nastiest, most drug-resistant pathogens." Powerful antibiotics can be dangerous in such a setting because they kill off harmless bacteria that create competition for drug-resistant colonizers, which can then proliferate. The result: hospital-acquired infections have become a leading cause of death in critical-care units.

"We also see serious problems in the outside community," Donskey says, because of inappropriate antibiotic use. The consequences of disrupting the body's bacterial ecosystem can be minor, such as a yeast infection, or they can be major, such as the overgrowth of a relatively common gut bacterium called Clostridium difficile. A particularly nasty strain of C. difficile has killed hundreds of hospital patients in Canada over the past two years. Some had checked in for simple, routine procedures. The same strain is moving into hospitals in the United States and the United Kingdom.

Jeffrey Gordon, a gastroenterologist turned full-time microbiologist, heads the spanking new Center for Genomic Studies at Washington University in Saint Louis. The expansive, sun-streaked laboratory sits above the university's renowned gene-sequencing center, which was a major player in powering the Human Genome Project. "Now it's time to take a broader view of the human genome," says Gordon, "one that recognizes that the human body probably contains one hundred times more microbial genes than human ones."

Gordon supervises a lab of some twenty graduate students and postdocs with expertise in disciplines ranging from ecology to crystallography. Their collaborations revolve around studies of unusually successful colonies of genetically engineered germ-free mice and zebra fish.

Gordon's veteran mouse wranglers, Marie Karlsson and her husband, David O'Donnell, manage the rearing of germ-free animals for comparison with genetically identical animals that are colonized with one or two select strains of normal flora. In a cavernous facility packed with rows of crib-size bubble chambers, Karlsson and O'Donnell handle their germ-free charges via bulbous black gloves that serve as airtight portals into the pressurized isollettes. They generously supplement sterilized mouse chow with vitamins and extra calories to replace or complement what is normally supplied by intestinal bacteria. "Except for their being on the skinny side, we've got them to the point where they live near-normal lives," says O'Donnell. Yet the animals' intestines remain thin and underdeveloped in places, bizarrely bloated in others. They also prove vulnerable to any stray pathogen that slips into their food, water, or air.
All of Gordon's protégés share an interest in following the molecular crosstalk among resident microbes and their host when they add back a component of an animal's normal microbiota. One of the most interesting players is Bacteroides thetaiotaomicron, or B. theta, the predominant bacterium of the human colon and a particularly bossy symbiont.

The bacterium is known for its role in breaking down otherwise indigestible plant matter, providing up to 15 percent of its host's calories. But Gordon's team has identified a suite of other, more surprising skills. Three years ago they sequenced B. theta's entire genome, which enabled them to work with a gene chip that detects what proteins are being made at any given time. By tracking changes in the activity of these genes, the team has shown that B. theta helps guide the normal development and functioning of the intestines - including the growth of blood vessels, the proper turnover of epithelial cells, and the marshaling of components of the immune system needed to keep less well behaved bacteria at bay. B. theta also exerts hormonelike long-range effects that may help the host weather times when food is scarce and ensure the bacterium's own survival.

Fredrik Bäckhed, a young postdoc who came to Gordon's laboratory from the Karolinska Institute in Stockholm, has caught B. theta sending biochemical messages to host cells in the abdomen, directing them to store fat. When he gave germ-free mice an infusion of gut bacteria from a conventionally raised mouse, they immediately put on an average of 50 percent more fat, even though they were consuming 30 percent less food than when they were germ-free. "It's as if B. theta is telling its host, 'Save this - we may need it later,'" Gordon says.

Justin Sonnenburg, another postdoctoral fellow, has documented that B. theta turns to the host's body for food when the animal stops eating. He has found that when a lab mouse misses its daily ration, B. theta consumes the globs of sugary mucus made every day by some cells in the intestinal lining. The bacteria graze on these platforms, which the laboratory has dubbed Whovilles (after the dust-speck metropolis of Dr. Seuss's Horton Hears a Who!). When the host resumes eating, B. theta returns to feeding on the incoming material.

Gordon's team is also looking at the ecological dynamics that take place when combinations of normal intestinal bacteria are introduced into germ-free animals. And he plans to study the dynamics in people by analyzing bacteria in fecal samples.

Among the questions driving him: Can we begin to use our microbiota as a marker of health and disease? Does the makeup of this "bacterial nation" shift when we become obese, try to lose weight, experience prolonged stress, or simply age? Do people in Asia or Siberia harbor the same organisms in the same proportions as those in North America or the Andes?

"We know that our environment affects our health to an enormous degree," Gordon says. "And our microbiota are our most intimate environment by far."

A couple hundred miles northeast of Gordon's laboratory, microbiologist Abigail Salyers, at the University of Illinois at Urbana-Champaign, has been exploring a more sinister feature of our bacteria and their role in antibiotic resistance. At the center of her research stands a room-size walk-in artificial "gut" with the thermostat set at the human intestinal temperature of 100.2 degrees Fahrenheit. Racks of bacteria-laced test tubes line three walls, the sealed vials purged of oxygen to simulate the anaerobic conditions inside a colon. Her study results are alarming.

Salyers says her research shows that decades of antibiotic use have bred a frightening degree of drug resistance into our intestinal flora. The resistance is harmless as long as the bacteria remain confined to their normal habitat. But it can prove deadly when those bacteria contaminate an open wound or cause an infection after surgery.

"Having a highly antibiotic-resistant bacterial population makes a person a ticking time bomb," says Salyers, who studies the genus Bacteroides, a group that includes not only B. theta but also about a quarter of the bacteria in the human gut. She has tracked dramatic increases in the prevalence of several genes and suites of genes coding for drug resistance. She's particularly interested in tetQ, a DNA sequence that conveys resistance to tetracycline drugs.

When her team tested fecal samples taken in the 1970s, they found that less than 25 percent of human-based Bacteroides carried tetQ. By the 1990s that rate had passed the 85 percent mark, even among strains isolated from healthy people who hadn't used antibiotics in years. The dramatic uptick quashed hopes of reducing widespread antibiotic resistance by simply withdrawing or reducing the use of a given drug. Salyers's team also documented the spread of several Bacteroides genes conveying resistance to other antibiotics, such as macrolides, which are widely used to treat skin, respiratory, genital, and blood infections.

As drug-resistant genes become common in bacteria in the gut, they are more likely to pass on their information to truly dangerous bugs that move only periodically through our bodies, says Salyers. Even distantly related bacteria can swap genes with one another using a variety of techniques, from direct cell-to-cell transfer, called conjugation, to transformation, in which a bacterium releases snippets of DNA that other bacteria pick up and use.
"Viewed in this way, the human colon is the bacterial equivalent of eBay," says Salyers. "Instead of creating a new gene the hard way - through mutation and natural selection - you can just stop by and obtain a resistance gene that has been created by some other bacterium."

Salyers has shown that \textit{Bacteroides} probably picked up erythromycin-resistant genes from distantly related species of staphylococcus and streptococcus. Although neither bug colonizes the intestine, they are routinely inhaled and swallowed, providing a window of twenty-four to forty-eight hours in which they can commingle with intestinal flora before exiting. "That's more than long enough to pick up something interesting in the swinging singles bar of the human colon," she quips.

Most disturbing is Salyers's discovery that antibiotics like tetracycline actually stimulate \textit{Bacteroides} to begin swapping its resistance genes. "If you think of the conjugative transfer of resistance genes as bacterial sex, you have to think of tetracycline as the aphrodisiac," she says. When Salyers exposes \textit{Bacteroides} to other bacteria, such as \textit{Escherichia coli}, under the disinhibiting influence of antibiotics, she has witnessed the step-by-step process by which the bacteria excise and transfer the tetQ gene from one species to another.

Nor is \textit{Bacteroides} the only intestinal resident with such talents. "In June 2002 we passed a particularly frightening milestone," Salyers says. That summer epidemiologists discovered hospital-bred strains of the gut bacterium \textit{Enterococcus} harboring a gene that made them impervious to vancomycin. The bacterium may have since passed the gene to the far more dangerous \textit{Staphylococcus aureus}, the most common cause of fatal surgical and wound infections.

"I am completely mystified by the lack of public concern about this problem," she says. With no simple solution in sight, Salyers continues to advise government agencies such as the Food and Drug Administration and the Department of Agriculture to reduce the use of antibiotics in livestock feed, a practice banned throughout the European Union. She supports the prescient efforts of the Tufts University microbiologist Stuart Levy, founder of the Alliance for the Prudent Use of Antibiotics, which has been hectoring doctors to use antibiotics more judiciously.

Yet just when the message appears to be getting through - judging by a small but real reduction in antibiotic prescriptions - others are calling for an unprecedented increase in antibiotic use to clear the body of infections we never knew we had. Among them is William Mitchell, a Vanderbilt University chlamydia specialist. If antibiotics ever do prove effective for treating coronary artery disease, he says, the results would be "staggering. We're talking about the majority of the population being on long-term antibiotics, possibly multiple antibiotics."

Hudson cautions that before we set out to eradicate our bacterial fellow travelers, "we'd damn well better understand what they're doing in there." His interest centers on chlamydia, with its maddening ability to exist in inactive infections that flare into problems only for an unlucky few. Does the inactive form cause damage by secreting toxins or killing cells? Or is the real problem a disturbed immune response to them?

Lately Hudson has resorted to a device he once shunned in favor of DNA probes: a microscope, albeit an exotic $250,000 model. This instrument, which can magnify organisms an unprecedented 15,000 times, sits in the laboratory of Hudson's spouse, Judith Whittum-Hudson, a Wayne State immunologist who is working on a chlamydia vaccine. On a recent afternoon Hudson marveled as a shimmering chlamydia cell was beginning to morph from its infectious stage into its mysterious and bizarre-looking persistent form. "One minute you have this perfectly normal, spherical bacterium and the next you have this big, goofy-looking doofus of a microbe," he says. He leans closer, focusing on a roiling spot of activity. "It's doing something. It's making something. It's saying something to its host."
A. PEER-REVIEWED ARTICLES


B. ABSTRACTS


Dihydropyridine-influenced gingival enlargement: a review
Jeffrey Wessel, DDS

Introduction

Drug-influenced gingival enlargement has been associated with a variety of medications, including an anticonvulsant (e.g. phenytoin), an immunosuppressant (e.g. cyclosporine A), and calcium channel blockers (e.g. nifedipine, verapamil, diltiazem, sodium valproate).\(^1\) The prevalence and oral health implications of drug-influenced gingival enlargement led to the inclusion of these conditions in the most recent classification of periodontal diseases and conditions by the American Academy of Periodontology.\(^2\) Under the current classification system, ‘Drug-influenced gingival diseases’ are under the heading ‘Gingival diseases modified by medications’ within the broader category of ‘Dental-plaque induced gingival diseases.’\(^2\) Enlargement of the gingiva in response to medications was first reported in 1939 and was associated with phenytoin.\(^3\) Since that original publication, numerous case reports and studies have been published linking a variety of medications to gingival enlargement.

Calcium channel blockers are a class of drugs that are commonly prescribed as antihypertensive, antiarrhythmic and antianginal agents. These drugs exert their effect on voltage-gated Ca\(^{2+}\) channels in vascular smooth muscle and cardiac muscle. Calcium channel blockers exert their primary action on Ca\(^{2+}\) channels that carry the slow inward Ca\(^{2+}\) current resulting in a variety of cardiovascular responses, including decreasing SA node automaticity, AV node conduction and myocardial contractility.\(^4\) Additionally, calcium channel blockers can induce coronary and peripheral arterial dilation which provides efficacy as antianginal and antihypertensive agents.\(^4\)

Calcium channel blockers can be classified into two broad categories: non-dihydropyridines and dihydropyridines (Table 1). Non-dihydropyridines include verapamil, which was the first calcium channel blocker, and diltiazem. Verapamil, a diphenylalkylamine derivative, and diltiazem, a benzothiazepine, exert their predominate effect directly on cardiac conduction and contractility.\(^5\) Dihydropyridines are the largest category of calcium channel blockers of which nifedipine is the prototype. Dihydropyridines primarily affect vasodilation and do not greatly affect Ca\(^{2+}\) channels in the heart.\(^4\)

The first case reports of drug-influenced gingival enlargement due to nifedipine were published in 1984.\(^5,6\) Soon after that the first case reports of verapamil- and diltiazem-influenced gingival enlargement were published.\(^7,8\) Since these early reports significant attention has been given to calcium channel blocker-influenced gingiva enlargement, mostly dihydropyridines. Due to the common use of dihydropyridines and effectiveness of nifedipine in management of patients who do not respond sufficiently well to other antihypertensive medications\(^9,10\), dihydropyridine-influenced gingival enlargement remains a significant periodontal problem.

Methods

MEDLINE literature searches were conducted, using terms related to dihydropyridines (including names of specific dihydropyridines: amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine and oxodipine) in combination with terms related to gingival enlargement, epidemiology and therapy, to identify English language literature published up to March 2006 on the relationship between dihydropyridines and drug-influenced gingival enlargement. Relevant prospective and retrospective studies as well as case series and case reports were retrieved and their bibliographies hand searched for any additional relevant literature.

To review the literature on the potential pathogenetic mechanisms implicated in the effects of dihydropyridine-influenced gingival enlargement related terms were also combined with the following terms: collagen, fibroblasts, extracellular matrix, oral hygiene, inflammation, cytokines, immune system, and genetics.

Epidemiology

Drug-influenced gingival enlargement has been associated with administration of several dihydropyridines in addition to nifedipine. The first case report of nifedipine-influenced gingival enlargement was published in 1990.\(^1,1\) In 1991 the first report of felodipine-induced gingival enlargement was published.\(^1,2\) Following this the first case of amlodipine-influenced gingival enlargement was reported in 1994.\(^1,3\) Reports of gingival enlargement have also been associated with administration of nisoldipine and nicardipine.\(^1,4\) Oxodipine has been associated with gingival enlargement in dog\(^1,5,16\) and rat\(^1,7\) models but no evidence of gingival enlargement has been associated with administration of oxodipine in humans. The doses of oxodipine associated with gingival enlargement in dogs were 24 to 73 times the recommended human dose and in rats were 225 to 675 times the recommended human dose.\(^1,5,17\) The evidence indicates that it is unlikely for oxodipine to cause gingival enlargement in humans at the therapeutic doses of 0.1 to 1.5mg/kg/day.\(^1,7\)

Continued on Page 14
A majority of the data on prevalence of dihydropyridine-influenced gingival enlargement has focused on nifedipine. While the prevalence of nifedipine-influenced gingival enlargement is generally accepted to be approximately 20%, wide variations in the prevalence have been reported with a range of 6.3% to 83% (Table 2).18-24 The highest prevalence of nifedipine-influenced gingival enlargement of 83% was reported by Fattore et al21 among 19 out of 23 subjects from a VA Medical Center in Chicago. Other studies on hospital-based populations have been done by Barclay et al23 who reported a prevalence of 21% among 19 subjects, Steele et al19 who reported a prevalence of 38% among 29 subjects, and Nery et al18 who reported a prevalence of 43% among 181 subjects. Miranda et al22 evaluated a population from a primary care center and found the prevalence of gingival enlargement to be 33.8% among 65 subjects taking nifedipine and significantly more prevalent than gingival enlargement in a control population. The largest community-based study on nifedipine-influenced gingival enlargement was done on 911 subjects recruited from general medical practices in England, of which 442 were taking nifedipine. The prevalence of nifedipine-influenced gingival overgrowth was 6.3% and significantly greater than a control population and individuals taking amlodipine or diltiazem.22

The prevalence of nifedipine-influenced gingival enlargement has been reported to be higher in males than females in humans22,24-26 and in rat models.27 Among humans, Ellis et al22 reported males were 3.3 times as likely as females to develop gingival enlargement in response to nifedipine than females. Out of 34 cases of nifedipine-influenced gingival enlargement, Barak et al24 reported that 72% of the cases were in males. A relationship between androgen metabolism and nifedipine-influenced gingival enlargement has been proposed as a possible reason for male predominance.28 The evidence of the relationship of age to nifedipine-influenced gingival enlargement is equivocal. Some reports indicate no association with age18,19,22,26 while others indicate that older individuals are more susceptible to gingival enlargement.20

The literature supports that nifedipine is significantly associated with gingival enlargement. Variations in population characteristics across these studies have been associated with the wide range of reported prevalence. Differences in geographic location as well as other demographic variables vary significantly among the published reports on nifedipine-influenced gingival enlargement. Additionally, the use of hospital-based patients, which often have problems with the control of their cardiovascular symptoms and require special monitoring, may not be representative of patients at large taking these medications.23 Further studies will continue to provide more information about the epidemiology of nifedipine-influenced gingival enlargement across various populations.

Nifedipine also seems to interact with cyclosporine, an immunosuppressant which is also associated with gingival enlargement. Nifedipine and cyclosporine are often used together in patients who have undergone renal transplants. The cyclosporine acts as an immunosuppressant to prevent graft rejection while nifedipine controls hypertension in these patients and reduces cyclosporine-induced nephrotoxicity.29,30 The prevalence and severity of drug-influenced gingival enlargement in patients receiving both cyclosporine and nifedipine has been reported to be higher than with the use of cyclosporine alone in rat models31-33 and humans.34-36 Among the human studies, Khoori et al34 reported a prevalence of marked gingival enlargement in 52% of subjects taking both cyclosporine and nifedipine (n=21) compared to 6% in those taking cyclosporine alone (n=98). The severity of gingival enlargement, as measured by a gingival overgrowth index, was also significantly greater in those subjects receiving both medications.34 Thomason et al15 reported 62% of subjects taking cyclosporine and nifedipine (n=63) compared to 25.8% of subjects taking cyclosporine alone (n=31) presented with clinically significant gingival enlargement requiring surgical correction. The severity of gingival enlargement was also greater in subjects on the combined medication regimen. In contrast, in a separate study Thomason et al16 reported no significant difference in prevalence of clinically significant gingival enlargement, defined as >30% of clinical crown covered by gingiva, among subjects taking nifedipine and cyclosporine or cyclosporine alone. Although there was no difference in prevalence, the severity of gingival enlargement was significantly greater in the subjects taking both medications.30 The effect of combined nifedipine and cyclosporine on gingival enlargement is supported by evidence in the literature and future research will continue to evaluate the effect of the combined medication regimen on both prevalence and severity of gingival enlargement.

Data on the prevalence of drug-influenced gingival enlargement is limited for other dihydropyridines. The only other studies concerning dihydropyridine-influenced gingival enlargement prevalence have evaluated amlodipine.22,37 Jørgensen17 determined the prevalence of amlodipine-influenced gingival enlargement to be 3.3% among a population of 150 subjects. All cases of gingival enlargement associated with amlodipine were classified as mild, with no more than one-third of the clinical crown covered by gingiva.37 Although no control population was used in this study, the reported prevalence of amlodipine-influenced gingival enlargement (3.3%) is no different that prevalence of gingival enlargement in control populations from other studies not taking medications associated with gingival enlargement (4.2%).18 Ellis et al22 reported the prevalence of amlodipine-influenced gingival enlargement to be 1.7% among a community-based population including 181 subjects taking amlodipine. The prevalence of gingival enlargement was not significantly different for amlodipine than it was for the control population.22 The limited available evidence indicates that amlodipine-influenced gingival enlargement may not be a significant periodontal concern. Conclusions cannot be drawn regarding other dihydropyridines at this time due to lack of sufficient evidence.
Pathophysiology

The exact pathophysiology and mechanisms of dihydropyridine-influenced gingival enlargement have not yet been identified, although several theories and possible contributing factors have been suggested. Histopathologically, dihydropyridine-influenced gingival enlargement is characterized by epithelial changes including slight to moderate hyperkeratosis, thickening of the spinous layer, and elongated tubular rete pegs (Table 3). Immunohistochemical studies indicate that an abnormal accumulation of type VI collagen molecules is associated with nifedipine-influenced gingival enlargement. In vitro experiments have shown that human gingival fibroblasts from individuals with nifedipine-influenced gingival enlargement show significantly greater proliferation rates, DNA synthesis, collagen synthesis, and epidermal growth factor (EGF) receptors along with decreased collagenase activity. Similar findings are associated with gingival fibroblasts from nicardipine responders. In vitro studies in rats have shown that the excess accumulation of collagen nifedipine-influenced gingival enlargement is more associated with a decrease in collagen degradation due to significant reductions in collagen phagocytosis by gingival fibroblasts rather than by increased collagen production. The mechanisms for increased fibroblast proliferation, increased collagen production, and decreased collagen degradation have been associated with increased expression of or responsiveness to endothelin-1 (ET-1), connective tissue growth factor (CTGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), and decreased expression of cathepsin-L and nitric oxide. A summary of the epithelial pathophysiology is presented in Table 6.

Dysregulation of the immune system and inflammatory response to periodontal bacteria have also been implicated in the pathophysiology of dihydropyridine-influenced gingival enlargement (Table 7). Enlarged gingiva from individuals taking nifedipine has been shown to have significant reductions in number and density of Langerhans cells compared to individuals not taking nifedipine. The reduction of Langerhans cells is hypothesized to modify the inflammatory reaction and tissue homeostasis leading to gingival enlargement. Significant increases in the number of the lymphocytes, mostly B cells, have been reported in the inflammatory infiltrate in gingiva enlarged due to nifedipine therapy. Bullon et al reported ten times greater number of B cells in enlarged gingiva from individuals taking nifedipine compared to gingiva from healthy, non-medicating individuals. The increased number of lymphocytes results in a greater immune response to oral bacteria. Significant reductions in CD4/CD8 cell ratio and increases in CD68-labeled macrophages in enlarged gingiva from individuals taking nifedipine have also been reported.

In addition to changes in numbers of immune and inflammatory cells, qualitative changes have also been reported in the immune and inflammatory responses. Cytokine expression in nifedipine-influenced gingival enlargement has been shown to have a predominate Th1-profile with significant increases in interleukin-2 (IL-2) and interferon-gamma (INF-γ) expression. The predominate expression of Th1 cytokines and presence of gingival overgrowth has been shown to persist even following control of inflammation with non-surgical periodontal therapy, indicating a role of Th1/Th2 cytokine ratio in the pathogenesis of nifedipine-influenced gingival enlargement. A stronger expression of androgen receptors has also been shown by immune cells in nifedipine-influenced enlarged gingiva. The number of T cells expressing androgen receptors also remains high following non-surgical periodontal therapy and is believed to alter the development of T cells and contribute to the predominate Th1 activity. Modellus, a neutrophil elastase-like proteinase, is also up-regulated in enlarged gingiva from rats and humans taking nifedipine. Modellus plays a role in host defense and immune cell regulation and has been implicated in the pathogenesis of nifedipine-influenced gingival enlargement.

While the precise contribution of all these observed changes and proposed mechanisms to dihydropyridine-influenced gingival enlargement is not yet known, the evidence indicates that the pathophysiology is most likely multi-factorial and involves a combination of effects on the epithelium, connective tissue, inflammatory response, and immune system.
Therapy and Evidence-Based Outcomes

Dihydropyridine-influenced gingival enlargement can be treated by a variety of methods and the appropriate therapy may depend on several factors, including the severity of enlargement, the patient’s medical condition, and the patient’s overall periodontal health. First line treatment includes extensive oral hygiene instructions and plaque control. Evidence indicates that the presence and severity of dihydropyridine-influenced gingival enlargement can be related to the amount of gingival inflammation or the amount of plaque present. In vitro studies have shown that human gingival fibroblasts exposed to both nifedipine and interleukin-1β show significant increases in collagen production compared to exposure to either one alone. Additionally, the proliferation rate and DNA synthesis of human gingival fibroblasts is significantly increased in the presence of nifedipine and interleukin-1α compared to nifedipine alone. In a rat model, Morisaki et al demonstrated that nifedipine-influenced gingival enlargement is significantly greater in the presence of gingival inflammation and plaque.

In vivo human studies have presented some equivocal results on the relationship between plaque and inflammation and gingival enlargement. Tavassoli et al reported significantly higher gingival index scores were associated with increased amount of gingival enlargement among 97 patients taking nifedipine. Individuals with no gingival enlargement had a mean gingival index of 1.53 compared to a mean gingival index of 1.97 for those with moderate to marked gingival enlargement (p<0.05). There was no significant association between plaque score and gingival enlargement, however. Bullon et al found a positive association between the amount of enlargement and plaque score in 18 patients taking nifedipine. No significant association was found, however, between the amount of gingival enlargement and bleeding index.

The lack of consistent results regarding the clinical relationship between plaque and inflammation and dihydropyridine-influenced gingival enlargement in humans is also reflected reports regarding treatment of dihydropyridine-influenced gingival enlargement with plaque control and non-surgical periodontal therapy. Hancock and Swan reported significant reductions in gingival enlargement in a 58 year old man who had been taking 60mg of nifedipine for 18 months following scaling and root planing and oral hygiene instruction. Seven weeks after therapy began, probing depths decreased from 7-10mm to 4-5mm. Gingival enlargement had not returned at 18 months following treatment and no changes were made to the patient’s medication regimen. The use of tetracycline fibers in combination scaling and root planing has also been shown to provide significant reductions in gingival enlargement up to 12 months post-treatment of nifedipine-influenced gingival enlargement. Additionally, significant reductions in probing depth and bleeding on probing and significant gains in clinical attachment level were achieved with the use of adjunctive therapy. In contrast to these positive results, several reports have reported no significant reduction in gingival enlargement with plaque control and scaling and root planing alone. The differences in results in these various reports could be explained in part by the amount of emphasis and reinforcement placed on meticulous daily home care and the quality of scaling and root planing. Despite the equivocal results and case reports, thorough non-surgical periodontal therapy may be beneficial in treatment of dihydropyridine-influenced gingival enlargement by providing a reduction in inflammation and improved tissue integrity prior to surgical therapy even without providing significant reductions in the amount of enlargement.

A second treatment option for dihydropyridine-influenced gingival enlargement is discontinuing the causative drug and switching to a different class of medication. A consultation with the patient’s physician and description of the periodontal considerations should be completed prior to recommending any changes to the patient’s medication regimen. Case reports have described regression of gingival enlargement due to dihydropyridines by discontinuing the medication. Regression of gingival enlargement has been reported as soon as 4 weeks following discontinuation of nifedipine in combination with good home care. Morisaki et al reported a significant reduction in gingival enlargement within 2 months of cessation of amlodipine treatment in a 49 year old female. Failure to control hypertension led to the patient’s physician re-prescribing amlodipine with subsequent recurrence of gingival enlargement. Benefit has also been shown from switching nifedipine to isradipine, a dihydropyridine not associated with gingival enlargement. Following eight weeks of isradipine treatment, 60% of subjects exhibited a decrease in gingival enlargement while 66% of subjects remaining on nifedipine demonstrated an increase in gingival enlargement. Isradipine-treated subjects had a mean decrease of 0.59mm in probing depth at eight weeks and 0.74mm at twelve weeks.

If plaque control, non-surgical therapy, and discontinuing the causative drug are ineffective or not recommended, surgical therapy may be needed for correction of dihydropyridine-influenced gingival enlargement. Surgical treatment has been shown to be effective in treatment of dihydropyridine-influenced gingival enlargement. Mild cases of gingival enlargement may be treated conservatively by gingivoplasty but more severe cases require use of gingivectomy. The most significant concern in treating these cases is likely the stability of post-surgical results and prevention of recurrence of overgrowth. While some reports indicate that success of surgical treatment requires the medication to be discontinued or replaced, stability of post-surgical results has been reported up to one year post-operatively even with continuation of the patient’s nifedipine regimen.
Patient compliance can influence stability of post-surgical results. Ilgenli et al. evaluated recurrence of nifedipine-influenced gingival enlargement over 18 months in 16 patients treated with a periodontal flap technique. Seven of the patients (43%) experienced recurrence of severe gingival enlargement 18 months following surgical treatment. Individuals experiencing recurrence of gingival enlargement were of a significantly younger age, demonstrated more severe gingival inflammation, and attended recall appointments less frequently. These results demonstrate the importance of good oral hygiene and regular professional maintenance in preventing recurrence of gingival enlargement following surgical correction. Stability of post-surgical results can also differ based on the method of surgical therapy. Pilloni et al. evaluated ten patients demonstrating nifedipine and cyclosporine A-influenced gingival enlargement up to one year following surgical treatment by with either gingivectomy or periodontal flap. Significantly shallower probing depths were maintained in the periodontal flap group (mean PD=3.22mm) compared to the gingivectomy group (mean PD=6.40mm) one year post treatment. Pocket reduction achieved by periodontal flap was sustained for a longer period of time and may reduce the need for recurrence. The available evidence indicates that surgical treatment of dihydropyridine-influenced gingival enlargement can be successful with or without cessation of the causative drug but has increased stability with a periodontal flap surgical technique and optimal patient oral hygiene and compliance with maintenance.

Conclusions

Dihydropyridine-influenced gingival enlargement represents a significant periodontal problem. Education of patients, as well as physicians, is important in the recognition and management of this condition. With the continual development and introduction of new medications, it is possible that the prevalence of dihydropyridine-influenced gingival enlargement may be reduced in the future with discovery of novel cardiovascular medications. Presently, however, nifedipine remains to be an efficacious medication in the management of various cardiovascular conditions. The multi-factorial nature of this condition will continue to present a challenge to oral health care professionals and optimal oral hygiene and patient compliance will continue to be paramount in patient management. Future research may help to clarify the exact mechanism and pathophysiology of dihydropyridine-influenced gingival enlargement which could lead to improved preventative and therapeutic options.

References

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### Table 1
Calcium Channel Blocker Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Generic Name</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dihydropyridines</td>
<td>Diltiazem</td>
<td>Cardizem, Dilacor, Calan, Isoptin, Verelan</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Calan, Isoptin, Verelan</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>Amlodipine</td>
<td>Norvasc</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Plendil</td>
</tr>
<tr>
<td></td>
<td>Isradipine</td>
<td>DynaCirc</td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td>Cardene</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>Adalat, Procardia</td>
</tr>
<tr>
<td></td>
<td>Nimodipine</td>
<td>Nimotop</td>
</tr>
<tr>
<td></td>
<td>Nislodipine</td>
<td>Nisocor, Sular</td>
</tr>
<tr>
<td></td>
<td>Nitrendipine</td>
<td>Baypress</td>
</tr>
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</table>

### Table 2
Prevalence of Nifedipine-Influenced Gingival Enlargement

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study Population</th>
<th># of Subjects taking Nifedipine</th>
<th>Mean Age (years)</th>
<th>Prevalence of gingival enlargement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barak et al, 1987</td>
<td>Israel; dental school patients</td>
<td>34</td>
<td>63</td>
<td>14.7%</td>
</tr>
<tr>
<td>Fattore et al, 1991</td>
<td>Chicago, IL; VA medical center patients</td>
<td>23</td>
<td>62</td>
<td>83%</td>
</tr>
<tr>
<td>Barclay et al, 1992</td>
<td>England; hospital patients</td>
<td>19</td>
<td>55</td>
<td>21%</td>
</tr>
<tr>
<td>Steele et al, 1994</td>
<td>Madison, WI; VA medical center patients</td>
<td>29</td>
<td>63</td>
<td>38%</td>
</tr>
<tr>
<td>Nery et al, 1998</td>
<td>Milwaukee, WI; VA medical center patients</td>
<td>181</td>
<td>65</td>
<td>43.6%</td>
</tr>
<tr>
<td>Ellis et al, 1999</td>
<td>England; community based population</td>
<td>442</td>
<td>64</td>
<td>6.3%</td>
</tr>
<tr>
<td>Miranda et al, 2001</td>
<td>Spain; community based population</td>
<td>65</td>
<td>61.5</td>
<td>33.8%</td>
</tr>
</tbody>
</table>

### Table 3
Epithelial Histopathology in Dihydropyridine-influenced Gingival Enlargement

- Slight to moderate hyperkeratosis
- Thickening of spinous layer/Acanthosis
- Elongated tubular rete pegs

Continued on Page 21
### Table 4
Epithelial Pathophysiology in Dihydropyridine-influenced Gingival Enlargement

<table>
<thead>
<tr>
<th>Physiologic Alteration</th>
<th>Possible Mechanisms</th>
</tr>
</thead>
</table>
| Increased epithelial cell mitosis | - Increased expression of p53 protein by epithelial cells in nifedipine-treated rats and humans  
- p53 protein over-expression leads to increased cell proliferation |
|                        | - Increased keratinocyte growth factor (KGF) gene expression and secretion by human gingival fibroblasts  
- KGF mediates mesenchymal-epithelial interactions and increases epithelial cell proliferation |
| Decreased epithelial cell apoptosis | - Increased expression of bcl-2 protein by epithelial cells in nifedipine-treated rats  
- bcl-2 protein over-expression suppresses epithelial cell apoptosis |

### Table 5
Connective Tissue Histopathology in Dihydropyridine-influenced Gingival Enlargement

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| Increased quantity of collagen bundles | Increased number of capillaries  
Increased vasodilation of capillaries  
Presence of perivascular inflammation  
Fibroblast proliferation  
Increased fibroblast secretory granules |
### Table 6
Connective Tissue Pathophysiology in Dihydropyridine-influenced Gingival Enlargement

<table>
<thead>
<tr>
<th>Physiologic Alteration</th>
<th>Possible Mechanisms</th>
</tr>
</thead>
</table>
| Increased fibroblast proliferation | - Increased expression of Endothelin-1 (ET-1) and Endothelin-1 receptors by human gingival fibroblasts in response to nifedipine  
- ET-1 increases fibroblast proliferation  
- Increased basic Fibroblast Growth Factor (bFGF) production by human gingival fibroblasts from nifedipine responders  
- bFGF increases fibroblast proliferation  
- Increased progression of cell cycle of human gingival fibroblasts from nifedipine responders in response to bFGF  
- Increase production of cyclins and cyclin-dependent kinases (CDKs) by human gingival fibroblasts from nifedipine responders in response to bFGF  
- Cyclins and CDKs upregulate fibroblast proliferation  
- Increased production of Connective Tissue Growth Factor (CTGF) by human gingiva from nifedipine responders  
- CTGF increases fibroblast proliferation  
- Decreased production of Nitric Oxide (NO) in combination with nifedipine administration in rats results in significant increases in gingival enlargement  
- Decreased NO is associated with increased expression of Epidermal Growth Factor and increased fibroblast proliferation  
- Increased Transforming Growth Factor-β (TGF-β) production by human gingival fibroblasts from nifedipine responders  
- TGF-β increases fibroblast proliferation |
| Increased collagen production | - Increased production of Connective Tissue Growth Factor (CTGF) from human gingiva from nifedipine responders  
- CTGF increases collagen production  
- Increased Transforming Growth Factor-β (TGF-β) production by human gingival fibroblasts from nifedipine responders  
- TGF-β increases collagen production |
| Decreased collagen degradation | - Decreased expression of Cathepsin-L activity and mRNA by murine gingival fibroblasts from nifedipine responders  
- Decreased activity and production of Cathepsin-L (a lysosomal cysteine protease) decreases digestion of proteins and leads to excess accumulation of extracellular matrix |

### Table 7
Inflammatory and Immune System Pathophysiology in Dihydropyridine-influenced Gingival Enlargement

| Decreased number and density of Langerhans cells  
| Increased number of B lymphocytes  
| Decreased CD4/CD8 cell ratio  
| Increased number of CD68 labeled macrophages  
| Increased Th1 cytokine profile expression (IL-2, INF-γ)  
| Increased expression of androgen receptors by T cells  
| Increased medullasin-positive cells in epithelium |
OSU Periodontal Alumnus Profile

Dr. Robert (Bob) Ferris

In each issue of The Cutting Edge, we will be devoting a section of the newsletter to highlight an OSU Periodontology alumnus. In this issue of The Cutting Edge, we are highlighting the distinguished career of Dr. Robert (Bob) Ferris.

Dr. Ferris received his DDS from Emory University in 1961. He received his Certificate in Periodontics and MS from Ohio State in 1964 and went on to complete his PhD at Ohio State in 1967. He was chairman of the Department of Periodontics at Case Western Reserve University from 1968 to 1971 and has been teaching Periodontology at the University of Florida College of Dentistry since 1976, where he is a currently a Clinical Professor of periodontics. Dr. Ferris has been in private practice limited to Periodontics in Altamonte Springs, Florida since 1971.

Dr. Ferris’ long career has included extensive public service in dentistry at local, state, regional and national levels. Highlights include President of the Florida Dental Association (1998-1999), President of the Florida Society of Periodontists (1986), President of the Southern Academy of Periodontology (1989), and President of the American Association of Dental Examiners (1991-1992). He has been a member of the American Dental Association Council of Dental Education and the Commission on Dental Accreditation. In 2006 he was first Vice President of the ADA.

Dr. Ferris has many accomplishments in the American Academy of Periodontology. He was President of the American Academy of Periodontology (1997), and Chairman and Director of the American Board of Periodontology (1998-2004). He has been active on many levels in the AAP including the Executive Council (1986-1989) and the Board of Trustees (1989-1992).

Continued on Page 24
Dr. Ferris has received numerous awards in recognition of his service. They include Dentist of the Year-Florida (1982, 1990) and The F. Leon Schwartz Lifetime Service Award, Florida (2001). He was inducted as a fellow of The American College of Dentists (1981), The International College of Dentists (1982) and The Pierre Fauchard Academy (1983).

Most notably, Dr. Ferris has received many prestigious awards given by the American Academy of Periodontology. He was a recipient of the AAP Special Citation Award (1987 and 1993) the AAP Presidential Award 2001, the AAP Gold Medal Award (2003), and is a Fellow of the American Academy of Periodontology.

In addition to Bob’s accomplishments in organized dentistry, he has also been active in civic organizations, serving as President of the Maitland-South Seminole Chamber of Commerce (1978) the Greater Seminole Chamber of Commerce (1982) and the Rotary Club of Seminole County South.

On the personal side, Bob’s daughter, Leah received a PhD in Educational Psychology and has a practice in Learning Disabilities in the Atlanta area. She has 2 children, Grace and Elise. Dr. Ferris’ son, Bob, received an MD and PhD from Johns Hopkins, and currently is Chief of Head & Neck Oncology/Surgery in the Otolaryngology Department at the University of Pittsburgh Medical School. He has 2 daughters, Rachel and Anna, and a new grandson, Adam Robert.

In addition to Dr. Ferris’ professional accomplishments, he has business interests in apartment houses, a convenience store chain, shopping centers, and has started three banks. His leisure activities include golf, downhill skiing and spending time at his places in New Smyrna Beach, Fl. and Summer Harbor, Maine.

All the faculty members in the Section of Periodontology at Ohio State and graduates of our program congratulate Dr. Ferris on his many accomplishments during his long and dedicated career.

Dr. Ferris provided us with a personal memory about Ohio State.

“The remarkable opportunities that were made available to me at OSU are still most impressive. Fresh out of 2 years in the US Navy Dental Corps, very little in savings, and Dr. John R. Wilson rescued me. As Chairman of Periodontics, he put me on an NIH Teaching Fellowship, which paid tuition and a stipend while I completed the M.Sc. in Periodontology. As Dean of the College of Dentistry, he encouraged me to go on for the Ph.D. in Microbiology/Immunology with Dr. Matt Dodd, and he made that possible with an NIH Research Fellowship, which also covered tuition, stipend and lab and dissertation expenses. Dr. Charles Conroy was directing the graduate program in Periodontics, and he arranged with Dr. Morgan Allison, Chair of the Department of Oral Surgery (as it was called at that time), for me to be a dental/oral surgery intern at University Hospital in my second perio year and my first immunology year. This gave me 6 months of general anesthesia training that was incredible.

So in my 4 years in Columbus, I was able to do the internship, the Master’s in Perio and the PhD with Dr. Dodd. Yes, it took a lot of work, but I cannot imagine any other place in the country that would have or could have made so many educational and training opportunities available to a willing student. My gratitude to Drs. Wilson, Conroy, Allison and Dodd can never be adequate for the career which they helped me to enjoy.”
Dr. Mariotti speaks out against periodontal disease!

Dr. Claman receiving the 2006 Outstanding Periodontal Educator award.
Dr. Mariotti addresses the alumni and students at the Buckeye Reception in San Diego.

Drs. Emecen, Leblebicioglu, Claman with Drs. Pao-Ying (Paul) Lin and Jen-Tai (Jeremy) Chen.

Residents at the reception.
Enjoying the beautiful city of San Diego!

Dr. Tatakis and his 2007 graduating residents: Drs. Burrell, Chou, Khoury and Wessel.

At lunch across from the beautiful convention center.
Traditional Thanksgiving dinner at Dr.Claman’s, November 2006

At dinner with the Claman family.

Picture time: “smile please!”

The famous Claman turkey!

“That was a great meal!”
Section Christmas party at Dr. Mariotti’s, December 2006

Residents with Dr. and Mrs. Mariotti.

Drs. Silva, Burrell, Stilley, Chang, with Ms. Linda Hallberg-Henson and Dr. Claman.

Merry Christmas! Our first years: Drs. Ho, Salas, Papapostolou and Kelsey.

Happy faces go with great spreads!
Honor Roll of Giving

Gifts to the Section of Periodontology can be conferred to the following funds:

Endowed Chair for Periodontology: To help ensure the long-term health and stability of the Section of Periodontology at the OSU College of Dentistry, alumni and friends of the section have established a Campaign to raise $1.5 million to create an Endowed Chair in Periodontology. For the section to not only retain outstanding faculty, but to also recruit new faculty to fill the open positions today and in the future, it must distinguish itself even further from the other periodontal programs across the country. One of the best ways to do this is through the establishment of an endowed chair. For more information on what an endowed chair is and does or to talk about your interest in supporting this campaign, please contact Jim Mahony, Director of Development and Alumni Affairs, at (614) 292-1780.

The George R. App Periodontal Endowment Fund: Interest from the Endowment is used to support graduate student education and development with special interest in providing funds for travel to meetings by Ohio State University periodontal graduate students.

Periodontal Research and Training Fund: This fund is used to support a wide variety of periodontal activities by the Section of Periodontology in the College of Dentistry. More specifically this fund is used for but not limited to the purchase equipment for the graduate program, support of alumni activities (e.g. the annual AAP Buckeye Reception, CE courses, mailings, etc.), endowment of graduate research projects, purchase of food for graduate student activities, etc.

Center for Research in Periodontology: Periodontal research in the Section of Periodontology involves both basic science and clinical science research projects.

Donors to the Periodontal Endowed Chair

Donations and Pledges ($25,000 and up):
- Dr. Ronald and Mrs. Marcia Garvey
- Dr. Joseph and Mrs. Melanie Koberlein
- Dr. Winfield and Mrs. Jayne Meek
- Dr. James and Mrs. Patricia Palermo
- Dr. Fred and Mrs. Jody Sakamoto
- Dr. R. Jeffrey and Mrs. Diana Stephens

Donations and Pledges ($2,500-$4,999) Project Advantage
- Dr. Barry and Mrs. Denise Blank
- Dr. Laurie McCauley

Donations and Pledges (up to $500)
- Dr. Charles and Mrs. Doris Solt

Total Pledges and Gifts: $206,750
Goal: $1,500,000
Balance: $1,293,250

For more information, please do not hesitate to contact our development office at 614-366-1393 or visit our website at http://dent.osu.edu/alumni/support.php.
THE VOLPE PRIZE recognizes the best clinical research in periodontology by periodontal residents in accredited post-graduate programs in Canada, Mexico, and the U.S. Finalists were selected to make oral presentations at The Ohio State University in Columbus on May 4, 2007. The winner of the Volpe Prize will receive $3,500 and a certificate of recognition.

The twelve finalists who will make oral presentations for the Volpe Prize in Columbus are: Drs. Jeffrey Burke (Univ. of Illinois, Chicago), Ryan Clagett (Univ. of Louisville), Robert Durand (University of Minnesota), Isabel Gay (Univ. of Alabama at Birmingham), Daniel Engler-Hamm (Tufts University), Cathy Hsu (Univ. of Washington), Giuseppe Intini (University of Buffalo), Jill Rogers (University of Michigan), Christopher van Kesteren (UTHSCSA), Jeffrey Wessel (The Ohio State University), Danny Wong (Univ. of Texas Health Science Center) and Jing Zhou (Indiana University).

Volpe Presentation Schedule for Friday, May 4, 2007:

8:15 – 8:30 AM: Blackwell Hotel
Welcome by Dr. Volpe
8:30 – 11:30AM: Blackwell Hotel
6 presentations by candidates
11:30 – 1:00PM: Blackwell Hotel
Lunch
1:00 – 4:00PM: Blackwell Hotel
6 presentations by candidates
4:30 – 5:30PM: Postle Hall
Tour of OSU College of Dentistry (optional)

Periodontal Research Day/Graduate Dinner
June 8, 2007

Please join us for the Periodontal Research Day and Graduate Dinner (Perio Prom). The Research Day will be held in the Medical Heritage Center. The speaker announcement, registration form and Perio Prom location will be mailed in the near future.

The Program Agenda:

8:30 – 9:00 Registration
9:00 – 12:00 Resident Research Presentations
12:00 – 1:00 Lunch Break (provided)
1:00 – 4:00 Lecture

(CE Credit: 6 hours)
Upcoming Events

March 8-10th, 2007   Academy of Osseointegration, San Antonio TX
March 21-24th, 2007   American Association of Dental Research, New Orleans LA
May 4th, 2007   Volpe Prize, Columbus, OH
June 8th, 2007   OSU Periodontal Research Day and Perio Prom, Columbus, OH
October 27-30th, 2007   American Academy of Periodontology, Washington, DC

It’s Noteworthy

*The Cutting Edge* is available electronically! If you would like to receive it by email, please email us at [osugradperio@osu.edu](mailto:osugradperio@osu.edu) and let us know where you would like it delivered. It can also be accessed on the web:

We encourage all alumni of our program to visit The Section of Periodontology on the OSU College of Dentistry Website. The website has been recently updated and is very detailed.

1. The web address of the college is [http://dent.osu.edu](http://dent.osu.edu)
2. Click on Academic sections
3. Click on Periodontology and you will be on Periodontal Homepage

You can then navigate to the Section of Periodontology’s History, Faculty, Staff, Predoctoral Program, Postdoctoral Program, Research, Service, Continuing Education, Alumni, Patients and the upcoming Volpe competition.

To access current or past cutting edge issues:
1. Click on alumni
2. Click on The Cutting Edge
3. Click on any issue to open or download

The direct Web address for the Cutting Edge is: [http://dent.osu.edu/perio/alumni_the_cutting_edge.php](http://dent.osu.edu/perio/alumni_the_cutting_edge.php)
College of Dentistry
Section of Periodontology
Postle Hall
305 West 12th Avenue – Room #4129
Columbus, Ohio 43210
Meter: 21550-011000-61801-10000 E4A11