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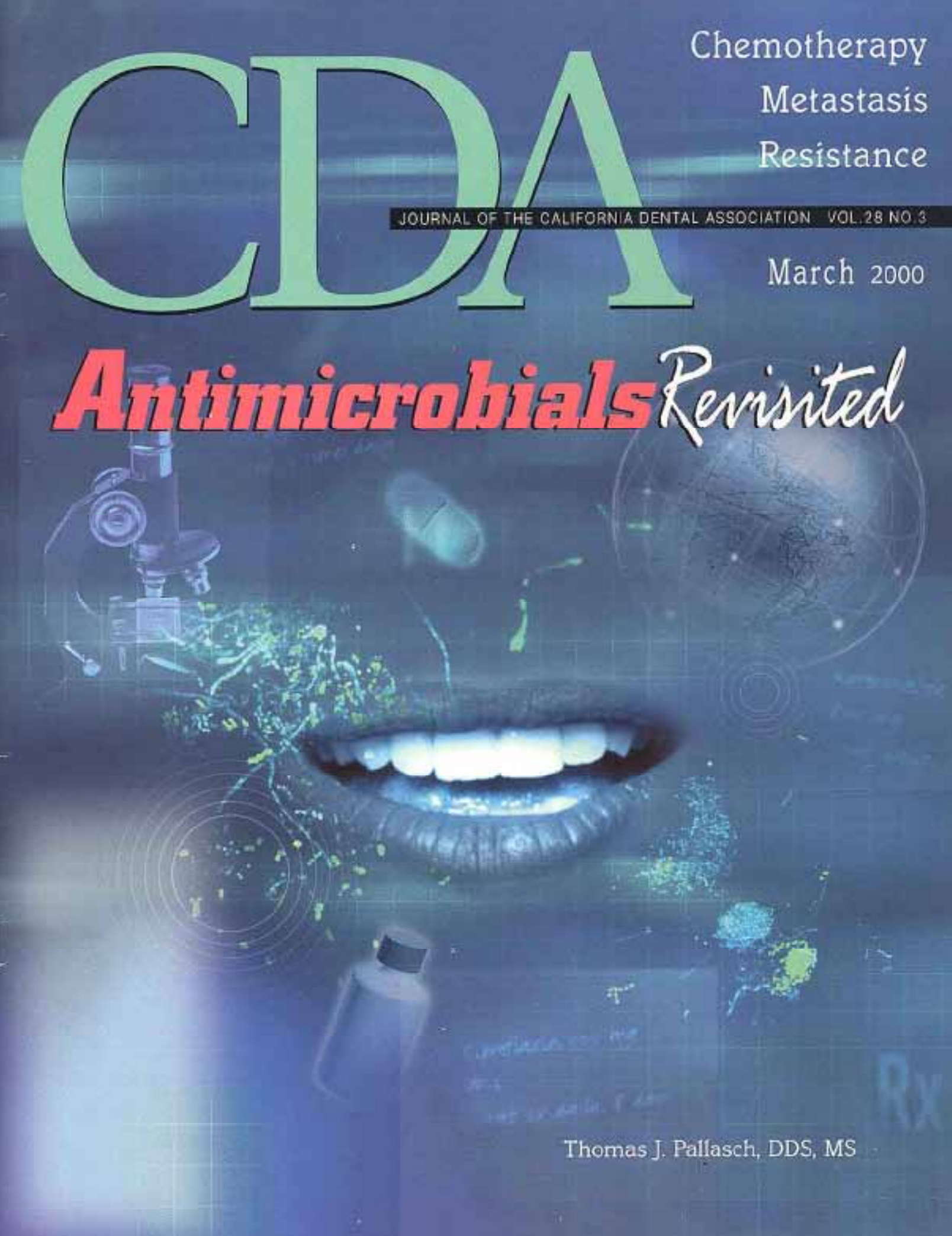
Antimicrobials Revisited



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Letting Go

Jack F. Conley, DDS

From the perspective of many longtime members of organized dentistry, its tripartite membership structure has always been the glue that holds dental professionals together. However, in the past decade, the market share and percentage of the active profession that holds continuous membership has declined. Dentistry is unique among professional organizations in that the tripartite has helped organized dentistry to build unified support from a majority of professional colleagues. However, in view of changing demographics in recent years, there has been increasing concern that membership may continue to decline unless new answers can be found to make organized dentistry more relevant and more attractive.

Traditionally, the local, state, and national associations that form the tripartite have provided what have been considered to be the needs and wants of the membership via the democratic process. That process utilizes the collective decision-making of committees, boards, and Houses of Delegates. One of the problems we have seen with this process is that leadership and staff energies are directed in a proactive manner to develop needed programs or policies or to defend against a new challenge from outside. They are left with little time to analyze, modify, or eliminate existing policies and services that might have outlived their usefulness. With changing times and demographics, the types of needs and wants that once fulfilled the expectations of most members may no longer dominate the wish list of the current membership. If out-of-date programs remain in place without modification or removal, they contribute unnecessarily to the cost of association operation. Combined with the cost of new programs approved by members, they add to a high total dues bill that either discourages renewals or is unattractive to nonmembers.

However, for members and nonmembers alike, we see some positive changes on the horizon that should make membership more relevant to the average dentist. Change will start with leadership. Evidence of the changes that can be expected from the California Dental Association depend to a significant degree on the changes in new leadership detailed in this space several months ago. Recently, the year 2000 Executive Committee and the senior staff of CDA held meetings to assess the issues and directions of the association for the coming year. Similar meetings have been held annually in recent years. However, this year, the tenor of the discussions and the conclusions adopted for further discussion by association committees and decision-making bodies was exciting and far-reaching.

As American Dental Association Editor Lawrence Meskin observed in his recent JADA editorial on building the ADA membership base, the thinking has to be "outside the box." The creative thinking on the planning done by CDA leadership was definitely outside the box. They displayed a commitment to supporting President Kent Farnsworth's theme of "Foundation for the Future."

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Traditional philosophies and policies were not protected from critical analysis. Changes that would improve the function of the organization and provide programs or benefits attractive to nonmembers or wavering members were central to the discussions. Some of the planning would require significant change in how CDA relates to its membership at the local level and is not without risk. But, risk-taking is essential in any effort to improve the relevance and function of an organization.

Perhaps it is because of the realization that we now reside in a new century that a strong spirit for change is evolving. However, it will depend upon a leadership and an association staff that have committed themselves to effecting necessary changes that will lead to a more vital and desirable membership-driven organization. We believe the commitment to change is genuine. However, it will take time for boards and individual leaders at the local and state level to approve the changes that will be at the heart of continuing discussions in the coming months.

It will also take time for members to accept and adapt to change. One of the characteristics of individual business owners such as dentists is that we find it difficult to move away from the comfort of a long-term policy or philosophy. That is a significant part of our message regarding organizational change, namely, "letting go." We must be willing to let go of traditional programs or policies that no longer are beneficial to the majority. We must be willing to accept and support change that will enable organized dentistry to become stronger in numbers and to demonstrate relevance to all segments of the membership.

Successful advocacy in matters of legislation and regulation has been one of the greatest achievements of organized dentistry. Individual members often do not understand nor appreciate how much is regularly accomplished on their behalf by staff and volunteers of their organizations at all levels. That activity must continue and, in many cases, expand. New programs and philosophies that are relevant to dentists of every ethnicity and at every age level must receive fair consideration.

Given such a scenario, it is impossible to adopt new programs and a new attitude without giving something up. To add new programs with a heavy price tag will not appeal to long-time members or to new members, particularly those carrying a heavy educational debt load. Thus, there will be an absolute necessity to let go of some long-held philosophies and programs if we are to progress.

It will not be easy. It will take creative thinking and sacrifice at all levels of leadership and membership for organized dentistry to move forward successfully. For now, the possibilities have already excited a few. It is anticipated that the process of change will become exciting to all segments of the membership as the goals and preliminary plans achieve support and approval.

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Bug Hunt May Turn up Keys to Periodontal Disease

By David G. Jones

Mostly good bugs, they abound on our teeth and gums to help the digestive process and help fend off less-kindly bugs that can produce periodontal and systemic disease.

Investigation during the past 20 years has identified hundreds of oral microbes. Now, researchers at Stanford University Medical Center have joined in the search for more elusive microbes in an effort to close in on an eventual cure for periodontal disease.

"Our data suggest that a significant proportion of the resident human bacterial flora remain poorly characterized, even within this well-studied and familiar microbial environment," says David Relman, MD, assistant professor of medicine and of microbiology and immunology at the Stanford Medical Center.

Relman, along with lead author Ian Kroes, MD, and Paul W. Lepp, PhD, published their study in the Dec. 7 issue of the Proceedings of the National Academy of Sciences.

The Stanford study looked at one 39-year-old male, studying his dental plaque sample in two ways, using the traditional culture method and the newer molecular technique. Researchers prepared DNA directly from the plaque and studied each genetic sequence that had a bacterial signature. When the results were compared, they found that the DNA-based molecular technique found 31 never-before-seen bacteria, and the culture method found six more new microbes.

Lepp says that the study sought to establish a baseline of the normal oral bacteria flora.

"We need to characterize a lot more information before we can determine if what we found produces any diseases," he said. "But to better characterize those bacteriological communities, we've taken what amounts to a first step to find out what is there to start with."

The next step, according to Lepp, is to investigate oral disease cases to better determine the prevalence of the bacteria in a larger-scale study. The Stanford research team is collaborating with Gary C. Armitage, DDS, MS, chair of periodontology at the UCSF School of Dentistry. He is clinically characterizing the periodontal disease in patients and collecting samples. Relman's team then applies the molecular technique to describe the sample's microbial diversity.

"If you don't know what's causing the infection, you can't target a therapy," Armitage says. "So it's a hunt for potential pathogens. These specific targets will allow specific therapies to be targeted against them."

Similar work is also under way on the East Coast. Floyd Dewhirst, DDS, PhD, head of the Department of Molecular Genetics at Boston's Forsyth Institute, the nation's oldest nonprofit dental research organization, is studying organisms that may be involved in periodontal disease. Dewhirst's study includes a larger number of patients than Relman's.

"What Dr. Relman's and my groups agree on is: Of the easy-to-cultivate bugs we've already picked up, there are maybe a dozen bad guys responsible for periodontal disease," says Dewhirst, a 1973 graduate of the UCSF School of Dentistry.

Dewhirst, Relman, and Armitage assume that about 50 percent of total oral bacterial flora are unknown, so it is likely that the yet-undiscovered group will include more pathogens.

"Once we make associations through clinical studies by looking at the bugs with DNA probes, we can begin to identify these other difficult or impossible-to-cultivate bugs and develop therapies to eliminate them," Dewhirst says.

An example of how molecular research can result in improved periodontal health can be found in relationship to a particularly bad pathogen, Porphyromonas gingivalis. Dewhirst says the bug is principally responsible for periodontal disease. In collaboration with the Institute for Genomic Research in Rockville, MD, Dewhirst's group is determining its entire genome, a step toward developing a specifically targeted therapy to kill it.

"We've determined all 2.4 million bases of its DNA, and we're now in the process of identifying and writing up the 2,000 genes in the organism, describing each," he says. "Later this year, we hope to have the manuscript ready describing this organism."

Dewhirst says that a good analogy for what is now happening in periodontal research can be found in the changing view of stomach ulcer treatment.

"For many years, people thought ulcers were from stress and poor diet," Dewhirst says. "When the bacteriological link was finally discovered, patients could be cured with antibiotics, so it completely changed how ulcers are treated. Periodontal disease is now treated by scaling, root planing, surgery, and supplemental antibiotics. As we understand more about the organisms that are involved in the disease, hopefully we can come up with some very specific therapies to eliminate the particularly virulent ones."

According to Dewhirst, periodontal research is headed in a direction characterized by his and Relman's studies, and research yet to come.

"We're looking at what organisms are present; and, given that, we're finding the best ways to eliminate the bad ones."

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Live Long(er), and Prosper

By the close of 2001, humankind will realize numerous scientific and medical phenomena that will revolutionize the delivery of health care in the next five years. As a result, the human lifespan will lengthen and the quality of life will improve.

Those predictions were part of the discussion at the Seventh International Congress on Anti-Aging Medicine and Biomedical Technologies, hosted by the American Academy of Anti-Aging Medicine in Chicago in December.

According to academy President Ronald M. Klatz, MD, DO, the next two years hold enormous promise for the realization of boundless youth and vitality. Among his predictions:

- Fleets of miniature robotic warriors will fend off disease on a cellular level, collect information to diagnose cellular functions, and deliver site- and time-specific medications to target tissues.
- Baldness will be beaten. With laboratory-based hair cloning already a success in human test subjects, genetic therapies that will eliminate male pattern baldness are soon to become widely available to the general public.
- Alzheimer's disease will be halted. Genetic therapies, including manipulation of the predisposing Apolipoprotein-E factor, will become available to battle this disease.
- Age-related vision loss will be counteracted by implanted biochips that will stimulate tissue growth to slow or reverse macular degeneration as well as stimulate the visual center of the brain to create artificial or enhanced sight.
- Spinal cord injury will be reversed. Based on new research from the University of California, it is anticipated that implantable biochips and nerve growth factors that stimulate repair and regrowth of nerve tissue will be a reality.

Fees for Service

Dental Economics has released the results of its latest dental fee survey. Following is a list of sample fees drawn from the 1999 report. For the full results, see the December 1999 issue of Dental Economics.

National Median of Select Dental Fees

Code	Procedure	Median Fee
00150	Comprehensive exam	$35.34
00210	X-rays (complete)	71.92
01110	Adult prophylaxis	49.63
02140	One-surface amalgam	63.25
03330	Molar root canal	550.33

Crafting an Image Is Another Key To Practice Success

By Dell Richards

Many professionals think that as long as their work is good, their image doesn't matter.

But it does, and creating, presenting, and maintaining a positive image can go a long way toward ensuring a positive perception of a professional enterprise -- including a dental practice.

Image is not a concern reserved for a select few. Increased media savvy makes skillful presentation of one's practice a key ingredient in competing successfully. And, although they are corporate giants, companies such as Coca-Cola and IBM offer time-honored lessons about how to build an image -- lessons that comfortably apply to small businesses such as dental practices.

Coca Cola is a modern-day icon not just because of design and longevity, but because the whole package -- from the theme of the advertising to the color of the logo and the shape of the original bottle -- works together to present one image.

It will benefit dentists to objectively assess their offices, stationery, logos, dress and mannerisms to determine what they convey to prospective patients. The message being received might be surprising.

Here are a few ways to think about image:

Be color-wise. Colors have an enormous impact on people's responses. When it comes to color, no one can beat IBM.

IBM has used a particular blue for so long that it has become known as "IBM blue." The color is widely used by other entities because the rich blue projects authority, trustworthiness, and dependability -- attributes IBM wants associated with its products.

Coca-Cola's fire-engine red is a polar opposite. It creates a sense of excitement, energy, and activity -- all in line with Coke's desired product image.

Colors convey specific characteristics, and care should be exercised when choosing colors with which to associate an enterprise. Cool colors such as dark green and blue tend to be more classical and traditional, and they present few negative connotations. Warmer colors such as red, orange, and yellow have positive associations such as liveliness, but they also can be associated with anger, loudness, even jaundice, and should be used sparingly.

Pure primary tones should be avoided. Instead, more muted tones with gray added to enhance subtlety are more effective.

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Be sophisticated. Because of its superb design, the Coca-Cola logo is practically timeless, reflecting excellent use of graphic art. As with Coke, dentists should find a good logo and image and stick with them, not change them every few years.

A design conveying simple elegance usually is more expensive than one featuring down-home appeal. Dentists should be mindful of that when searching for a designer. Graphic -- or interior -- design is an important investment, and a professional should not skimp in these areas.

Similarly, written materials should be top quality. High grades of paper should be used for brochures, stationery, and other hard-copy consumer communications.

Watch out for clutter. A brown box full of brochures stored on an open shelf or a pile of papers on a desk can be forgotten and become part of the furniture.

Disorganization spells lack of attention to detail. While new patients may not be conscious of the disarray, a messy office will have a negative impact on their impression of the dentist.

Non-essential material should be removed; and, in the waiting room, magazines relevant to health and dentistry should be featured. For children, fun material with dental themes are available.

Nothing should get in the way of the sophisticated image a dentist wants to present.

Be consistent. Coca-Cola's advertising may change year to year, but the theme -- good times, basically -- does not. That consistency creates the feeling of certainty and stability, a necessary quality for any product or service. Everything that is associated with a practice should send one message.

The design, colors, and material of the logo, stationery, brochures, advertising, office decor, and uniforms should closely relate and project a consistent image. Conscious management of creation and maintenance of an image helps ensure that patients are receiving the messages that the sender intends.

Dell Richards is the owner of Dell Richards Publicity in Sacramento, Calif.

Honors

Teran Gall, DDS, CDA's director of Special Projects, has been elected to the Board of Directors of the American Society for Geriatric Dentistry. He will be inducted as a fellow in that organization later this spring.

Steven E. Schonfeld, DDS, PhD, chair of CDA's Council on Education and Professional Relations, has been appointed to the Professional and Technical Advisory Committee of the Joint Commission on Accreditation of Healthcare Organizations.

Dudley Glick, DDS, will be inducted this month into the Hall of Fame of the University of Southern California School of Dentistry. He is the director of endodontics in the general practice residency program at Cedars-Sinai Medical Center in Los Angeles.

Protection Gets in Your Face

Full-face shields are significantly better than half shields at protecting against dental and facial injuries in hockey players. Despite speculation to the contrary, they do not increase the risk of concussions, neck injuries, or other injuries, according to an article in the Dec. 22/29 issue of the Journal of the American Medical Association.

A team from the University of Calgary in Alberta studied risks for head or neck injuries when full-face and half-face shields are used by intercollegiate hockey players. A half shield is a clear plastic visor that is attached to a helmet and extends to the tip of a player's nose. A full-face shield extends to the bottom of a player's chin and covers the entire face.

The research team, led by Brian W. Benson, MSc, and Willem H. Meeuwisse, MD, PhD, conducted the study during the 1997-1998 Canadian Inter-University Athletics Union hockey season. The study subjects were 642 male hockey players (mean age 22 years) from 22 teams. Athletes from 11 teams wore full-face shields, and athletes from 11 teams wore half-face shields during play. From the first practice of the season, team therapists used standardized weekly exposure sheets to record the level of individual participation (full, partial, or none) and the type of face shield worn for every practice and game throughout the season. If a player sustained an injury that met the reportable injury definition, team therapists, physicians, or both were required to complete an injury report form.

"Although we found a significant difference in rates of head and facial injuries between the two groups, there was no significant difference in risk of sustaining a concussion, neck, or other injury for athletes wearing half shields compared with those wearing full-face shields," the authors write. The finding that seven of the 11 athletes who suffered dental injuries in the half-shield group were wearing mouth guards at the time of injury suggests that use of such protective equipment in combination with half shields is not enough to offer protection from those injuries.

The authors recommend that sports governing bodies at the intercollegiate level of competition should seriously consider mandating full facial protective equipment for all participants under their jurisdiction.

"Ice hockey associations from Canada and the United States have introduced head and neck risk management strategies, the most significant being the mandatory use of full facial protection for athletes across many different age groups and levels of play," the authors write.

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Web Watch: Fluoridation

With fluoridation in the news, patients may be asking their dentists for information to help them separate fact from fiction. The following Web sites explain the benefits of water fluoridation.

http://www.ada.org/public/topics/fluoride/fluoride.html
The ADA's main index of fluoride information.

http://www.www.nidr.nih.gov/fluoride.htm
The story of fluoridation from the National Institute of Dental and Craniofacial Research.

http://www.cdc.gov/nccdphp/oh/flintro.htm
The surgeon general's statement on community water fluoridation and other general fluoride information.

http://fluoride.oralhealth.org
The Web site for the National Center for Fluoridation Policy and Research.

A listing here does not constitute endorsement by the California Dental Association. As is the case with all web sites, content is subject to frequent change.

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Microbial Chemotherapy, Resistance, and Metastasis

THOMAS J. PALLASCH, DDS, MS

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"The great tragedy of science: The slaying of a beautiful hypothesis by an ugly fact."
-- Thomas Henry Huxley

Judging from the lay media, programmed dental conferences, and selective readings of the scientific literature, it would appear that a new age of dentistry is upon us: We will now treat caries, pulpal disorders, periodontal diseases, and possibly even occlusions not only for the basic pathology they present but to prevent or ameliorate coronary heart disease and infant preterm births. We will possibly no longer treat periodontal disease mechanically but will have a plethora of chemicals to manage this disorder that presently demands dedicated faculty teaching skills and avid practitioners to control its progress. Surely heaven has blessed us with the resurgence of the focal infection theory of diseases with the mouth as once again its central character. No more voids in the appointment books.

Until now, the proponents of these hypotheses have held the field of play. This is so because of the time required to review and critically analyze all of the past and current studies that either support or negate these proposals, prepare them in an objective scientific manner, and pursue the long process of manuscript preparation, peer review, manuscript revision, and eventual publication. Now this process has been completed, and another side of the story can be told.

The focus of this issue of the Journal is to address three central themes: the role of antimicrobials in the management of periodontal disease, the influence that the world epidemic of microbial resistance to antibiotics may have on our clinical judgment as to when and how antimicrobials should be employed in dentistry, and what factual evidence is extant to justify the return of the focal infection theory of disease. As corollaries to these themes, information is presented regarding the influence of antimicrobial misuse in our daily personal lives; how we may gain critical judgment in determining the veracity of claims of epidemiological "associations" or "causations" that may

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affect patient care or our personal health decisions; and, not insignificantly, the medicolegal dangers inherent in promoting the oral cavity as a source of systemic disease.

To these ends, Drs. Michael Jorgensen and Jørgen Slots have prepared an expert discussion of the role of antimicrobials in periodontal therapy with a clearly formulated decision tree as a clinical blueprint for patient periodontal management. Dr. Slots has also added his expertise in the evaluation of both the medical and dental studies on the role of microorganisms in the etiology of cardiovascular disease. Dr. Michael Wahl is virtually unique in that he has published several papers in medical journals on dental metastatic infections. These efforts have substantially altered the attitudes of our medical colleagues regarding just how often dental professionals are truly responsible for metastatic infections. Dr. Wahl's experience in this regard and his fascination with 19th century dental literature aided greatly in the analysis of the theory of the focal infection of disease. Finally a concise guide to the evaluation of epidemiological studies was deemed appropriate.

Some may disagree with our interpretations of the literature, our personal insights, and ultimate conclusions. This is everyone's prerogative as the essence of science is open discussion, re-evaluation of opinions, and presentations of new hypotheses as our data and insight increase. However, it is hoped that such dissent is reasoned and based upon facts and not hopes. The authors collectively researched more than 3,000 journal papers to gain our conclusions, with a fifth or so listed as references. Hopefully, this type of effort will form the basis for future discussions.

The authors wish to thank the information sources that were so valuable to us, including the library resources of the American Dental Association and the University of Southern California School of Dentistry, and in particular Ms. Sylvia Flores at USC who was unfailingly cheerful and professional in gathering the printed word, particularly from more than a century ago.

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Responsible Use of Antimicrobials in Periodontics

Michael G. Jorgensen, DDS, and Jørgen Slots, DDS, DMD, PhD, MS, MBA

ABSTRACT New products and treatment modalities for the management of periodontal disease continue to offer the clinician a large number of choices, many of which involve antimicrobials. Specific pathogenic bacteria play a central role in the etiology and pathogenesis of destructive periodontal disease. Under suitable conditions, periodontal pathogens colonize the subgingival environment and are incorporated into a tenacious biofilm. Successful prevention and treatment of periodontitis is contingent upon effective control of the periodontopathic bacteria. This is accomplished by professional treatment of diseased periodontal sites and patient-performed plaque control. Attention to community factors, such as water contamination and bacterial transmission among family members, facilitates preventive measures and early treatment for the entire family. Subgingival mechanical debridement, with or without surgery, constitutes the basic means of disrupting the subgingival biofilm and controlling pathogens. Appropriate antimicrobial agents that can be administered systemically (antibiotics) or via local delivery (povidone-iodine) may enhance eradication or marked suppression of subgingival pathogens. Microbiological testing may aid the clinician in the selection of the most effective antimicrobial agent or combination of agents. Understanding the benefits and limitations of antibiotics and antiseptics will optimize their usefulness in combating periodontal infections.

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During the past few years, a number of new commercial products have become available for use in treating periodontal disease. Media attention has generated interest in these products from patients; and, as often occurs with new treatment modalities, the practitioner's enthusiasm and desire to offer the latest technology has to be restrained by sound clinical judgement. Oversimplification of potential product benefits and failure to achieve a proper periodontal diagnosis can easily lead to inappropriate treatment. While short-term improvement in periodontal status is a desirable initial outcome, ideal therapy must result in long-term maintenance of the dentition in a state of health, comfort, function, and esthetics. To accomplish these goals in managing destructive periodontal disease, it is necessary to utilize a multifaceted antimicrobial approach that will not only temporarily reduce periodontal pathogens, but also prevent these organisms from returning to levels that may initiate further disease activity. Current periodontal therapy employs mechanical debridement ranging from plaque removal to scaling to root planing to surgical procedures and may include antibiotics and antiseptics. The purpose of this article is to review available scientific evidence that will facilitate successful, predictable

integration of antimicrobials into the management of periodontal disease, thereby enhancing long-term treatment outcomes.

Etiology

While it has not been possible to completely satisfy Koch's postulates to show a causal relationship between specific bacterial species and periodontal disease, it is generally accepted that the primary etiology is bacterial plaque. The composition of dental plaque varies considerably among patients and among sites in the same patient. Whereas nonspecific plaque accumulations are associated with gingival inflammation, a limited number of specific pathogens have been identified that are associated with loss of connective tissue attachment and alveolar bone. The 1996 World Workshop of the American Academy of Periodontology assigned etiologic significance to periodontal bacteria. Important pathogens in periodontitis are Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, and Bacteroides forsythus. Organisms of probable periodontopathic significance include Prevotella intermedia, Campylobacter rectus, Peptostreptococcus micros, Fusobacterium species, Eubacterium species, Treponema species, and perhaps various enteric rods.1 The same microbial pathogens have been implicated in peri-implantitis, and many principles for treating periodontitis are applicable for treatment of implants failing due to infectious complications. Recent findings have also associated some herpesviruses (cytomegalovirus and Epstein-Barr virus type 1) with destructive periodontal disease.[2] Just as the microbiota associated with gingivitis is different from that of periodontitis, different forms of periodontitis show variations in the pathogens colonizing periodontal pockets. Slowly progressing chronic adult periodontitis is unlikely to exhibit high levels of A. actinomycetemcomitans or P. gingivalis, whereas these pathogens are frequently recovered from patients with early-onset periodontitis and refractory adult periodontitis. As our knowledge of the microorganisms involved in the pathogenesis of periodontal disease increases, we are able to more effectively incorporate antimicrobial therapy as part of our armamentarium for optimum treatment. In developing an enlightened approach to periodontal treatment for the 21st century, it is necessary to consider the continuum of infectious disease management that ranges from the society to the family to the individual mouth to sites within the mouth.

Controlling Exogenous Sources

Disease prevention is preferable to development of pathologic changes and subsequent treatment. Since many periodontal pathogens are not inherently endogenous oral flora, it is possible to take steps to prevent initial colonization. In many parts of the world, contamination of drinking water and food is a source of periodontal enteric rod infection.[3] As community sanitation standards improve, the incidence of infectious diseases, including periodontal disease, should be reduced. Transmission of periodontal pathogens between spouses (kissing), and from parents to children (caring, playing) has been reported.[4,5] While periodontal pathogens thrive in inflamed periodontal pockets, they also reside on the tongue and mucosal surfaces and in saliva. Saliva serves as the vehicle for bacterial transmission among family members. P. gingivalis is less likely to be transmitted from parent to child than A. actinomycetemcomitans, whereas both of these pathogens are transmitted with a frequency of 25 percent to 33 percent between spouses. Children of parents with A. actinomycetemcomitans periodontal infections should be screened microbiologically to ensure early detection and eradication of pathogenic periodontal infections.

For disease to develop, bacterial transmission must be followed by colonization, which requires a susceptible host and a suitable local microenvironment. Gingival inflammation and associated outflow of nutrient-rich gingival crevicular fluid create an environment favoring colonization of periodontal pathogens. Recent evidence strongly suggests that herpesvirus infection of the periodontium facilitates the subgingival colonization and overgrowth of P. gingivalis and other periodontal pathogens.[6] Since herpesviruses enter periodontal sites via infected inflammatory cells, including monocytes/macrophages, T-cells, and B-cells, influx of herpesviruses to gingiva will be markedly reduced by controlling gingivitis. By reducing salivary levels of periodontal pathogens and thereby the risk of person-to-person transmission and by reducing the degree of gingival inflammation, the incidence of destructive periodontal disease will decrease.

Initial Disinfection

Antimicrobial treatment is not only the use of pharmacologic agents, but also mechanical disruption of bacterial colonies. Reduction of salivary levels of periodontal pathogens can be accomplished by bacterial plaque removal on teeth and the dorsum of the tongue. Patients should be instructed in thorough brushing and flossing of teeth, perhaps also in tongue cleaning and the occasional prescription of an antimicrobial mouthrinse such as chlorhexidine. In addition, dental professionals must reduce periodontal pathogens by scaling and root planing, use of antimicrobial agents, and possibly surgical pocket reduction. Pathogenic organisms that thrive in a deep subgingival environment will proliferate less effectively in a shallow, noninflamed gingival sulcus. Thus, reduction of the depth of diseased periodontal pockets by surgical or nonsurgical means is important for establishing a periodontal microbiota compatible with health.

Patient-Performed Plaque Control

Chronic gingivitis can be reduced or eliminated in most patients with effective daily plaque control. By allowing patients to see the positive results of their home care, many individuals will be motivated to continue. Periodontitis-susceptible patients must perform diligent supragingival plaque control daily to avoid initiation or recurrence of disease activity. While conventional brushing may be effective for some individuals, several studies have shown advantages to electric toothbrushes, both in children and adults.[7,8] Not only is plaque removal more effective with the electric devices, but the incidence of gingival abrasion is also reduced.[7] Dental floss and/or interdental brushes provide access to interproximal areas, and for most patients these additional steps are necessary to accomplish effective plaque removal. Dentifrices containing triclosan/copolymers have been evaluated in clinical trials and seen to enhance reduction of supragingival plaque and gingivitis.[9] Recently, however, concerns have been raised about potential multidrug resistance developing in Escherichia coli and Pseudomonas aeruginosa species, present in the mouths of some patients, due to widespread use of triclosan.[10] Mouthrinses, such as chlorhexidine, should be considered adjunctive means of supragingival plaque control and are generally used in selected situations for a limited time. Supragingival plaque control can significantly delay colonization of subgingival pathogens.[11] Effective supragingival plaque control may even reduce levels of existing subgingival periodontal pathogens.[12,13] Patients must understand that effective daily plaque control is essential for control of periodontal disease, regardless of which treatment modality the dentist has employed.

Subgingival Instrumentation

Patients with chronic gingivitis who have not experienced periodontal attachment loss may have deposits on teeth that cannot be removed by brushing and flossing. These plaque-promoting factors must be removed by scaling and polishing to permit effective plaque control. In patients with periodontitis, attachment loss has occurred and the root surfaces are involved. Scaling and root planing is the foundation of procedures designed to transform a diseased subgingival environment into one compatible with health. Calculus and necrotic cementum are removed, and the biofilm formed by subgingival organisms is disrupted. As periodontal probing depth increases, the effectiveness of scaling and root planing decreases; improved subgingival bacterial removal may be achieved by utilizing antiseptics delivered by commercial irrigators or possibly by using modified thin tip ultrasonic scalers.[14,15] Surgical procedures can improve access in sites with deep probing depths and where roots present elusive anatomic features, such as flutings, grooves, concavities, and furcations (**Figure 1**). As discussed above, pocket reduction has the potential to alter the periodontal microbiota to one consistent with health as well as discourage recolonization of pathogenic microorganisms.16 In advanced periodontitis, including cases where bacteria have invaded tissues of the periodontium, microbiological culturing to identify specific pathogens followed by administration of appropriate systemic antibiotics will greatly assist in managing the infection.[17]

Systemic Antibiotics in Periodontal Therapy

Antibiotics include naturally occurring or synthetic organic substances that inhibit or destroy selective microorganisms, usually at low concentrations. A position paper by the American Academy of Periodontology discusses indications and choice of antibiotic regimens in periodontal disease treatment.[18] Briefly, systemic antibiotics can be of significant value for treatment of certain types of severe

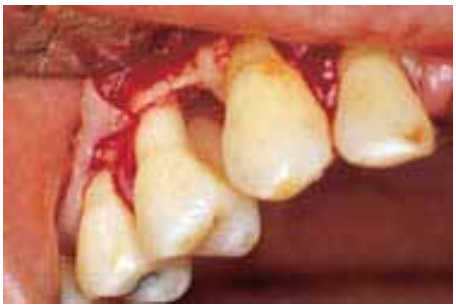
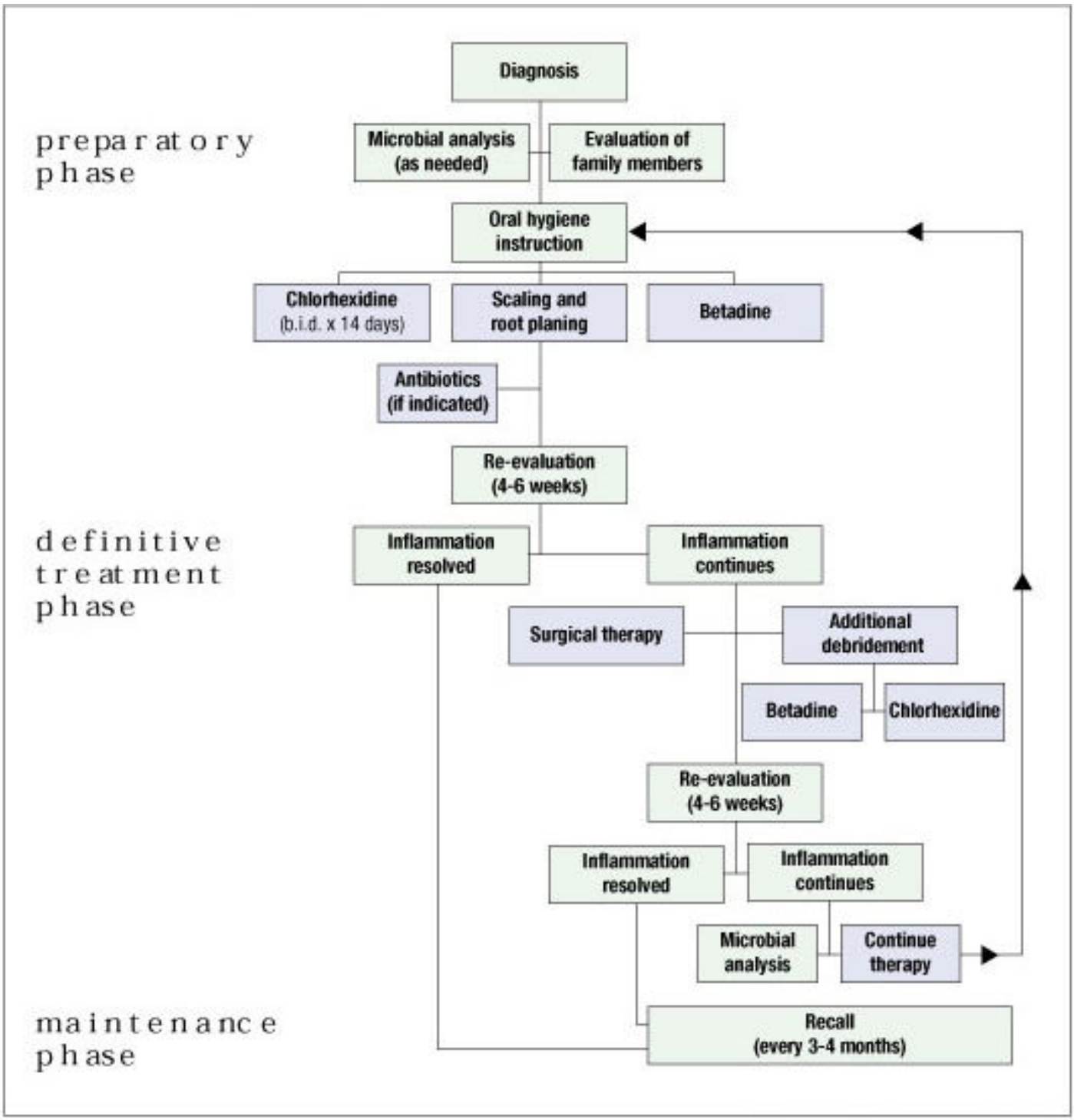


Figure 1. A deep concavity is seen on the mesial aspect of the maxillary first premolar. Surgical access facilitates debridement of the root surface.

periodontitis and refractory periodontitis, for peri-implantitis, for acute periodontal infections with systemic manifestations, and for medical indications such as endocarditis prophylaxis. Patients who are immunocompromised or suffering from diabetes mellitus may also warrant consideration for adjunctive systemic antibiotic therapy.[19] Otherwise, the majority of patients with chronic adult periodontitis can be successfully treated with conventional mechanical therapy alone, including surgical procedures when indicated. Adverse consequences of antibiotic administration include toxicity, allergic-hypersensitivity reactions, interaction with other medications, development of resistance, superinfection with resistant pathogens, and colonization by opportunistic pathogens.20 When needed, systemic antibiotics in periodontal treatment are selected based on the microbial composition of the pathogenic microbiota and the patient's medical status and current medications. Antibiotics commonly used in periodontics, either singly or in combination, include metronidazole, amoxicillin, clindamycin, and ciprofloxacin. When metronidazole is prescribed, the patient must be instructed to avoid consuming alcohol; consideration must also be given to possible potentiation of anticoagulant medication. Clindamycin has been associated with ulcerative colitis but not following the relatively short-term administration

Figure 2. Periodontal therapy utilizing antimicrobials.



generally used in periodontal treatment. Ciprofloxacin has been shown to disrupt cartilaginous growth in laboratory animals and therefore may not be a suitable choice for children or teenagers. Tetracyclines were previously prescribed for localized juvenile periodontitis and other types of advanced periodontal disease but tend now to be replaced by more-effective combination antibiotic therapies.[17]

Advantages and disadvantages of employing antimicrobial drugs in combination instead of a single drug must always be considered. Combination drug therapy is frequently warranted in mixed periodontal infections involving multiple pathogens with different antimicrobial susceptibility. Each drug is aimed at one or several important pathogenic microorganisms. Also, combination drug therapy can delay the emergence of microbial mutants resistant to one drug by using a second noncross-reacting drug. Moreover, the simultaneous use of two drugs can achieve bactericidal synergism, allowing significant reduction in dose or shorter course of therapy and thus avoiding toxicity while still providing satisfactory antimicrobial action. For example, amoxicillin-metronidazole combination drug therapy acts synergistically against A. actinomycetemcomitans. Disadvantages of using combination drug therapy include greater risk for adverse drug reactions or for patients to become sensitized to drugs. Antagonism may take place by combining a bacteriostatic drug (e.g., tetracycline or chloramphenicol) and a bactericidal drug (e.g., penicillin, metronidazole, or quinolones). Also, combination therapy with broad-spectrum antibiotics may promote superinfection with resistant organisms. Careful consideration of the risks vs. benefits should precede all use of antibiotics. Microbiological evaluation can help dentists select the optimal antibiotic therapy for individual periodontitis patients.

Locally Delivered Antibiotics

Local delivery of antimicrobial agents allows the use of concentrations up to 100 times higher than when systemic routes of administration are employed.[21] For a local antibiotic to be effective and clinically useful, it must be delivered to the base of the pocket at microbiologically efficacious concentrations and sustain those concentrations long enough to suppress the targeted organisms.[22] Because of the rapid flow of gingival crevicular fluid, antimicrobials placed subgingivally must be either rapidly bactericidal within five minutes of application or be retained and slowly released in the periodontal pocket by a controlled drug delivery device. Vehicles that have been employed for sustained delivery in periodontics include pastes, ointments, gels, fibers, strips, spheres, discs, and chips. Tetracycline, minocycline, doxycycline, and metronidazole have been used in sustained drug delivery devices. Most local drug delivery systems have been evaluated as adjunctive treatment to scaling and root planing, and some additional benefits have been reported for some delivery systems, though most studies are relatively short-term in nature. Locally delivered antibiotics have little or no effect on A. actinomycetemcomitans and other periodontal pathogens invading gingival connective tissue. While some studies have shown limited benefits of subgingival antimicrobials used without concomitant periodontal debridement, periodontal therapy based solely on sustained drug delivery devices is not advocated at this time.[23]

Antiseptics

Antiseptics are employed extensively in hospitals and other health care settings, and constitute an important aspect of periodontal therapy. Biguanides (chlorhexidine) and halogen-releasing agents (iodone [iodophors] and chlorine [household bleach] compounds) are examples of antiseptics used in periodontal therapy.

Chlorhexidine is probably the most widely used antiseptic product in dentistry. Chlorhexidine exhibits broad-spectrum efficacy, substantivity to tooth surfaces and mucosa, low toxicity, and dental-plaque-inhibiting properties. However, the antimicrobial activity of chlorhexidine is markedly reduced in the presence of organic matter.[24] The relatively low concentration of proteins in saliva permits chlorhexidine to exert considerable antimicrobial activity in most of the oral cavity; however, because of high protein content of the serum-derived gingival crevicular fluid, chlorhexidine shows diminished activity when applied in inflamed periodontal pockets. Also, because of relatively slow bactericidal activity, chlorhexidine has to be retained in subgingival sites by a support device. Clinical studies have revealed little or no benefit from subgingival chlorhexidine irrigation.[25-27] Controlled subgingival delivery of chlorhexidine has recently been introduced to dentists in the United States; short-term benefits seem limited, and long-term data on safety and efficacy are not yet available.[28]

Iodine exhibits rapid antimicrobial action, even at low concentrations. Swift killing of bacteria allows for direct application of iodine in subgingival sites. Problems associated with irritation and excessive staining have been overcome by the development of iodophors. The most widely used iodophore in dentistry is povidone-iodine (Betadine [Moore Medical Corp., New Britain, Conn.] or generic equivalent). Betadine contains approximately 10 percent povidone-iodine and 1 percent free iodine. Patients who report sensitivity to iodine should not be treated with Betadine, although the sensitization rate of povidone-iodine is very low,[29] and inadvertent administration to most iodine-allergic individuals will cause only minor, transient irritation. Betadine should be used with caution during pregnancy and lactation due to the possibility of inducing transient

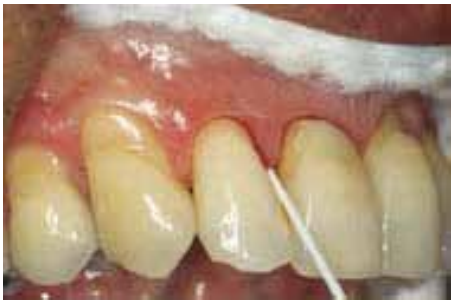


Figure 3. Antimicrobial sampling: After removal of supragingival plaque and isolation of the sample site, a sterile paper point is inserted to the depth of the periodontal pocket. After 10 to 15 seconds, the paper point is removed and immediately placed in the anaerobic transport medium provided by the microbiology laboratory. The vial is labeled and shipped to the laboratory, and in 10 to 12 days the results are returned to the practitioner.

hypothyroidism in newborns.[30] Rosling and co-workers revealed improved clinical healing after subgingival Betadine application by either a syringe or an ultrasonic scaler.15 As more dental units are converted to closed-water systems to comply with waterline decontamination standards, the use of irrigants such as povidone-iodine during ultrasonic scaling will become increasingly more practical. Manufacturers' recommendations must always be considered prior to introducing any solution into the waterlines.

Clinical Guidelines

Figure 2 illustrates a practical approach to integrating antimicrobial therapy into the course of treatment of periodontal disease. A complete and accurate periodontal diagnosis is essential to ensure that appropriate treatment is instituted. Microbiological testing for subgingival pathogens may be required for concise periodontal diagnosis and to facilitate further treatment strategies (**Figure 3**). After removal of supragingival plaque, the microbial sampling area is isolated with a cotton roll. Thin endodontic paper points are then inserted to the depth of the pocket for 10 to 15 seconds, removed and placed into an anaerobic transport medium and promptly sent to a laboratory capable of identifying and quantifying periodontal pathogens. If a specific periodontal infection is discovered, screening and possible treatment of family members is indicated. In addition, oral hygiene instruction should be performed and continually reinforced.

Supragingival and subgingival plaque are in many important aspects similar to biofilms on a variety of solid surfaces. Compared to microbes in planktonic growth, biofilm microorganisms demonstrate notably diminished susceptibility to antibiotics or antiseptics due to reduced growth rates and reduced access of antimicrobial agents to cells within the biofilm. Production of neutralizing compounds, chemical interaction between an antimicrobial agent and biofilm components, and genetic exchange between cells in a biofilm may also account for decreased sensitivity of microorganisms within a biofilm. Therefore, the importance of mechanically breaking up dental biofilms prior to application of antimicrobial agents cannot be overemphasized. While debridement of deep periodontal pockets is essential, due to the phenomenon known as "critical probing depth," subgingival scaling and root planing should not be performed in sites that probe 3 mm or less, as this is likely to traumatize the periodontium and cause permanent attachment loss.[31] During appointments for mechanical debridement, contributing factors for periodontal disease must also be addressed; these include poorly contoured restorations, overhanging margins, open contacts, occlusal disharmony, and endodontic pathology. Because smoking is associated with increased severity of periodontal disease as well as poorer healing response after treatment, patients who smoke must be encouraged to pursue smoking cessation.

Reduction of periodontal pathogens can be markedly enhanced by locally delivered antiseptics, such as chlorhexidine for supragingival areas and povidone-iodine or chlorine for subgingival sites. Patients might benefit from rinsing with 10 to 15 ml of 0.12 percent chlorhexidine solution for 30 seconds twice daily for 14 days. A frequent side effect of chlorhexidine is dark staining of teeth and restorations, particularly in smokers and coffee or tea drinkers; patients should be cautioned about this and assured that the stain is generally easily removed by professional tooth polishing. However, chlorhexidine staining that penetrates into marginal defects of tooth-colored restorations can cause irrevocable discoloration. Patients using commercial irrigating devices at home may add one teaspoon of chlorine bleach to the water reservoir, creating a 0.05 percent solution of sodium hypochlorite. The concentration of chlorine may be reduced somewhat for patients who find the taste objectionable. Iodine solution for use with ultrasonic scaling is prepared by mixing one part Betadine with nine parts water; even less water may be used at the clinician's discretion. Iodine solution for subgingival application by means of an irrigating syringe equipped with a thin cannula may consist of equal parts of Betadine and water (**Figure 4**). The Betadine solution should fill up and remain in the periodontal pockets for at least five to 10 minutes. Prior placement of retraction cord or repeated subgingival application may help retain the Betadine in the periodontal pocket.

For specific infections, including juvenile periodontitis and rapidly progressive periodontitis, systemic antibiotic therapy, guided by microbiological testing, should strongly be considered. Single-agent antibiotic therapy in periodontics includes metronidazole (250 to 500 mg, three times a day for eight days) and ciprofloxacin (500 mg, two times a day for eight days)(adult dosage). Common combination therapy in periodontics includes metronidazole and amoxicillin

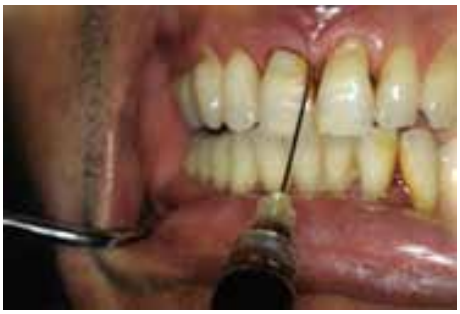
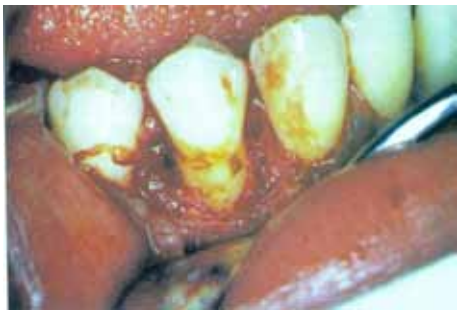


Figure 4. Subgingival irrigation: To enhance the reduction of periodontal pathogens, a solution of equal parts Betadine and water is introduced into the periodontal pocket and allowed to remain for five to 10 minutes.



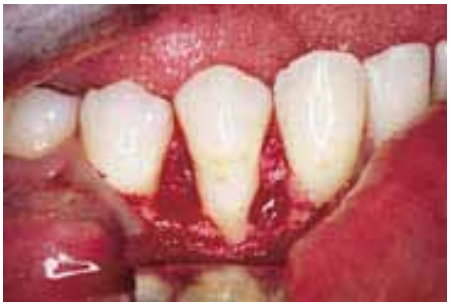


Figure 5. Reflection of a surgical flap revealed residual subgingival calculus (left) that was then removed by mechanical debridement (right).

(250 mg each, three times a day for eight days), and metronidazole and ciprofloxacin (500 mg each, two times a day for eight days). Patients who are allergic to penicillin and amoxicillin may be prescribed clindamycin (300 mg, two times a day for eight days). Systemic antibiotic therapy begins immediately following completion of mechanical debridement. If scaling and root planing is performed at multiple appointments, as is often the case, administration of systemic antibiotics begins after the final appointment.

Four to six weeks following completion of scaling and root planing, the periodontal condition is re-evaluated. Optimal healing is associated with decreased edema of gingival tissue and reduction of bleeding. Shrinkage of gingival tissues may reveal residual calculus, which then must be removed. If clinical signs of inflammation, including bleeding upon probing, have resolved, then the patient may enter the maintenance phase of treatment. If signs of inflammation persist, then it is necessary to continue definitive therapy. Effective subgingival debridement in deep periodontal pockets often requires surgical access (**Figure 5**), and in general, periodontal surgery resulting in pocket elimination is more effective in combating periodontal pathogens than are procedures that allow residual deep probing depths to remain.[32] Following surgical procedures patients may rinse with 0.12 percent chlorhexidine solution twice daily until effective daily mechanical plaque control is possible, generally in one to two weeks. In most cases additional debridement, frequently with surgical access, will accomplish a reduction in periodontal pathogens to levels compatible with health. Periodontal conditions are again evaluated in four to six weeks, and if inflammation has resolved, the patient enters the maintenance phase. If inflammation still persists, then additional definitive therapy is required. If the patient is performing reasonably effective daily plaque control and the clinician has accomplished thorough debridement, then the case may be considered refractory to conventional therapy. In managing refractory periodontitis, microbial analysis is strongly recommended to assist the clinician in selecting an appropriate antimicrobial regimen to be used in conjunction with additional debridement procedures.

Once periodontal pathogens have been eradicated or reduced to levels compatible with health, it is necessary to monitor and control their recolonization to prevent recurrence of disease. While each patient should receive an individually designed recall program, intervals of three to four months are generally appropriate. At recall appointments, evaluation of and renewed instruction in oral hygiene procedures are performed. To ensure continued low levels of periodontal pathogens, patients may rinse twice daily with chlorhexidine for eight to 14 days, and the clinician may repeat subgingival irrigation with iodine solution (equal parts Betadine and water) for five to 10 minutes. In case of recurrent disease activity, which may be characterized by repeated episodes of bleeding upon probing or progressive loss of clinical attachment, more-definitive treatment must be instituted. By following the sequence of therapy illustrated here, a practical, effective and scientifically based approach to periodontal treatment can be pursued.

Summary

A multifaceted yet straightforward approach is presented for the management of destructive periodontal disease. While in the past antimicrobial therapy in periodontics was predominantly mechanical in nature,

today both mechanical and pharmacologic approaches are available. By considering bacterial specificity in periodontitis and the various therapeutic modalities available to identify and suppress or eradicate periodontal pathogens, a scientifically based treatment plan will emerge. Mechanical debridement remains the first line of defense against bacterial plaque, and a suitable maintenance program is the key to long-term success. Antibiotics are best administered systemically and should be prescribed based upon microbial analysis and thorough patient evaluation. Antiseptics may be employed as mouthrinses or irrigants or delivered locally via sustained-release vehicles. Attention to community factors, such as water contamination and bacterial transmission among family members, facilitates preventive measures for the entire family. By appreciating the advantages as well as the limitations of antibiotics and antiseptics, the dental professional can optimize the usefulness of antimicrobial agents in combating periodontal disease.

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The Focal Infection Theory: Appraisal and Reappraisal

THOMAS J. PALLASCH, DDS, MS, AND MICHAEL J. WAHL, DDS

ABSTRACT This paper discusses the past, present, and future of the focal infection theory of disease. A focal infection is a localized or general infection caused by the dissemination of microorganisms or toxic products from a focus of infection. The resurgence of the focal infection theory of disease has been greeted with great enthusiasm in some quarters; however, the present evidence for the relationship of oral microorganisms and systemic disease is very limited due not only to a dearth of prospective studies and a complete lack of interventional studies but also to very significant methodological difficulties associated with the clinical studies that have been performed.

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Ideas rarely disappear completely, and so the focal infection theory of disease is now making a comeback after most applications of it were disproved by the emerging science of the 1930s and 1940s. It has been kept alive all these years by the American legal tort system as health care practitioners and dentists in particular are still blamed routinely for virtually any infection in the body that can be remotely associated with a distant putative source such as the oral cavity. Others may now envision focal infection as a means to convince patients that extensive dental treatment is required to "prevent" coronary artery disease or other maladies "caused" by dentally induced bacteremias or to give dentistry greater medical significance by linking oral microorganisms with systemic disease causation. It goes unappreciated that dental treatment could just as easily be considered the "cause" of patient systemic disease placing dentists in legal jeopardy.

It is timely to review the history of the focal infection theory of disease in the context of modern health care. Scientific methods have improved such that we can revisit this concept with greater acumen and the realization that this moment in time differs from the past in that we are now much more under the scrutiny of the legal profession for good or ill. Our hypotheses must now be more rigorously tested before public media dissemination, and we must scrupulously avoid the common practice of presenting doctrine without data. Otherwise, we will face an avalanche of ill-conceived lawsuits and risk having our scientific credibility

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further eroded in the public eye.

A focus of infection has been variously described but probably best as a circumscribed and confined area that:

- Contains pathogenic microorganisms;
- Can occur anywhere in the body; and
- Usually causes no clinical manifestations.[1]

A focal infection is a localized or general infection caused by the dissemination of microorganisms or toxic products from a focus of infection.1 Some of its harshest critics have euphemistically described a focus of infection as: "anything that is readily accessible to surgery."[2]

Foci of infection have typically been said to arise from the tonsils, oral cavity, or sinuses, but also from the prostate, appendix, bladder, gall bladder, and kidney with pyorrhea alveolaris (periodontitis), alveolar abscesses, and pulpless teeth (treated or untreated) being the principal oral culprits and the viridans group streptococci as the prime microbial pathogens.[1,3,4] Focal infections ascribed to foci of infection include: arthritis, neuritis, myalgia, nephritis, osteomyelitis, endocarditis, brain abscess, skin abscess, pneumonia, asthma, anemia, indigestion, gastritis, pancreatitis, colitis, diabetes, emphysema, goiter, thyroiditis, Hodgkin's disease, obscure fever (fever of unknown origin), and nervous diseases "of all kinds."[1,3-5] The pathways for the dissemination of infection are by direct spread or by blood or lymphatic metastasis of the infecting organisms, their toxic products, or tissue immunologic reactions to the organisms or their products.[6]

The application of the focal infection theory eventually fell from scientific favor for many reasons including the:

- Improvement in dental care;
- Advent of antibiotics;
- Small percent of "cures";
- Inability of science to prove the value of the theory;
- Eventual unfavorable reaction to the "orgy"of dental extractions and tonsillectomies;
- Inability to replicate the experiments of its advocates;
- Occasional exacerbation of the disease by the removal of the focus; and
- Lack of controlled clinical studies.[7,8]

This introduction to the focal infection of disease should not be construed to mean that the theory has no basis in fact. There is little doubt that under certain circumstances microorganisms can move from one area of the body to another to establish their customary pathology in another locale. It would be untenable to think otherwise. Bacteria metastasize to the heart, brain, kidney, liver, joints, gastrointestinal tract, and skin from other areas of the body, including the mouth. The key questions are how often does this occur and is there any reasonable and prudent way to prevent such metastasis with an acceptable risk-benefit ratio in this era of microbial resistance to antibiotics.

The ensuing discussion of the history of the focal infection theory of disease is important because many of its present advocates appear to be unfamiliar with its history, fail to distinguish between acute and chronic infections (confusing endocarditis with the purported oral bacterial causation of chronic heart disease, two vastly different pathologies), do not expose current theories to the rigorous scientific scrutiny and methodologies currently available, commit the same mistakes as earlier investigators regarding extrapolation beyond the data, and appear unaware of the medicolegal consequences of unfounded theories. Let us know the past so as not to repeat it.

The Past

The idea that removing a focus of infection could prevent or cure systemic diseases goes back to ancient times, as Hippocrates is said to have reported the cure of arthritis after removal of a tooth.[9] In the early 1800s, Benjamin Rush, an American physician and signer of the Declaration of Independence, is said to have observed the cure of a case of arthritis of the hip by tooth extraction.[9] The Americans were much behind the Europeans in the acceptance of the germ theory of disease, and American science virtually disappeared in the 1850s only to see a major resurgence with Koch's demonstration of the causation of tuberculosis by Mycobacterium tuberculosis in the early 1880s.[10] Shortly thereafter, bacteriology became a scientific fad with many excesses[10] including the autointoxication theory (that bacterial stasis in the colon caused systemic disease), which reached its apogee in 1913 as the purported cause of gastric cancer, peptic ulcer, neuritis, headache, endocarditis, mental apathy, stupidity, arthritis, and various other disorders.[5] The purposeful removal of the colonic microbial flora by purging is still practiced today with possibly the only result being a decrease in colonization resistance (ability of the intestinal flora to resist invasion by foreign organisms) and an increased risk of colon infections.

In 1890, the dentist and physician, W.D. (Willoughby Dayton) Miller published "The Micro-Organisms of the Human Mouth: The Local and General Diseases Which Are Caused by Them" in Germany.11 A year later in a Dental Cosmos article,[12] Miller used the term "focus of infection" for the first time. Although he was writing before the discovery of radiographs, Miller did not necessarily recommend removing teeth considered to be a focus of infection and also suggested "treating and filling root-canals." In the same issue of Dental Cosmos, he emphasized the importance of disinfecting instruments so as not to spread infection.[13]

In 1900, the English physician William Hunter reported in the British Medical Journal on "Oral Sepsis as a Cause of Disease" blaming poor dental health and "conservative dentistry" (the preservation of the dentition by dental treatment) as the cause of the plethora of systemic

diseases listed above.[14] However, it was not until his address to the medical students at McGill University in Montreal in 191115,[16] that the dental and medical professions took serious notice of focal infections: "No one has probably had more reason than I have had to admire the sheer ingenuity and mechanical skill constantly displayed by the dental surgeon. And no one has had more reason to appreciate the ghastly tragedies of oral sepsis which his misplaced ingenuity so often carries in its train. Gold fillings, crowns and bridges, fixed dentures, built on and about diseased tooth roots form a veritable mausoleum over a mass of sepsis to which there is no parallel in the whole realm of medicine and surgery. A perfect gold trap of sepsis of which the patient is the proud owner and no persuasion will induce him to part with it, for it cost him much money and it covers his black and decayed teeth.

"The worst cases of anemia, gastritis, colitis, obscure fevers, nervous disturbances of all kinds from mental depression to actual lesions of the cord, chronic rheumatic infections, kidney diseases, are those which owe their origin to, or are gravely complicated by the oral sepsis produced by these gold traps of sepsis. Time and again I have traced the very first onset of the whole trouble to a period within a month or two of their insertion. This form of sepsis is particularly severe and injurious, because it is dammed up in the periosteum and alveolus and can not be eliminated by any ordinary medical antisepsis the doctor can administer, moreover it being locally painless and insidious in action, it goes on accumulating in severity without giving any symptom or warning."[15,16]

Hunter apparently knew that there were many good dentists: "For while a large body of that profession are engaged in dealing successfully with the difficult problems of dental disease and of oral sepsis, another body is no less steadily engaged in promoting sepsis of the worst character and degree by ignoring the fundamental principles connected with the anatomy, physiology, and pathology of the tissues with which they deal."[15,16]

Modern restorative dentistry and endodontic therapy were essentially a development of American ingenuity, and it is possible that rival interests between Britain and America were a part of this problem;17 yet, in the words of E.C. Kirk: "Unfortunately, however, Dr. Hunter in his enthusiasm for his cause has failed to make as plain as he should make it the distinction which he has clearly implied between such work skillfully executed and intelligently applied and the monstrous anatomical and physiological insults which are palmed off upon an ignorant public by equally ignorant charlatans under the general term of American crown and bridge work."[16]

Sir William Osler declared that the neglect of the teeth of the people in England "is a national disgrace,"[16] a fact possibly overlooked by Hunter. Hunter's condemnation of "American" dentistry led to the British dental profession largely subscribing to his opinions until after World War II17 and the creation of a nation of the edentulous and dentured. Hunter's opinions, however, were very useful in the quest of both the American and British dental associations for greater professional status and elimination of the untrained, uneducated, and unscrupulous "practitioners" by licensing requirements.[18]

In 1912, the physician Frank Billings formally and independently introduced the concept of focal infection to American physicians.[19,20] Again, as with Hunter, he reported a number of case observations where he ascribed distant infections to various pathologies and went the further step to state that cures were attained with tonsillectomies or dental extractions.

Billings was of the opinion that "most of the infections and contagious diseases may be classed as preventable; most of them are filth diseases, and they cannot exist in the presence of perfect cleanliness." This was not an unreasonable position at the time of Billing's statement (1898) as public and professional sanitation was in its infancy and cholera, rheumatic fever, typhoid, typhus, poliomyelitis, and other social contact diseases were endemic and at times epidemic. Billings further claimed that cultured organisms from arthritic patients and injected into rabbits caused arthritis in these animals.[21]

E.C. Rosenow was an ardent pupil of Billings at the Rush Medical College and later conducted experiments at the Mayo Clinic where he developed the theories of "elective localization"22 and "transmutation"23 in which he claimed that microorganisms had affinities for certain organs of the body and that microorganisms could change their characteristics: viridans streptococci could "transmutate" into beta-hemolytic streptococci or pneumococci. The theory of bacterial transmutation conveniently explained why other researchers were unable to duplicate the results of Rosenow as the original bacteria injected into animals had "transmuted" to other bacteria.[24] As prominent physicians such as Charles Mayo[25]and Russell Cecil[26] joined Hunter, Billings, and Rosenow in advocating the focal infection theory of disease and its remedy by surgery, millions of tonsils and teeth were removed in what was later described as an "orgy of extractions."[27]

Many physicians recommended surgical procedures, particularly extractions or tonsillectomies, as the only sure cure for various diseases. Many physicians and dentists recommended extracting all endodontically treated teeth ("one hundred percenters"),[17] some recommended extracting all nonvital or "suspicious" teeth, and others recommended that all teeth be removed for the sake of prevention as well as treatment ("therapeutic edentulation").

In 1918, the dentist Josef Novitzky assailed dentists who performed root canal therapy as "almost criminal,"[27] and Widdowson quoted a well-known

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dentist who claimed that a dentist who did crown and bridge work should receive "six months hard labour."[28] Fortunately reason began to prevail in 1920 when C. Edmund Kells, the founder of dental radiography, presented an entirely opposite view of criminal behavior: that indiscriminate extraction of teeth to cure focal infections was "the crime of the age" and recommended that dentists refuse to operate upon physicians' instructions to needlessly remove teeth.[29]

In 1919, Lillie and Lyons recommended tonsillectomy in every case of arthritis promising a marked improvement in up to 80 percent of all cases,[30] and Cotton claimed "impregnable" evidence in the Journal of Dental Research that dental extractions or tonsillectomy prompted cure or improvement in mental disease and insanity.[31] Cotton advocated the extraction of all capped and "pivot" teeth and the removal of all fixed bridgework while acknowledging that 5 percent of such work was good but the risk was too great to leave alone. Two hundred thousand tonsillectomies were performed every year in England and Wales and "It may be inferred that in many cases financial considerations played a role since the operation is three times as common among the well-to-do as among the poor."[32] In the United States, the tonsillectomy rate was double in large income families as compared to poor ones.[32]

As the 1930s dawned, observations appeared that: "If this craze of violent removal goes on, it will come to pass that we will have a gutless, glandless, toothless – and I am not sure that we may not have , thanks to false psychology and surgery – a witless race"[33]and as reported in the American Journal of Ophthalmology: "Stripped of tonsils and teeth, often the victim of colonic irrigation, abdominal, and genito-urinary operations, the patient may finally be reduced to only those organs necessary for existence, while all the time his ocular disease progresses remorselessly to blindness."[34]

In 1938, Cecil (a former proponent of focal infection) and Angevine concluded that "focal infection is a splendid example of a plausible medical theory which is in danger of being converted by its enthusiastic supporters into the status of an accepted fact."[2] and published an analysis of 200 cases of rheumatoid arthritis that documented no benefit of tonsillectomy or dental extractions and which, in some cases, resulted in exacerbation of the arthritis.[2] The authors concluded that "the time has arrived for a complete revaluation of the focal infection theory." In 1939, Vaizey and Clark-Kennedy demonstrated that those made edentulous for "medical" reasons ("the clean sweep," "therapeutic edentulation") subsequently developed arthritis and dyspepsia. Rather than being a cure for indigestion, they observed, the lost teeth caused chewing difficulties; and such edentulism was actually a cause of indigestion.[35]

In 1940, Reimann and Havens published the most influential critique of the focal infection theory with the findings that:

- The theory of focal infection has not been proved;
- The infectious agents are unknown;
- Large groups of people whose tonsils are present are no worse than those whose tonsils are out;
- Patients whose teeth and tonsils are removed often continue to suffer from the original disease for which they are removed;
- Beneficial effects can seldom be ascribed to surgical procedures alone;
- Beneficial effects that occasionally occur after surgical measures are often outweighed by harmful effects or no effects at all; and
- Many suggestive foci of infection heal after recovery from systemic disease, or when the general health is improved with hygiene and dietary measures.[32]

The focal infection theory was (is) elegant in its simplicity and offered quick and easy (as well as lucrative) solutions to a myriad of problems for which medicine had no answers. It also afforded medicine the chance to deflect the blame from its ignorance to relative defenseless and unwitting victims: dentists and patients. As in all eras of great discoveries (in this case the germ theory of disease), the revelation was carried to the extremes of extrapolation. All of its proponents were infected with the concept that "after it, because of it" for which even today there is no vaccine. Bearing the above in mind, it is useful to now examine the resurgence of the focal infection theory of disease in its newer guises.

The Present

The resurgence of the focal infection theory of disease has been greeted with great enthusiasm in some quarters[36-38] particularly as there is now possible limited evidence that periodontal microbial pathogens may be a risk factor for cardiovascular disease. The current evidence for such an association has been reviewed in a companion paper in this journal issue.[39] That oral microorganisms/ oral disease could be responsible for some forms of systemic diseases is attractive as it would give dentistry greater professional participation in the health care process, would stimulate basic and clinical research in this area, and encourage the public to take better care of their mouths. It is always wise to resist generalizations from limited data (particularly via the media), and the profession should be well aware of the consequences of encouraging patient treatment without documented benefit.

That bacteria may move from the oral cavity to other areas of the body has never been seriously challenged for good reason: It happens. Viridans group streptococci, particularly Streptococcus milleri, have been isolated from brain, liver, and pulmonary abscesses; cardiac vegetations; sinuses; urinary tract infections; and the mediastinum.[40-43] The most common cause of both brain abscesses and bacterial endocarditis is Streptococcus sanguis.44

Periapical abscesses have been blamed for necrotizing fasciitis, cavernous sinus thrombosis, mediastinal abscesses, and fever of unknown origin.[45] That such metastatic infections occur should not be the major issue but rather how often do they occur and are they preventable within any reasonable risk-benefit ratio.

The risk for a brain abscess after dental treatment has been calculated in a worst case scenario to be 0.09 to 0.84 cases per million population per year (one chance in a million to one in 10 million).[44] If we accept that dental treatment-associated bacteremias may cause prosthetic joint infections (although there has never been a single well-documented case of such an occurrence), then the worst-case scenario has been estimated to be 0.03 percent to 0.04 percent (30 to 40 cases per 100,000 prosthetic joints).[44] If we then agree that bacteremias are 1,00046 to 8,00047 times more likely to be caused by daily oral procedures such as oral hygiene and eating than dental treatment, then the worst-case scenario for dental treatment causation of prosthetic joint infections is one chance in 2.5 million to 20 million patients with orthopedic prosthetic joints.[44]

A recent study of patients with endocarditis who either did or did not have dental treatment in a reasonable interval before the onset of the disease concluded that there was no relationship between dental treatment and bacterial endocarditis (although the study did demonstrate a strong relation between cardiac valve pathology and endocarditis).48 Other studies have also supported a very low risk rate for endocarditis with dental treatment[49,50] as have a number of literature analyses.[44,46,51-54] The most recent American Heart Association guidelines for the prevention of endocarditis clearly state that "the vast majority of endocarditis due to oral organisms is not related to dental treatment procedures."[55]

It is very often exceedingly difficult if not impossible to determine direct causation between oral bacteria and metastatic infection sites, particularly regarding temporal associations as the organisms from the mouth and infected site are rarely examined to see if they are genetically identical, although techniques such as the polymerase chain reaction are available. Other difficulties are also apparent. The term "alpha-streptococcus" is often equated in medicine with viridans group streptococci although enterococci, Streptococcus pneumoniae, and group D streptococci also turn blood agar green. The authors are unaware of a single case of endocarditis due to the common periodontal pathogens, Porphyromonas gingivalis or Prevotella intermedia, probably because the oxygen-rich environment of the heart is not conducive to anaerobic growth. Periodontal pathogens are rarely if ever a cause of endocarditis.[44] It is also poorly appreciated that viridans group streptococci are ubiquitous microorganisms found not only in the oropharynx, but also in the nose, large intestine, female genitourinary tract, and on the external genitalia.[56] Considering the epidemic of antibiotic-resistant microorgansims,[57] antibiotic toxicity and allergy,[53] and the very low risk of serious sequellae to metastatic oral microbes, a systemic chemotherapeutic approach to prevention (endocarditis antibiotics prophylaxis would be a notable exception[55]) has a generally unacceptable risk-benefit ratio.

The Future

The present evidence for the relationship of oral microorganisms and systemic disease, particularly that of the coronary arteries, is very limited due not only to a dearth of prospective studies and a complete lack of interventional studies but also to very significant methodological difficulties associated with the clinical studies that have been performed.[39] Also, the occurrence of metastatic infections from the mouth to distant bodily sites is rare. It would then appear wise to refrain from embracing the focal theory of infection in any guise until the proper research is conducted and corroborated by independent investigators. Presently all we have is the resurgence of a previously discredited theory with no more substantial evidence now than then. The dental profession should refrain from the temptations to gain economically from the focal infection theory, to justify dental treatment solely on the basis of prevention of systemic disease, or to use this theory to criticize another practitioner's efforts. What we need now is sound science not jubilation that focal infection is the savior of dental practice.

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A Guide to Evaluating Epidemiological Studies

Thomas J. Pallasch, DDS, MS

ABSTRACT Epidemiological studies that fail to follow established principles can lead to or promote false assumptions. Attention to the principles of epidemiological studies and avoidance of extrapolation beyond the data can remove much of the confusion that presently exists among the health professions and general public. This article offers guidelines to evaluating epidemiological studies.

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Professionals and the lay public alike are besieged by reports and claims that a given observation or treatment supports or proves that two health care events are linked; and, therefore, an association or causation is involved. At times, this "association/causation" amounts to no more than the simplistic "before it, therefore because of it." Almost universally, such claims are later disproved; but they are rarely so reported in the media or scientific publications, leading to inappropriate behavior or outright disillusionment that science has misled us again.

It is then appropriate that the guidelines for the proper establishment of epidemiological studies and their interpretation be set forth in a manner that can be readily understood and applied to any of these claims. Hopefully, this may help to avoid future misinterpretations and improve the quality of epidemiological studies.

Criteria for Epidemiological Studies

Since data from experiments in humans to prove causation are generally unavailable due to ethical reasons, determination of association/causation relationships in human disease rely to a great extent on epidemiological findings. **Table 1** lists the principal criteria necessary for the establishment of such relationships.[1-3]

Virtually all these criteria apply to formulating an association and not causation. Causation can only be proven epidemiologically with prospective

Table 1. Principal Criteria for Epidemiological Studies.[1-3]

- The prevalence of the disease should be significantly higher in those exposed to the putative (proposed) cause than in those not exposed.
- The exposure to the putative cause should be more commonly present in those with the disease than those without the disease when all risk factors are held constant.
- The incidence of the disease should be higher in those exposed to the putative cause than in those not so exposed as documented in prospective studies.
- The disease should follow the exposure to the putative cause.
- There must be a certain strength of association (dose-response relationship).
- The cause must be related in time and place to the effect.
- A consistency of association must exist: agreement among observers in different places by different researchers using different techniques.
- Elimination or modification of the cause should decrease the incidence of the disease.
- A coherence of association should exist: the cause and effect interpretation should not conflict with the known pathology of the disease.
- The entire concept of the relationship must make epidemiological and biological sense.

interventional studies that eliminate or alter the course of the disease.[4,5] Purely observational studies cannot prove or disprove causality.[4,5]

Clinical vs. Statistical Significance

All too often, clinical studies synonymously equate statistical significance with clinical significance, leading to probable misinterpretations of the data presented.[6] The statistical significance of a study is the result of a statistical test that yields a sufficiently small "P" value (the probability that the observed difference is due to chance) and leads to a rejection of the null hypothesis of no difference between treatments.[6] Clinical significance is the smallest change in a measurement between treatment groups that would result in a decision to modify treatment.[6] A clinical result could easily be statistically significant without being clinically significant and, due to the methodology of the study, the reverse might also occur: that the difference in treatment groups was medically but not statistically significant. If these differences are not clearly stated in the study or attempts are made to equate statistical with clinical significance, then serious difficulties exist with the data and conclusions.

P values are arbitrary and commonly considered significant at the 0.05 level (a 5 percent probability that the results were due to chance). If the P value were 0.01 percent (a 1 percent probability that the results were due to chance) or of "high statistical significance" then there would be greater confidence in the rejection of the null hypothesis. Nonsignificant P values would support the probability that either there was no difference between the treatment and control groups, no significant differences between treatments, or that the sample size was too small.[7]

The Null Hypothesis

It is commonly stated that a study is proposed to "prove" that a particular treatment or effect does or does not occur. This is a complete misuse of the null hypothesis (that no differences exist between treatment groups) and implies an automatic bias in the study toward "proving" one result or another. It is imperative in epidemiological studies that the null hypothesis be strictly adhered to and that every effort be made to disprove that differences exist between treatment groups.[8] If differences are then found and the null hypothesis is rejected, sound science has likely occurred; and some degree of confidence can be placed in the conclusions.

Meta-Analyses

A meta-analytical study is a combination of the research results from several studies[9,10] and is commonly used to assess weak risk factors that have potentially large public impact (passive smoking, microorganisms and cardiovascular disease, low-level radiation.)[11] When done properly, a meta-analysis can provide a more objective appraisal of evidence than traditional narrative reviews, offer a more precise estimation of treatment effects, and explain apparent difference between studies.10 However, meta-analyses can be misleading or erroneous depending on any biases toward including or excluding given studies, the database used to search for the studies, data pooling, failure to consider all variables, and the sometimes serious disagreement in results with large, controlled randomized studies that are unlikely to be wrong.[9-11]

Odds Ratios and Risk Ratios

Odds or risk ratios are often employed to present the relative medical significance of a particular association. The risk ratio is the number of people who experience an event divided by the total number of people at risk for the event.12 It is expressed as a proportion (percentage): risk ratio of 0.1 = 10 percent; risk ratio of 0.5 = 50 percent. An odds ratio is the number of people who experience the event divided by those that do not.12 It is expressed as a number from zero (will never happen) to infinity (certain to happen): an odds ratio of 6.0 (6:1) means that six will experience the

event for every one that does not; an odds ratio of 1.5 means that 1 1/2 people will experience the event for every one that does not.12 An odds ratio of less than one implies a reduction in risk and odds ratios of 1.5 to 2.0 are weak associations that commonly are later found to be associated with confounding variables not controlled for or detected in the study.[13]

Confidence Intervals

Increasingly, clinical trial results are expressed with confidence intervals: the limits within which the "real differences" between the treatments is likely to lie and, therefore, the strength of the inferences that can be drawn from the results.[7] For example, an association may be expressed as an odds ration of 3.0 (95 percent confidence interval, 1.5-6.0) or an odds ration of 3.0 with 95 percent probability that the "real effect" lies between 1.5 and 6.0.7 The narrower the confidence interval, the more likely the result is to be definitive; the larger the confidence interval, the weaker the association.[7] If the confidence interval overlaps zero (95 percent confidence interval, -2.0-4.0), then this is a negative result (trial) or a very weak association.

Conclusions

Epidemiological studies can be very well-performed leading to reasonable conclusions or, as with many, fail to follow established principles and lead to or promote false assumptions. Epidemiological studies can only prove causation with prospective interventional studies, which document that elimination or modification of the proposed cause of the disease decreases or eliminates the disease. Attention to the principles of epidemiological studies and avoidance of extrapolation beyond the data can remove much of the confusion that presently exists among the health professions and general public.

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Oral Microorganisms and Cardiovascular Disease

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ABSTRACT The list of etiological factors for cardiovascular disease is long, complicated, intertwined, and yet to be completed. This paper will evaluate the current evidence for the pathogenic role of certain microorganisms, including those of the oral cavity, in the etiology of cardiovascular disease.

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The concept that infectious agents might be involved in the etiology of cardiovascular disease has been espoused since the early 1900s.[1,2] The hypothesis gained credence with the demonstration in 1978 that avian herpesvirus could induce arterial atherosclerotic disease in chickens resembling that seen in humans.[3,4] Possible pathophysiological mechanisms include either acute precipitation of atherosclerotic plaque rupture and subsequent thrombosis or the promotion of atherosclerotic plaque growth via direct endothelial injury, endothelial dysfunction, smooth muscle proliferation or the production of local inflammation.[4]

Microorganisms would then initiate or promote ("trigger") the "response to injury" theory of vascular endothelial dysfunction whereby inflammatory cells (primarily macrophages) adhere to damaged endothelial walls; become foam cells; and, along with T lymphocytes and smooth muscle cells, initiate the "fatty streak" that begins atherosclerotic disease.[5] The resulting inflammatory process gives rise to release of pro-inflammatory cytokines including tumor necrosis factor-alpha, various interleukins, and coagulation factors such as macrophage colony stimulating factor and macrophage chemoattractant protein –1.[2] Ongoing inflammation would then contribute to the formation of complex atheromas and/or destabilization of the atheroma and subsequent thrombogenesis (ischemia begets ischemia).[2]

The interest in a microbial causation

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of cardiovascular disease is fostered by the realization that many acute coronary events (death, myocardial infarction) occur in individuals with no apparent cardiovascular risk factors.[6,7] However cardiovascular disease is a classic multifactorial disease with potentially more than 100 risk factors or markers for the disease (**Table 1**).[8,9] Nonmodifiable factors include age, gender, and family (genetic) history.[8] Modifiable risk factors include cigarette smoking, obesity, hypertension, diabetes mellitus, physical activity, total blood cholesterol, elevated low-density lipid-cholesterol, low high-density lipid-cholesterol, air pollution, and unaccustomed strenuous exercise (50 to 100 times greater risk for an acute myocardial infarction).[8] Other risk factors include time of day for acute myocardial infarction (6 a.m. to noon),[10] enterovirus infection,[11] blood iron levels,[12] thrombomodulin,[13] nitric oxide,[14] maternal hypercholesterolemia during pregnancy[15] and heat shock proteins.[16]

Unfortunately, the most significant factor for acute myocardial infarction or thromboembolic stroke cannot yet be adequately identified: the "vulnerable" atherosclerotic plaque that, following disruption, may result in local or systemic thrombogenesis or local blood-flow disurbances.[17] Atherosclerosis without thrombogenesis is commonly a benign disease rendered life-threatening by acute thrombosis resulting in acute myocardial infarction, unstable angina, or sudden death.[17] The reason some atheromas are thrombosis-resistant while others are vulnerable to disruption, thrombosis formation, and life-threatening sequellae is a major question yet to be answered.[17]

The most dangerous atherosclerotic plaques have a core of soft lipid-rich atheromatous "gruel" that are unstable and vulnerable to rupture.[17] Sclerosed plaques with a thick stable collagen "cap" are unlikely to be involved in thrombogenesis. Macrophage infiltration at the edge (shoulder) of the plaque may render it more vulnerable to rupture. Current diagnostic methods cannot reliably distinguish between plaques that are vulnerable to disruption and those that are relatively benign.[17]

The list of etiological factors for cardiovascular disease is long, complicated, intertwined, and yet to be completed. The ensuing discussion will evaluate the current evidence for the pathogenic role of certain microorganisms, including those of the oral cavity, in the etiology of cardiovascular disease.

Confounding Epidemiological Variables

The following variables may have a profound effect on the course of cardiovascular disease but are commonly left unaddressed in epidemiological studies on risk factors. Partly this is due to the difficulty or expense of controlling for these variables; however, the conclusions of any study must be tempered with the knowledge that such confounding variables are always present and may be particularly significant in studies showing relatively low odds ratios (range 1.5 to 3.0).

Genetics

Coronary artery disease in a population does not segregate as a simple Mendelian genetic trait attributable to a single gene with large effects but rather as a large number of genes (possibly up to 50).[18] Coronary artery disease is a multifactorial disorder caused by the additive effect of multiple genes each with a modest effect and confounded by the gene-environment interaction.[19]

Ethyl Alcohol

Very few clinical studies – including those that attempt to relate oral microorganisms to cardiovascular disease – address the important variable of alcohol consumption. The relation between alcohol and total mortality is depicted as a J shaped curve with the lowest mortality in those who consume one to two drinks per day and then with increasing mortality with the greater number of drinks in excess of two per day.[20]

Heavy alcohol consumption increases the risk for stroke, hypertension, and cardiac muscle and arterial damage.[20] Excess alcohol consumption is also a suppressant of the immune system,[21] particularly with regard to infectious diseases;[22] an independent risk factor for ischemic cerebral infarction;[23] a cause of cardiomegaly,[24] cardiac arrhythmias[25] and sudden death; and a major factor in all-cause mortality.[26] Inattention to alcohol ingestion in study subjects could mask both its protective and deleterious effects on cardiovascular disease.

Homocysteine

The first report that very high blood levels (100 to 450 micromoles/liter) of homocysteine, a sulfur-containing amino acid, were strongly associated with atherosclerotic disease appeared in 1969[27] and has led to the homocysteine theory of cardiovascular disease: Atherogenesis is secondary to hyperhomocysteinemia caused by dietary deficiencies in folic acid and vitamin B6 with cholesterol and low density lipids (LDL) as carriers of homocysteine to form LDL-HC aggregate precursors of foam cells in atheroma lesions.[28] Homocysteine may damage vascular endothelial cells by oxidative stress, hydrogen peroxide and superoxide production and inactivation of nitric oxide leading to endothelial dysfunction, platelet activation and thrombus formation.[28,29]

The preponderance of evidence appears to support a role of elevated plasma levels of homocysteine as a risk factor for atherosclerosis[30-40] with a minority view that:

- As more stringent criteria are applied to the clinical studies, the association weakens;[41]
- An apparent relationship exists, but no prospective placebo-controlled interventional studies have been performed;[42]

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Table 1. Proposed, potential, or documented risk factors or markers for cardiovascular disease.[8,9]

Nonmodifiable Risk Factors

- Age
- Sex
- Genetics

Modifiable Risk Factors

- Cigarette smoking
- Obesity
- Diabetes mellitus
- LDL-cholesterol
- Psychosocial factors
- Air pollution
- Physical activity
- Hypertension
- Total cholesterol
- HDL-cholesterol
- Alcohol intake
- Diet

Proposed or Potential Markers or Risk Factors

- Homocysteinemia
- Fibrinogen
- PAI-1
- Cholesterol transfer protein
- Apolipoprotein A-1
- TPA/PAI-1 complex
- Interleukins
- Platelet size
- Factors VIIc and VIIa

Proposed or Potential Markers or Risk Factors (continued)

- VLDL receptor
- Plasminogen activator inhibitor 1
- Plasmin – alpha 2-antiplasmin complex
- Vascular/cellular fibrinogen adhesion molecules
- Hyperinsulinemia
- Plasminogen
- TPA
- Factors V, VII, VIII
- Hepatic lipase
- Clot lysis time
- Serum amyloid A
- Platelet volume
- Fibrin degredation products
- Lipoprotein oxidation
- Lecithin-cholesterol acyl transferase
- Thrombin-antithrombin III complex
- Apolipoprotein E isoforms
- Lipoprotein (a)
- Thrombin
- Von Willebrand antigen
- LDL receptor
- C reactive protein
- Triglycerides
- Platelet aggregation
- Prothrombin fragments
- Protein C resistance

- Significant variables in the studies have not been addressed;[43] and
- No proven causal effect exists as the association weakens with prospective studies.[44]

Studies that support a role of elevated homocysteine in atherosclerotic disease generally report odds ratios of 1.4 to 3.[1,30,34,37,39,42,43] with some inconsistencies in what precisely constitutes "elevated" homocysteine blood levels. Five to 15 micromoles/liter in the fasting individual appears normal, 16 to 30 micromoles is moderate elevation, 31 to 100 is intermediate, and above 100 micromoles/liter is severe homocysteinemia.[38] The Physicians Health Study indicates that greater than 15.5 micromoles/liter (the top 20 percent) have a 3.4 odds ratio for cardiovascular disease as opposed to the bottom 10 percent and that, with each upward 5 micromole/liter increment, the risk for cardiovascular disease increases 1.6 to 1.8 times.[33] The same study indicates that plasma homocysteine levels 12 percent above the normal upper limit result in a threefold increase in risk for acute myocardial infaction.[37] A meta-analysis of the published literature prior to 1995 indicates that 10 percent of coronary artery disease may be attributable to elevated homocysteine levels.[45]

A healthy diet of fruits and vegetables or a multivitamin containing folic acid, B6, and B12 [38,42] can reduce plasma homocysteine levels; but the Nutrition Committee of the American Heart Association has not recommended any general public dietary intervention to lower blood homocysteine levels.[42] No study on the etiology of microorganisms in cardiovascular disease has included plasma homocysteine levels as a confounding variable.

Psychosocial Factors

Stress (the reaction of the body to deleterious forces that tend to diminish normal homeostasis[46]) can significantly depress the immune response with resulting decreases in natural killer cell activity, the proliferative lymphocyte response to mitogens; total CD3+, CD4+, and CD8+ T lymphocytes; antibody levels; and enodogenous hormones.[47-51] Stress may exacerbate both herpesvirus infections and periodontal disease.[51-53]

Psychosocial factors, including low socioeconomic status (with its limited access to health care), social isolation, mental depression, hostility, and anger,[54-57]

play a significant role in coronary artery disease. Negative emotional states incur a 2.5 times greater risk for rehospitalization for cardiac disease symptoms and a five times greater risk for acute myocardial infarction, death, and out-of-hospital cardiac arrest.[54] The risk rate for cardiac ischemia following negative emotions rises to 2.6 to 3.0 for tension, sadness, and frustration and can double the risk of myocardial ischemia some hours later.[58] Hostility and anger (not Type A behavior per se) are independent risk factors for coronary artery disease and acute myocardial infaction,[59,60] and their reduction can reduce recurrent myocardial infarction.[61] Mental depression and its accompanying stress can result in platelet aggregation and increased coronary ischemia, acute coronary events, and the risk of future coronary events.[55,56,62-69]

In the years from 1900 to 1950, coronary artery disease in the United States was a disease of affluence possibly because of the greater physical activity in the lower socioeconomic classes.[65] In the mid-1960s, the burden of cardiovascular disease shifted to the lower socioeconomic classes with less physical activity.[65,66] Cardiovascular disease rates are inversely proportional to educational level and are lower in those with greater leisure time activity and health knowledge.[67] Social and productive activities (getting out to movies or sporting events, shopping, gardening, socializing) that do not involve fitness activities lower all-cause mortality.[68] Conversely, employment that is associated with low personal control, repetitive tasks, less skills and variety, time pressures, and job insecurity increases the risk for cardiovascular disease and all-cause mortality.[69] These psychosocial factors (sometimes vaguely addressed as a "socioeconomic status" without further definition) are often not adequately addressed as confounding variables in epidemiologic studies. Granted this may be difficult to accomplish, but without such data caution is warranted in interpreting many cardiovascular disease studies

Viral and Non-Oral Bacterial Associations With Cardiovascular Disease

Cytomegalovirus

The evidence for an association between cytomegalovirus and cardiovascular disease is conflicting. Several studies implicate high cytomegalovirus blood antibody titers with an increased risk for coronary artery restenosis after cardiac interventional procedures [70-73] or renal artery stenosis after transplantation.[74] However, the majority of studies do not demonstrate a relation between cytomegalovirus infection and coronary artery disease or stroke.[75-78]

The difficulty with cytomegalovirus as with the putative microbial causes of cardiovascular disease is that the infectious agents can be ubiquitous: 50 percent of the population is infected with cytomegalovirus by early adult life and 90 percent older than 60 are infected. It presently appears that cytomegalovirus may be related to coronary restenosis after revascularization procedures but has little if any role in the etiology of cardiovascular disease.

Other Herpesviruses

Herpes simplex virus infections are widespread, and the nucleic acid sequences of the viruses have been found in atherosclerotic plaque. Herpes simplex viruses can induce atherosclerosis in animals and cause expression of growth factors and cytokines by inflamed or infected vascular endothelial cells.[79] However, three clinical studies have not correlated blood antibody levels against herpes simplex virus with carotid artery intimal thickening[80]or increased risk for acute myocardial infarction or stroke.[77,78]

Helicobacter Pylori

Most peptic ulcers and probably a significant number of gastric cancers are related to infection with H. pylori. This organism has been postulated to be a significant risk factor for cardiovascular disease,[81-84] particularly if the strain is of high virulence [81]or is found in patients with large vessel atheromas or diabetes mellitus.[82-84] Most evidence, however, does not support the contention that H. pylori is a risk factor for malignant hypertension,[85] intimal thickening of carotid arteries,[86] acute myocardial infarction,[84] coagulation defects,[87] or total or cardiovascular disease mortality.[88,89]

A meta-analysis of 18 epidemiological studies (10,000 patients) that measured serum antibody titers to H. pylori and risk factors for cardiovascular disease found a low correlation with body mass, blood pressure, HDL-C, and plasma viscosity, but not for white blood cell count, total cholesterol, triglycerides, fibrinogen, blood glucose, and C reactive protein. [90] This metanalytic study suggested that claims of an association between H. pylori and cardiovascular disease were either based on chance or publication bias (preferential publication of positive studies) or both.[90] Prospective studies have not shown a relationship between H. pylori blood antibody titers and coronary artery disase.[86,91,92]

Chlamydia Pneumoniae

The most likely candidate for an infectious etiological agent in cardiovascular disease is the respiratory pathogen, C. pneumoniae. The organism (rarely) or its DNA fragments (commonly) have been identified in atherosclerotic lesions (carotid, coronary, aortic, femoral/popliteal) by polymerase chain reaction, immunocytochemistry, and electron microscopy.[93] The organism itself has rarely been isolated from atheromas.[93] However, in spite of extensive study and some positive correlations with atherosclerotic disease (odds ratios of generally 1.2 to 2.5), the question is yet to be answered as to whether C. pneumoniae is a causative or associative agent of cardiovascular disease or merely an innocent bystander that finds atheromas a friendly place to survive.[4,93-95] Eventually,

data from antibiotic interventional studies may help to clarify the issue of causation of C. pneumoniae in cardiovascular disease.

C. pneumoniae infections are very common, often repetitive, and many times subclinical in symptomatology. Alveolar macrophages infected with Chlamydia pneumoniae may be transported to arteries where the organism may induce or accelerate the atherosclerotic process.[95] Experimental studies indicate that C. pneumoniae may induce atheromas in rabbits,[96-99] thereby establishing biologic plausibility.

Studies have demonstrated associations (odds ratios of 1.2 to 2.5[112]) between C. pneumoniae blood antibody titers (seropositivity) and cardiovascular disease or acute coronary events (acute myocardial infarction, unstable angina, death).[100-111] However, many other clinical studies do not support a relationship between C. pneumoniae and acute coronary events or atherosclerosis.[2,4,6,7,77,112-124] The trend of recent prospective studies that employ more stringent epidemiologic criteria is toward decreasing the significance of C. pneumoniae in the etiology of cardiovascular disease.

Differences in epidemiological studies on C. pneumoniae can be due to a number of factors:

- Inattention to confounding variables (alcohol, homocysteine, stress, socioeconomics);
- Difficulty in readily establishing whether cardiovascular disease due to C. pneumoniae clearly occurs in populations with a 50 percent lifetime risk for the disease;
- Inability to identify true incidence/prevalence by the detection methods used (immunofluorescence tests are particularly subject to interpreter bias and error);
- No established standards on what blood antibody levels constitute positivity;
- Difficulty in determining when the organism was acquired (past, current or recurrent);
- Difficulty in isolating C. pneumoniae from atheromas; and
- Generally small sample sizes.

Many studies of antibodies to C. pneumoniae (as well as those with other proposed viral or microbial etiologies of cardiovascular disease) commonly take single or only a few blood samples over time, making it virtually impossible to determine whether the C. pneumoniae infection is acute, chronic, latent, or a repeat episode. Blood antibody levels may be short-lived or persist for long periods after exposure to C. pneumoniae, even though the organism may no longer present in the host.

The best evidence for possible association or causation between C. pneumoniae (or other microorganisms) and cardiovascular disease will come from prospective interventional studies that correlate body levels of the organism (preventing or eliminating the infection) with the prevention or change in course of chronic cardiovascular or acute cardiac events. Two small and underpowered studies[125,126] have indicated that treatment with macrolide antibiotics (azithromycin, roxithromycin) may be effective in reducing the endpoints of acute myocardial infarction, unstable angina, or death. Prolonged doxycycline therapy had no effect on serologic or hemostatic markers for cardiac risk factors in patients with C. pneumoniae antibodies.[127]

Preliminary data have been published from two large ongoing prospective studies utilizing azithromycin with endpoints of reduction of anti-C. pneumoniae antibody levels[128] or acute coronary events.[129] A one-month course of azithromycin (total 8 grams) failed to reduce plasma IgG or IgA antibody titers to C. pneumoniae as determined at six months.[128] A 500 mg dose of azithromycin per day for three days followed by 500 mg weekly for three months significantly reduced C reactive protein, IL-6, and IL-1 levels at six months but failed to reduce anti-C. pneumoniae antibody titers or acute coronary events.[129] The conclusion in one of these studies[128] was that anti-C. pneumoniae antibody titers were likely a poor marker for a response to antibiotic therapy, however other interpretations might also be that the intervention therapy (antibiotics) does not affect the microorganisms or that the disease process remains unaffected. This conclusion128 poses another difficulty as many studies on microbial causation of cardiovascular disease use antibody titers as surrogate markers.

Several additional large ongoing studies (WIZARD, MARBLE, ACES, STAMINA, CROAATS) may be able to provide more definitive answers to the question of the relationship between Chlamydia pneumoniae and cardiovascular disease.[130] The WIZARD trial (Weekly Intervention with Zithromax Against Atherosclerotic-Related Disorders) has enrolled 3,500 subjects with a history of prior myocardial infarction to receive azithromycin weekly for 2.5 years. The ongoing ACES trial (Azithromycin Coronary Events Study) has enrolled 4,000 subjects with coronary artery disease to be treated for a one year with azithromycin followed by four years of observation.

In the various macrolide intervention studies to date, no dose-response (effect) relationships have been established for antibiotics employed in the trials with wide ranges in both the individual doses and length of therapy (a few days to three months). Also, no information has been provided to determine if the antibiotic actually reaches the target organism and, if so, whether it inhibits its replication. C. pneumoniae can exist in a metabolically active form (reticulate body), outside the mammalian cell as the elementary body, or in a metabolically inactive form (persistent body) that is unresponsive to antibiotic therapy.[131] If C. pneumoniae is dormant in the atheroma or arterial intima, then antibiotic therapy will be ineffective.

Oral Microbial Associations with Cardiovascular Disease

Several reviews are available on the putative association of periodontal microorganisms with cardiovascular disease and other systemic diseases.[132-137] The potential role of these microorganisms in the cascade of acute or chronic inflammatory responses in arteries is similar to that seen with C. pneumoniae, H. pylori and cytomegalovirus.[138,139]

The number of clinical studies relating periodontal disease to cardiovascular disease or acute coronary events are understandably relatively few[140-154] in comparison to those investigating C. pneumoniae, H. pylori, and cytomegalovirus. In general, odds ratios of 1.5 to 3.0 have been described for an association between periodontal disease and cardiovascular disease.[155] These odds ratios are too low to exclude the possibility of significant bias due to unappreciated confounding variables.[155,156] Furthermore, all published studies to date describe a statistically significant relationship between periodontal disease and cardiovascular disease. With such a wealth of confounding variables and the relatively low odds ratios, one might anticipate future studies that encounter nonsignificant relationships between periodontal disease and cardiovascular disease.

The clinical studies suffer from several significant difficulties other than the general problem with confounding variables. No clinical studies have controlled for the other putative microbial pathogens in cardiovascular disease (particularly C.a pneumoniae); and the reverse is true for the studies on C. pneumoniae, H. pylori, and cytomegalovirus. None have controlled for periodontal disease. Many of the periodontal studies have been performed in subject populations where cardiovascular risk factors can be extremely skewed (VA hospitals, homogenous populations in Finland) and where the influence of heavy alcohol intake may be endemic. Generally, the studies do not address a central issue: Do people with significant periodontal disease neglect not only their oral cavity but also their health in general so that a single element (periodontal disease) of the general health pattern cannot be readily dissected into a separate component?

The antibiotics employed in recent interventional studies would also affect periodontal microbiota. Considering the poor performance of antibiotics to date, it would appear that more-comprehensive periodontal therapy may be necessary or that significant caution is indicated about the strength of the periodontal disease-cardiovascular disease relationship.

The notion of viridans group streptococci, particularly Streptococcus sanguis, being a causative agent in cardiovascular disease (most notably in thrombogenesis[157-159]) suffers from a serious dichotomy. Viridans streptococci are predominant in the healthy periodontium; and if they are a significant risk for thrombogenesis and acute coronary events, then it should follow that periodontally healthy individuals would be at great risk for acute myocardial infarction, stroke, and unstable angina. It appears that to induce cardiovascular disease and coagulation disorders in rabbits with viridans streptococci, doses in the magnitude of 9, 14 and 40 billion colony forming units are required, which then reach concentrations of [160] million CFU/ml in rabbit blood, which is equivalent to 8 million CFU/ml in human blood (250 mls in rabbits and 5,000 mls in humans for total blood volume). In comparison, a dental treatment procedure typically induces as little as 1-10 CFU/ml in blood, which are usually rapidly cleared, while a seeding endocarditis-infected cardiac valve produces 10-100 CFU /ml.[160] Also, cardiovascular coagulation disorders are not specifically caused by viridans group streptococci but can be associated with gram-positive/gram-negative bacteria and viruses.[161]

In summary, retrospective and case-control studies have provided data on the proposed association between periodontal disease and cardiovascular disease.[162] There are only limited prospective data and no interventional studies to establish possible cause and effect. The present studies are best described as hypothesis-generating and not hypothesis-proving.[163]

Possibly the best summation of the evidence to date for an infectious etiology of cardiovascular disease has been given by Epstein and Zhu[163]: "In the end, the hope of achieving definitive conclusions about the intriguing infection-atherosclerosis hypothesis is probably an elusive goal given the complexity of the disease, the multitude of pathogens that may contribute to the disease, and the complexity of host-pathogen interactions. Perhaps a more realistic goal we might hope to eventually achieve is to agree simply that there exists a high probability of causality. However, even this modest conclusion can only be accepted if additional studies on pathogen-induced disease-related mechanisms, multiple prospective seroepidemiological studies of different populations, additional investigations using animal models of disease, and human studies demonstrating that pathogen-targeted therapy reduces disease incidence or manifestations, convey reasonably consistent evidence linking infection to atherogenesis."

Periodontal Disease and Preterm Birth

Periodontal disease has also been proposed in the causation of preterm (low birth weight) infants (born before 37 weeks gestation). The initial case-control study utilized 124 pregnant or postpartum volunteers who were examined for periodontal clinical attachment loss by periodontal residency students.[164] The results indicated a very significant association between preterm birth and clinical attachment loss.

The study did not provide pertinent information about:

- Standardization of probing techniques of the examiners;
- The method of selection of the "volunteers" (potential selection bias);

- The time of clinical attachment loss in relation to the pregnancy (before or during); and
- The periodontal microbiologic profile of the subjects (no cultures were taken). The article does not elaborate on the appropriateness of extrapolating beyond the data that 18.2 percent of the 250,000 low-birth-weight infants in the United States could now be attributed to periodontal infection even while the authors were warning that: "The limited scope of this case-control study does not enable broad generalization regarding the potential health care impact of these findings" and " caution must be exercised in interpreting the application of the current data."[164]

A second case-control study on low-birth-weight infants determined the presence of four periodontal microbial pathogens, the gingival crevicular fluid levels of a prostaglandin and an interleukin, clinical attachment losses, bleeding on probing, and probing depths.[165] The results indicated that periodontal disease activity was slightly worse in women delivering low-birth-weight infants but did not answer the question of whether increased periodontal disease was due to lack of personal attention to oral hygiene or other factors that might influence both low birth weight and periodontal disease development.

Data suggests that maternal infection (particularly bacterial vaginosis) accounts for 80 percent of preterm births and is associated with membrane rupture.[166] However, most antibiotic trials do not demonstrate a protective effect for preterm birth;[167] and antibiotics are not recommended routinely to prolong pregnancy.[168] If used, antibiotics should be directed toward preventing group B streptococcal sepsis[168] with the realization that antibiotic selection of resistant bacteria may complicate the treatment of neonatal sepsis should it occur.[169]

It has been calculated that a definitive study to determine if chronic maternal periodontal disease is associated with preterm low-birth-weight infants will require 800 mothers for sufficient power to detect an association with an odds ratio of 3.0 at 5 percent significance level.[170] Until data from such studies become available, any proposed association between periodontal disease and preterm low birth weight should be viewed as a hypothesis yet to be tested.

Medicolegal Aspects of Oral Microorganism and Systemic Disease

The resurgence of the focal infection theory of disease has been greeted with enthusiasm.[171,172] The potential link between oral microorganisms and systemic disease is seductive in its simplicity and possibly far-reaching in its consequences. Seemingly unappreciated is its potential medicolegal difficulties for health care providers, i.e., that the systemic disease could be blamed on dental treatment-induced bacteremias as easily as patient-induced bacteremias. As discussed in a companion paper[173] in this issue, the focal infection theory of disease is still in the infancy of scientific testing.

For dental health professionals who would wish to employ the limited database to imply to patients that causality exits between oral microorganisms and systemic disease and that expensive dental treatment is in order to prevent such systemic disease, it should be realized that it is impossible to determine between the systemic dissemination of oral microorganisms from normal daily bodily functions and from dental treatment procedures. Dentistry may then again face from a new direction the dilemma so often seen in the past with the causation of bacterial endocarditis – that any dental procedure done within six to nine months of the systemic infection may incriminate the dentist. Now that it is firmly established that dental treatment procedures are a low risk for endocarditis,[173] the notion of focal infection may put dental practitioners at renewed risk for malpractice litigation.

"Experts" will likely be available to testify that a given dental treatment or treatment plan was "below the standard of care" and therefore directly responsible for the deceased patient's myocardial infarction. Conversely, if it is ultimately proven that periodontal disease is merely one of many risk factors for cardiovascular disease, all differing in importance for each person, then the patient may become indignant that great expense was incurred for dental treatment that had little effect on his or her general health.

Conclusions

It is apparent that the relationship between microorganisms and cardiovascular disease or low-birth-weight premature births remains investigational. The trend with C. pneumoniae, H. pylori, and cytomegalovirus appears to be headed toward a weak or no association with somewhat stronger evidence for C. pneumoniae. Cytomegalovirus may be associated with coronary artery restenosis. The intervention trials with macrolide antibiotics against C. pneumoniae have to date been disappointing, and the final results of several large intervention trials are several years away.

The research on a potential relationship between periodontal disease and cardiovascular disease or preterm births is in its infancy with many questions yet unanswered and no interventional trials yet performed. Until adequate scientific data exist and are verified through independent investigators, substantial caution should be exercised before assigning or implying causality between periodontal disease and cardiovascular disease or preterm birth.

The use of the limited evidence garnered to date regarding oral microorganisms and systemic disease to influence dental patients toward dental treatment or to criticize another dentist's efforts is fraught with scientific and medicolegal difficulties.

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Global Antibiotic Resistance and Its Impact on the Dental Community

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ABSTRACT There is significant evidence that the global problems of microbial resistance to antibiotics has reached the dental community both in our practices and our family lives. This paper will present a global overview of microbial resistance, discuss how this problem directly affects the dental community, and show what we can do to change the situation, both as concerned citizens and as dental health care practitioners.

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It is tempting to live in a reverie where outside forces do not affect our daily lives. Cocoons are cozy until it is time to escape mortal danger. The sporadic media reports of a patient death from a microorganism totally resistant to all antibiotics, the death of a 30 (not 90)-year-old from a nosocomial (hospital-acquired) infection, or the demise of several school children from methicillin-resistant staphylococci acquired from a day care center create a moment of panic, but then it is business as usual: This could not happen to us.

Surely what is happening in Southeast Asia – particularly in Taiwan – with a rapid and massive increase in antibiotic resistance to the penicillins and macrolides in viridans group streptococci is of little apparent concern to us. However, it should be as these organisms are the most important pathogens in acute oral cellulitis and are on their way to us via the airplane. There is ample evidence that antibiotic-resistant microorganisms have no respect for geographic boundaries and travel easily from country to country and from locale to locale in our communities (long-term care facilities to tertiary-care hospitals and vice versa).

There is significant evidence that the global problems of microbial resistance to antibiotics has reached the dental community both in our practices and our family lives. There are increasing reports of viridans group streptococcal resistance to beta-lactam antibiotics (penicillins and cephalosporins); macrolides and tetracyclines; and beta-lactamase production in the periodontal and cellulitis pathogens, Prevotella intermedia and Porphyromonas gingivalis. Sporadic reports are appearing of significant resistance in Fusobacteria and Veillonella. These resistance patterns have resulted in anecdotal reports of difficulties in the antibiotic management of orofacial

infections and even outright antibiotic failures, a problem virtually unheard of in dentistry until recently. Unfortunately, our knowledge of the true scope of this problem is severely hampered by the lack of qualified microbiologists in dentistry and the virtual absence of research funding to support their efforts.

The dental community also includes our staff and immediate families. Children in day care centers and parents in long-term care facilities are part of this community. So too are the practices of the food production industry, pharmaceutical companies, and hospitals, which directly affect the form and extent of microbial resistance to antibiotics in the community. A discussion of the crisis in the resistance of HIV to antiviral agents may dispel the prevalent notion in our children and others that the war on AIDS is won and give some understanding of the lengths to which organisms will go to ensure their survival and why optimism can be short-lived.

The focus of this review is then threefold:

- To present a global overview of microbial resistance so that an appreciation is gained that the microbial revolt against chemicals permeates every aspect of our existence;
- To discuss how this problem directly affects the dental community (our practices, patients, and families); and
- To show how we got into this situation and what we can do to change it both as concerned citizens and as dental health care practitioners.

Before starting on this journey, a word of caution is advised. It is recommended that this paper be reviewed in discrete segments to better digest each aspect. This effort is a distillation of more than 2,000 papers read on microbial resistance with the selection of about one in 10 for referencing. As such, the references give the reader a place to start if he or she should wish to pursue a given segment in detail. This is what good reviews do. However, this is not the end of the story as hundreds of journal papers have been published since this review was completed, none of which require a modification of this saga. The tale of microbial resistance will continue for some time to come but, hopefully, with the good news that it is being taken seriously in all quarters and that redress of the problem is forthcoming.

How We Got Where We Are

In 1967, the U.S. surgeon general concluded that: "The time has come to close the book on infectious diseases." Considering that 17 million people died of infectious disease in 1993 (11.4 million due to bacteria, mostly in children), which was greater than the 15.6 million due to cardiovascular disease and cancer combined, this might seem to be a naïve statement. Yet, the surgeon general was simply echoing the "wisdom" of the medical community at that time that assumed we would always be able to stay ahead of the microbes with new antibiotics. In the late 1950s and early 1960s, introduction of the penicillinase-resistant penicillins, cephalosporins, clindamycin and new aminoglycosides dispelled the concerns about antibiotic-resistant nosocomial microbial pathogens. This assumption that we were smarter and more dedicated than the microbes again has proved that assumptions are the genesis of most mistakes. As Murphy advises: "Optimism indicates that the situation is not clearly understood."

The late 1950s were characterized by significant anxiety regarding the emergence of highly antibiotic-resistant staphylococci in hospitals. Also, some people began to realize that bacteria were capable of transferring between themselves the genetic information for resistance to chemicals intended to destroy their existence. Medicine paid little attention to the warnings of Rene Dubos, Maxwell Finland, and Ernest Jawetz that microbial resistance was here to stay and would not go away. Few read the 1946 Consumers Report prediction that: "The uncritical or promiscuous use of penicillin (may) lead to the persistence of strains of bacteria that will resist its action. Should this happen, it will have serious epidemiological significance."

The first report of microbial resistance to an antimicrobial agent appeared in 1886 with the "acclimatization" of Bacillus subtilis to phenol used as an operating room disinfectant.[2] Paul Ehrlich in 1907 described parasites resistant to fuchsin,[3] and the first report of clinical resistance was in six of 100 isolates of Neisseria gonorrhoeae resistant to sulfanilamide in 1937.[4] Rene Dubos detected microbial resistance to gramicidin in the early 1940s -- about the same time that Abraham and Chain described penicillinase.[3] In the mid 1940s, Dubos warned of staphylococci and other organisms resistant to penicillin, and in the late 1950s he warned of multidrug-resistant tuberculosis. The first general awareness of the real magnitude of the problem came in the late 1950s but was dispelled by the unbridled optimism of the 1960s on to the 1990s.[3]

In the 1840s in the United States, the average life span was about 40, which has now doubled at the millennium due to the two most significant medical advances: anesthesia and the control of bacteria and viruses. In 1900, infectious disease caused 30.4 percent of all deaths in children younger than 5 while today it accounts for only 1.4 percent of such deaths.[5] Now heart disease and cancer cause 54.7 percent of all U.S. deaths with only 4.5 percent due to pneumonia, influenza, and HIV.5 The public sanitation methods that began in the early 1900s in the United States contributed greatly to the decline in cholera, tuberculosis, typhoid fever, yellow fever, malaria, influenza, and pneumonia.[5] Vaccination has essentially eliminated tetanus, diphtheria, whooping cough, rubella, and poliomyelitis and completely eliminated smallpox.[5] Antibiotics have allowed for the control of streptococci, staphylococci, meningococci, pneumococci, gonococci, tuberculosis, and blood-stream infections. The effects of antibiotics were so miraculous that few bothered to study and/or promote proper usage. Most just assumed they would always be there for us.

Now we are faced with methicillin-resistant Staphylococcus aureus and coagulase-negative staphylococci; vancomycin-resistant enterococci and vancomycin-intermediate-resistant S. aureus; resistant viridans group

streptococci, Prevotella, Porphyromonas, Veillonella and Fusobacteria; and the multiple-antibiotic-resistant Mycobacterium tuberculosis, Shigella dysenteria, Salmonella enteritidis, Pseudomonas aeruginosa, and Streptococcus pneumoniae.

Our hospitals are now filled with immunocompromised patients. Both the young and the old die in hospitals (possibly as many as 300,000 a year in the United States) from infections they did not have when they entered the hospital. Our child day care centers and elderly extended care facilities are major reservoirs of antibiotic-resistant microbes that are transferred to acute care facilities and vice versa. All of this is compounded by the 22 million worldwide refugees, 25 million displaced people, and 500 million people a year crossing geographic borders. Microbes do not respect political distinctions.

Our problems with microbial pathogens have not disappeared but, rather, have taken another direction. We must realize that antibiotics are "societal" drugs as they affect people other than the ones taking the drugs.[6,7] The resistance genes that are created and selected by antibiotics can easily be transferred between people by human contact. Therefore, every antibiotic given to or taken by a single individual can affect other human beings. This may be bad enough when the drugs are used properly, but is intolerable when antibiotics are used improperly. If therapeutic and prophylactic errors are done daily by millions of practitioners, then these millions become billions over the course of a given year and place enormous selective pressure on microbes to resist their effects. As Sen. Everett Dirkson once said about government spending: "A billion here and a billion there, and all of a sudden you're talking about real money." The most difficult challenge in the control of microbial resistance is to convince all people (health care practitioners and patients alike) that everyone is responsible for the problem and its solution.

This discussion will not describe the mechanisms by which microbes evade the drugs intended to inhibit or kill them, nor will it be a general review of the immense complexity and nuances of microbial resistance to antibiotics. Suffice it to say that microbes have an incredible ability to outwit humans by formulating enzymes that destroy the antibiotic, limiting access of the drug to its microbial target site(s), altering these target sites to reduce antibiotic binding, or actively extruding the antibiotic from the microbial cell. Some antibiotics like metronidazole have essentially only one resistance mechanism (alteration of DNA gyrase binding), while the tetracyclines have them all. Microbes no longer defend themselves from chemicals by single chromosomal mutations every one billion or so cell divisions; but, now, because of their massive exposure to sustained chemical onslaught, they easily and rapidly transfer antimicrobial resistance genes via bacteriophages, plasmids, transposons, and integrons. No longer do they sit idly by when confronted by toxic chemicals but rather manage to express and/or transfer these genes (induced resistance) much more rapidly than if the chemical were not present. Excellent reviews are available on the general aspects of microbial resistance to antibiotics[8-15] and the mechanisms microbes employ to attain this end.[16-20]

Resistance to Specific Antibiotics

Vancomycin

The first published report of vancomycin-intermediate-resistant methicillin-resistant S. aureus was in El Salvador in 1996[21] quickly followed by a report in 1997 from Japan.[22] These reports heralded the realization that the worst fears of the infectious disease community may have been realized: that an already highly resistant organism had been rendered resistant to all known antibiotics. Subsequent reports of this resistant organism in the United States (Michigan, New Jersey, New York)[23,24] and France[25] have appeared. Vancomycin-intermediate-resistant S. aureus or glycopeptide-intermediate S. aureus has been disseminated throughout various Japanese hospitals,[26] caused death in Hong Kong, is a factor in surgical infection treatment failures, and has spread globally.[27] The resistance of vancomycin-intermediate-resistant S. aureus may be related to production of abnormal mucopeptides in cell wall synthesis or to an increase in the number of peptidoglycan units in the cell wall.[28]

All cases to date of vancomycin-intermediate-resistant S. aureus have appeared after prolonged (weeks of) intensive antibiotic (vancomycin) use in the hospital setting, and this presents the possibility that reduced vancomycin use may contain the spread of the organism. Also, vancomycin-intermediate-resistant S. aureus is sometimes sensitive to quinupristin/dalfopristin (Synercid), rifampin, chloramphenicol, penicillin, and beta-lactamase inhibitors combined with aminoglycosides and even sometimes tetracyclines.[29-32] A significant problem with vancomycin-intermediate-resistant S. aureus and glycopeptide-intermediate S. aureus is that they appear to be antibiotic-sensitive with the standard laboratory disc diffusion methods and will only be detected by agar or broth dilution or E test strips.[30]

The advent of vancomycin-intermediate-resistant S. aureus was not unexpected after the appearance of vancomycin-resistant enterococci in 1988 and glycopeptide resistance in coagulase-negative staphylococci. Vancomycin-resistant enterococci now account for more than 20 percent of all nosocomial enterococci and 14.8 percent of all surgical site infections.[33] In 1994, 61 percent of hospitals surveyed reported vancomycin-resistant enterococci as opposed to 23 percent in 1992.[34] Unfortunately, Enterococcus faecium is the major vancomycin-resistant enterococcus and is multiple-antibiotic-resistant rather than Enterococcus faecalis, which remains moderately sensitive to ampicillin and penicillin plus a beta-lactamase inhibitor.[34] Vancomycin-resistant enterococci may also be sensitive to erythromycin, tetracycline, chloramphenicol, rifampin, quinolones, quinupristin/dalfopristin, and aminoglycoside combinations with some of these agents.[34] Tetracycline has been proven effective against vancomycin-

resistant enterococcus.[34-36] Vancomycin-resistant enterococcus appears to be another example of marked resistance development due to intensive selection pressure in U.S. hospitals as has been the case with methicillin-resistant S. aureus, extended beta-lactamase producing Klebsiella pneumoniae, and imipenem resistance in P. aeruginosa.[34]

Vancomycin-resistant enterococci are endemic in the European population with a 15 percent carrier rate,[37] while the carrier rate in the U.S. population is very low. Alternately, the prevalence of vancomycin-resistant enterococci in U.S. hospitals is much higher than in Europe. Possibly the occurrence rate is similar if vancomycin-resistant enterococci are compared in livestock in Europe with hospitals in the United States. Vancomycin-resistant enterococci are very common in food, livestock, and humans in Europe due to the widespread use of avoparcin (an analogue of vancomycin) in animal husbandry prior to its ban in 1997.

In Denmark for example, 24 kg of vancomycin were used in humans in 1994 while 24,000 kg of avoparcin were employed in swine and poultry production (an amount of glycopeptide exceeding all human use in both Europe and the United States in that year).[38] While avoparcin was never approved for use in the United States, the use of vancomycin in U.S. hospitals rose from 100 kg orally and 1,900 kg parenterally in 1984 to 888 kg orally and 10,312 kg parenterally in 1996.[39]

Even more alarming than the appearance of vancomycin-resistant enterococci and vancomycin-intermediate-resistant S. aureus is the recently described vancomycin tolerance in S. pneumoniae, an organism responsible for millions of deaths annually in the world.[40,41] Antibiotic tolerance (conversion of the antibiotic activity from bactericidal to bacteriostatic) is generally considered to be an intermediate step between sensitivity and total resistance and cannot be detected by conventional laboratory testing as the organism appears to be sensitive.[40,41] Between 2 percent and 3 percent of all clinical isolates of the pneumococcus may be tolerant to vancomycin.[40]

The mechanism for tolerance to vancomycin in pneumococci is unique: a mutation in the sensor-response system that controls autolysin activity necessary to kill bacteria.[40,41] With this mutation, the sensor kinase remains inactivated; and autolysis of the bacterial cell is not triggered.[40] This sensor-response system is also required for the bactericidal activity of the beta-lactams, cephalosporins, aminoglycosides, and quinolones.[40]

S. pneumoniae is a major pathogen in lower respiratory tract infections, sinus and middle ear infections, and meningitis; and it is particularly lethal in the young and old. It is also highly resistant to the penicillins and macrolides. The acquisition of resistance by the enterococcus has demonstrated how a second-rate pathogen can become a first-rate clinical problem.[34]

The reports of vancomycin intermediate/tolerant resistance in staphylococci and pneumococci possibly herald total antibiotic resistance in these microorganisms. Future difficulties may be even worse. It appears that:

- Streptococci, staphylococci, and enterococci often share the same resistance genes;
- The penicillinase in enterococci is identical to that in staphylococci (shared genes);
- The enterococcus can transfer resistance genes to many other organisms (the vancomycin-resistance gene has been transferred to staphylococci in vitro and in animal models[42]);
- Staphylococci and enterococci are coinhabiting the skin;[43]
- The beta-lactamase gene in enterococcus likely came from staphylococcus in this environment; and
- Vancomycin resistance may one day appear in viridans group streptococci.[34]
- It may take years for these transformations to occur, or they may come rapidly as with penicillin resistance in streptococci and pneumococci; but occur they will.

Macrolides

The principal mechanism for resistance to the macrolides (azithromycin, clarithromycin, erythromycin) is via an erm gene that codes for enzymatic methylation of the adenine residue in the 23SrRNA, resulting in decreased macrolide binding to its receptor site.[44,45] Other mechanisms include enzymatic destruction, bacterial efflux, and altered bacterial membrane permeability. This altered ribosomal binding site can confer resistance simultaneously to macrolides, lincosamides, and streptogramin B (MLSB resistance).[44,45] The macrolides are over-the-counter-drugs in Taiwan and have resulted in resistance rates of 80 percent in methicillin-resistant S. aureus, 30 percent in non-methicillin-resistant S. aureus, 58 percent in S. pneumoniae, 37 percent to 42 percent in Streptococcus pyogenes (Group A streptococci), and significant resistance in enterococci, peptostreptococci and Bacteroides fragilis.[46] Epidemics of macrolide resistance in S. pyogenes occurred in Finland in 1988 and Italy in 1993 with 40 percent to 42 percent of isolates having MLSB resistance.[47] A 1993-1994 outpatient study at 12 major U.S. medical centers indicated a 16 percent incidence of macrolide resistance in penicillin-intermediate resistant S. pneumoniae and 57 percent macrolide resistance in penicillin-resistant S. pneumoniae while penicillin-sensitive strains were only 1.1 percent to 3.1 percent resistant to the macrolides.[48]

Metronidazole

Microbial resistance to metronidazole (Flagyl) is relatively low except in Helicobacter pylori probably because of its limited clinical use. Intracellular reduction of the nitro group of metronidazole leads to DNA strand breakage, helix destabilization, and eventual cell death.[49]

Resistance to metronidazole occurs in Trichomonas vaginalis, H. pylori, Bacteroides, Clostridia, Gardnerella vaginalis, Campylobacter fetus, Leptotrichia buccalis, and Treponema pallidum.[49-52] Mechanisms include decreased microbial production of hydrogen peroxide, superoxide radicals

or oxygen tolerance, reduced cellular uptake, or decreased reduction of the nitro group.[51] Resistance of H. pylori (a causative agent of peptic ulcer and gastric cancer) to metronidazole ranges from 10 percent to 50 percent in developed countries and 100 percent in developing countries because of its widespread use in treating parasitic diseases.[53] Treatment failures with clarithromycin occur more commonly in regions with high resistance rates of H. pylori to metronidazole; metronidazole resistance may increase macrolide resistance in H. pylori.[54]

New Antibiotic Agents

Quinupristin/dalfopristin (Synercid) is a streptogramin antibiotic recently approved in the United States for skin and soft tissue infections and part of combination regimens against vancomycin-resistant enterococci.[55] The new drug combination (a 30:70 ratio of quinupristin and dalfopristin) has a remarkable spectrum of activity: S. aureus including methicillin-resistant S. aureus, streptococci including peptostreptococci, E. faecium, N. gonorrhoeae, Haemophilus influenzae, Moraxella catarrhalis, Legionella, Listeria monocytogenes, mycoplasma, Bacteroides, Prevotella, Fusobacterium, Clostridia, Actinomyces, and Lactobacilli.[55,56] E. faecalis is totally resistant by an unknown mechanism. The primary targets of quinupristin/dalfopristin are S. pneumoniae, S. aureus and E. faecium.[56]

The streptogramin group also includes pristinamycin and virginiamycin used in humans (pristinamycin) in France and in agricultural animals (virginiamycin) throughout the world (including the United States) as growth promoters and to treat infections.[55] Streptogramin-resistant E. faecium was detected in animals before the drugs were used in humans, and virginiamycin is now banned in Denmark.[55] It is likely that streptogramin resistance can be transferred from animals to humans in food.[55]

Resistance to the streptogramins is through enzymatic modification, active efflux and altered ribosomal binding.[55,56] Quinupristin/dalfopristin bind sequentially to different sites of the 50S subunit of the 70S ribosome to prevent newly synthesized peptide chains from extruding from the ribosome and resulting in cell death.[55,56] Resistance via dimethylation of an adenine residue 57,58 is commonly coded on the erm gene, which also confers resistance to the macrolides and lincosamides (MLSB resistance).[56]

Enthusiasm for this new streptogramin antibiotic must be tempered by the following observations:

- Intermediate resistance in S. aureus has been detected;[59]
- Resistant E. faecium has been isolated in animals and humans outside the hospital;[60]
- The vancomycin-resistance gene and the streptogramin-resistance gene have been detected linked together on the same plasmid;[61]
- Resistance in E. faecium may develop during treatment with the streptogramins;[62] and
- Quinupristin/dalfopristin may select for superinfection with resistant E. faecalis during treatment.[63]

These tarnish the prospects for streptogramins unless they are used with great caution in hospitals and removed from animal husbandry.

Linezolid is an oxazolidinone antibiotic with bacteriostatic activity against staphylococci and enterococci including most gram-positive cocci, vancomycin-resistant enterococci, penicillin-resistant pneumococci, Legionella, and H. influenzae.[64] It was developed as a plant antibiotic in the 1970s, and resistance has appeared due to decreased ribosomal binding.[64]

Tetracyclines

Microbial resistance to the tetracyclines is widespread, inducible, easily acquired, often associated with multiple drug resistance, and possibly permanent (remains when the microbe is no longer exposed to the drug). The current tetracyclines probably act by binding to the 30S subunit of the bacterial ribosome thereby interfering with aminoacyl-tRNA binding and leading to inhibition of protein synthesis.[65] The major tetracycline resistance mechanisms are:

- Active drug efflux from the cell;
- Altered ribosomal binding sites (ribosomal protection); and
- Enzymatic destruction.

Altered cell wall permeability to tetracycline influx is of some significance under certain circumstances.[66]

High level tetracycline resistance is achieved by active energy-dependent drug efflux from the bacterial cell either by multidrug resistance pumps or tetracycline specific transporters.[66] Eleven classes of tetracycline resistance determinants encoding tetracycline-specific efflux proteins are known to date in both gram-positive and gram-negative bacteria.66 Ribosomal protection is encoded by six tet genes (M, O, P, Q, S, T) and three oxytetracycline genes.[65,67,68] Tetracycline can be inactivated by a cytoplasmic protein encoded by a tet gene that chemically modifies tetracycline.[67]

The long-term use of conventional doses of tetracyclines results in high levels of resistant organisms in the oral cavity ranging from an 11 percent to 85 percent occurrence rate.[69,70] Short-term (two weeks or less) conventional doses can select for resistance in viridans group streptococci, Veillonella parvula, Eikenella corrodens, and Fusobacterium nucleatum.[71] Tetracycline-resistant genes are widespread in the oral flora,[72,73] and low-level tetracycline doses promote the spread of tet genes to other bacteria[67,68,74] and better select for resistant bacteria than high levels of antibiotics.[6,15] Prolonged tetracycline use will select for both tetracycline and multiple-resistant bacteria[6,75] since tetracycline-resistance genes are often part of a larger transposon, integron, or plasmid containing other antibiotic resistance genes.[73]

The ongoing debate about the significance of tetracycline-resistant organisms in the oral cavity obscures two far more serious consequences associated with tetracycline use: 1) selective pressures for multiple-resistant organisms in other areas of the body and 2) the significant ability of the tetracyclines to induce antibiotic resistance by promoting the expression of tet genes and/or fostering the transfer of these genes to other bacteria via transposons or integrons either as a single resistance

gene or as part of a complex of multiple-antibiotic-resistance genes.

Tetracyclines in various doses can select for resistant microorganisms in the tonsils,[76] skin,[77-80] and colon.[6,81-84] There is considerable evidence that conventional oral daily doses,[85,86] as well as intravenous doses,[87] select for tetracycline-resistant intestinal K. pneumoniae, enterococci, Escherichia coli, yeasts, and multiple-antibiotic-resistant organisms. Such antibiotic resistance increases not only in patients taking the drugs but also close-contact relatives.[86] The oral microbial flora are generally opportunists that commonly only produce disease when host defenses are impaired. The colonic flora is dominated by highly pathogenic and multiply antibiotic resistant organisms: Bacteroides, Salmonella, Shigella, Serratia, E. coli, Providencia stuartii, Proteus mirabilis, Enterobacter cloacea, P. aeruginosa, and K. pneumoniae.

The issue of the transfer or expression of genes by tetracycline has been explored to some extent[88] but requires far greater study. Pre-exposure of the colonic flora to tetracycline increases the frequency of transfer of conjugative transposons in B. fragilis at a rate of 100 to 1,000 times greater[81] and the transfer of a transposon (Tn925) in B. subtilis 10 times faster82 than if the tetracycline were not present.67 Doxycycline at a dose of 100 mg/day for seven days can reduce the colon colonization resistance (the ability of the colon to defend itself against implantation of new pathogens) to K. pneumoniae, P. mirabilis, and E. cloacae.[89]

The advocates of low-dose doxycycline therapy ("subinhibitory concentrations") at 40 mg/day hold that the attained blood levels of 0.2-0.7 micrograms/ml [90,91]are "well below the concentration required to inhibit microorganisms associated with adult periodontitis"[92] and "too low to affect bacteria."[93] It is also claimed that when present in the colon, doxycycline is bound as a stable, non-antibacterial conjugate, but a number of studies contradict this contention.[89,94-98] There is a wealth of evidence from the 1960s to the present that tetracycline and doxycycline in particular are therapeutic antibiotics at minimum inhibitory concentrations as low as 0.015-0.04 micrograms/ml for both periodontal and non-oral microbial pathogens.[69,70,84,94,95,99-110]

It is generally assumed that the tetracyclines have limited therapeutic uses, and they are the only antibiotic group whose use has declined in the past 20 years.[68] However, the tetracyclines are presently the drugs of choice for the management of Chlamydia pneumoniae and trachomatis, Vibrio cholerae, Yersinia pestis, H. pylori, Lyme disease, mycoplasma, Brucella, and rickettsial infections, and alternate drugs for S. pneumoniae, Legionella, Campylobacter, and E. corrodens.[111] Possibly because of their rare use in hospitals over the last many years, it appears that some highly antibiotic-resistant and life-threatening organisms have lost their resistance to the drugs. Doxycycline is presently used for the management of vancomycin-resistant enterococci[34-36] and in at least one case at doses of 0.25 micrograms/ml[36] that is well within the blood level range achieved by low dose doxycycline. S. aureus isolates have been detected that are sensitive to very low doses of the tetracyclines, and these drugs may again be useful against these highly resistant and life-threatening pathogens.[31,32]

It would be a tragedy to lose the tetracyclines once again through inappropriate use now that they have regained their effectiveness against highly pathogenic microbes.

Resistance in Specific Microorganisms

Oral Microorganisms

A high rate of penicillin resistance in viridans group streptococci was first reported in 1987 in South Africa112 and subsequently confirmed in the United States and Europe.[113,114] This resistance in viridans group streptococci (S. milleri, S. mutans, S. salivarius, S. sanguis, and S. mitis groups) is due to an altered penicillin binding protein (PBP2B) that greatly decreases the binding of penicillin to its receptor.[115,116] Both S. pneumoniae and viridans group streptococci coinhabit the pharynx and share the gene for this altered penicillin binding protein, which may have originated in viridans group streptococci or vice versa.[117-119]

Reports of 23 percent to 81 percent of viridans group streptococci resistant to ampicillin or amoxicillin in both hospitalized patients and those in the community are not uncommon.[120-123] In the United States, 40 percent to 50 percent of the viridans group streptococci are resistant at concentrations equal to or greater than 0.25 micrograms/ml.124 In 1993-1994, [352] blood cultures of viridans group streptococci taken at 43 U.S. medical centers showed a resistance rate of 13.4% at minimum inhibitory concentrations greater than 4 micrograms/ml (high resistance) and 42.9% at minimum inhibitory concentrations of 0.25-2.0 micrograms/ml (intermediate resistance).[114] The same study indicated that 96 percent of viridans group streptococci were resistant to cephalexin at greater than 2.0 micrograms/ml. Japanese children may harbor penicillin resistance in viridans group streptococci at a 62.5 percent to 87.5 percent rate.[125] A cohort of Japanese children at high risk for endocarditis have a 31.7 percent prevalence of viridans group streptococci resistant to amoxicillin at 4-16 micrograms/ml and 28.3 percent showing minimum inhibitory concentrations of 4-8 micrograms/ml for penicillin G.[126]

The resistance rates to penicillins may vary greatly with the various viridans group streptococci with the least resistance in S. milleri and the greatest in S. mitis with an intermediate level in S. sanguis.[114,127-129] In addition to penicillin resistance, viridans group streptococci may be significantly resistant to the tetracyclines, clindamycin, and the newer macrolides (azithromycin, clarithromycin).[124] In a Taiwan study, clindamycin resistance in viridans group streptococci was 20 percent to 50 percent and for tetracycline was 30 percent to 70 percent in various viridans group streptococci.[128]

Beta-lactamase production is common in oral Prevotella, Porphyromonas,

and Fusobacterium species in both children and adults.[130-134] F. nucleatum has produced a fatal septicemia.[135] Up to one-third of moderately advanced periodontitis patients may harbor strains of P. intermedia/nigrescens, Fusobacteria and beta-hemolytic streptococci that are resistant to both amoxicillin and doxycycline.[136] Highly penicillin resistant oral strains of Veillonella, Capnocytophaga, E. cloacea, and K. pneumoniae have also been detected.[137-139] Specific strains of methicillin-resistant S. aureus may colonize the oral cavity for many years in those with natural dentitions and in those with dentures.[140-142] One-step fluoroquinolone-resistant determinants can be transferred from viridans group streptococci to pneumococci in vitro.[142] The oral cavity is now as much a part of the microbial resistance millieu as any other part of the body.

Helicobacter Pylori

Chronic gastritis, peptic ulcer, and gastric cancer have all been linked to causation by H. pylori.[143] This gram-positive organism colonizing the stomach has become highly resistant to metronidazole in many areas of the world, and as a consequence tetracycline has been added to the drug regimens used to treat this organism.

The classic therapy for H. pylori eradication is a three- or four-drug regimen including bismuth, a proton pump inhibitor (omeprazole), and one or more antibiotics (metronidazole, clarithromycin, amoxicillin, tetracycline).[144] Ranitidine has recently been added to the regimen.[144] Resistance to metronidazole due to a decreased ability to reduce its nitro group ranges from 10 percent to 50 percent in developed countries and approaches 100 percent in developing countries due to its widespread use in the treatment of parasitic diseases.[53] Resistance to clarithromycin and tetracycline is presently 5 percent to 10 percent due altered ribosomal binding.[145] Amoxicillin tolerance has also been detected in H. pylori.[146] Some studies detect a 30 percent to 60 percent reduction in eradication rates of H. pylori due to metronidazole resistance while others report little effect.[144] A vaccine will be the only mechanism to eliminate the pathology caused by H. pylori since resistance will likely increase in the future.[53] The widespread use of metronidazole in periodontics may be expected to add to the difficulties of the antibiotic control of peptic ulcer and gastric cancer.

Human Immunodeficiency Virus

The current therapy for HIV is highly active antiretroviral therapy employing a combination of drugs to interfere with several steps in viral replication. Difficulties have arisen with this therapy due to the ability of the virus to provide reservoirs of replication competent HIV in resting CD4 T lymphocytes persisting through years of intensive highly active antiretroviral therapy.[147] It is estimated that seven to 60 years of highly active antiretroviral therapy may be necessary to eradicate the virus from these reservoirs.[148]

The success of this therapy is critically dependent on two factors: patient compliance with the drug regimens and HIV resistance to the antiretroviral drugs (nonsuppressive antiretroviral therapy).[149] Drug therapy can be very complicated, with an average of 50 percent of affected individuals failing to adhere to the entire medication schedules for the entire duration of viral replicability.[150] Failure to take even one of the three drug regimens will lead to greater resistance to the two remaining drugs.[150,151] These difficulties are further compounded by recent reports that HIV already resistant to one or more antiretroviral drugs is being transferred to newly infected individuals, greatly complicating their treatment and prognosis.[149,152,153]

Antiretrovial therapy is greatly compromised by the nature of HIV: the reverse transcriptase enzyme of the virus makes one error on average per 10,000 bases copied in a virus that has a 9,200 base genome. Therefore, virtually every virus is slightly different from its forebearer.[151] This high error rate in reverse transcriptase activity coupled with a very high replication rate of the virus promotes an enormously variant virus population. With a viral replication rate of 1 billion per day, every single point mutation may occur at a rate of greater than 10,000 copies per day.[154] These HIV variants may then no longer be recognized by T lymphocytes or neutralizing antibodies.[151]

The current three drug regimens may greatly decrease the HIV viral burden for six to 24 months to less than detectable viral levels (20 copies/ml).[151] Some antiretroviral drugs (lamivudine, nevirapine) only require a single mutation to develop high level drug resistance while other agents (indivanir, zidovudine) need three or more mutations in a single viral genome and persistent viral replication and selective antiretroviral therapy for high level resistance development.[155] Any HIV variant less sensitive to an inhibiting drug will outgrow the "wild type" sensitive virus and be selected out by the drugs, but a high replication suppression rate can reduce the number of these mutants.[156] Significant resistance to indivanir and zidovudine may take six to 24 months to develop, while high-level resistance to nevirapine and lamivudine can take less than one month.[150] The idea that HIV can be readily and easily treated by drugs is folly. Possible solutions to these HIV-resistance problems have been discussed.[150,151,155,157]

Microbial Resistance in the Community

Worldwide Resistance

Seventy percent to 77 percent of all S. pneumoniae isolates in South Korea are resistant to penicillin, with 34 percent being multidrug-resistant to erythromycin, tetracycline, and chloramphenicol.[158] In Taiwan, 61 percent of hospital S. pneumoniae isolates are resistant to penicillin, with 40 percent of these displaying intermediate to high level resistance to cefotaxime and imipenem and 82 percent to 90 percent with resistance to erythromycin.[159] In Hong Kong, penicillin resistance in S. pneumoniae was detected at a rate of 6.6 percent in 1993 but rose to 55.8 percent in 1995 with multiple resistance to tetracycline, chloramphenicol, and erythromycin.[160]

In the United States in 1994, 36.5 percent of N. gonorrhoeae isolates were resistant to tetracyclines and penicillin and ciprofloxacin resistance was increasing.[161] In 1975, 18 percent of S. pneumoniae isolates in Hungary were resistant to penicillin, which rose to 58.8 percent in 1989.[162] In Poland, S. pyogenes resistance to tetracycline increased from 14 percent in 1976 to 80 percent in 1993.[162] In the United States, 33.4 percent of H. influenzae and 92.7 percent of Moraxella catarrhalis were beta-lactamase producers during the 1996-1997 respiratory disease season.[163] A multiresistant "Iberian" clone of methicillin-resistant S. aureus has spread from Spain to Portugal, Italy, and Scotland.[164] A highly chloramphenicol-resistant strain of Neisseria meningitidis has been isolated in Vietnam and France and has demonstrated the ability of an aerobic gram-negative coccus to acquire the resistance genes (Tn4451) from a gram-positive bacillus (Clostridium perfringens).[165]

Otitis Media

The use of antibiotics to treat middle ear infections is probably second only to antibiotic therapy for upper respiratory tract infections (most of which are viral) as a major factor in the rise and extent of antibiotic resistant microorganisms in the community. Otitis media takes several forms:

- Acute otitis media;
- Recurrent otitis media;
- Persistent otitis media;
- Otitis media with effusion;
- Chronic otitis media; and
- Chronic suppurative otitis media.[166]

Signs and symptoms include erythematous bulging of the tympanic membrane, otalgia, fever, irritability, and middle ear serous or purulent effusions.[166] The most common causative microorganisms are S. pneumonia (20 percent to 50 percent), H. influenzae (10 percent to 30 percent) and M. catarrhalis (5 percent to 20 percent).[166]

At least 60 percent of children have an episode of acute otitis media by age 1 and 75 percent by age 3.[166] Antibiotic prescriptions for otitis media in the United States have increased from 11.9 million in 1980 to 23.6 million in 1992, with an efficacy rate of 68 percent to 96 percent.[167] The resistance rates to penicillin are up to 31 percent in S. pneumoniae and greater than 90 percent in M. catarrhalis with 31 percent to 57 percent of H. influenzae producing beta-lactamase.[168] In a study of children with acute otitis media who received antibiotic therapy within the previous year, the resistance rate to penicillin in S. pneumoniae and H. influenzae increased from 38 percent to 58 percent in those who had received prior amoxicillin with or without clavulanate, the macrolides, or cephalosporins.[169] Prior use of the macrolides and cephalosporins also increased the rate of penicillin resistance (resistance increased not only for the prescribed antibiotic but also other antibiotics).[169] The longer the antibiotic treatment for otitis media, the greater the pressure for the selection of antibiotic-resistant S. pneumoniae.[170]

Pediatricians are currently the only medical specialty that is aggressively attempting to reduce unnecessary antibiotic use. It appears that acute otitis media is overdiagnosed and often unnecessarily treated with prolonged antibiotic therapy.[171] Typical resolution of acute otitis media occurs in two to five days, and it appears that five-day therapy (instead of the usual 10 days, a duration extrapolated from the treatment of streptococcal sore throat with penicillin) is effective for uncomplicated otitis media.[172] This short course may not be optimum therapy for children younger than 6 and particularly those younger than age 2.[173] Better attention to the diagnosis of otitis media and a reduction in duration of antibiotic treatment may reduce the total amount of antibiotics used in otitis media by one-half.[171]

Antibiotics in Agriculture

Antibiotic use in agricultural animals (primarily beef and veal cattle, broiler chickens, and hogs) began after World War II to treat bovine mastitis.[174] Streptomycin was added to feed to promote growth in chickens in 1946, and tetracycline was added in 1949.[174] Antimicrobials are used in animal husbandry to treat or prevent infections and to promote growth.[175] It is impossible to selectively treat animals with antibiotics when 120,000 hogs are confined to a single farm barn. The use of antimicrobials in feed adds 4 percent to 5 percent to the body weight of the farm animals.[176]

Approximately one-half of the 50 million pounds of antibiotics manufactured in the United States are used in agriculture and aquaculture. Fifty thousand pounds of streptomycin and tetracycline are employed for fruit trees each year.[177] In Denmark in 1994, 24 kg of vancomycin was used in humans and 24,000 kg of avoparcin (a vancomycin analogue) in animal feed. [38,178] From 1992 to 1996, Australia imported an average of 582 kg/year of vancomycin for human medical use and 62,642 kg of avoparcin for animal husbandry.[178]

The evidence is unequivocal that agricultural antibiotics have selected for microorganisms with multiple-antibiotic resistance to ampicillin, tetracycline, erythromycin, aminoglycosides, chloramphenicol, sulfonamides, methicillin/oxacillin, vancomycin, everninomycin and streptogramins.[176,179,180] These resistance genes are carried by staphylococci, Salmonella typhimurium, Campylobacter species, enterococci, E. coli, and Yersinia enterocolitica[176,181] with the same gene pattern in both animals and humans, indicating transfer between species.[175,176,179,181,182]

Human-disease-causing Salmonella enterica have been isolated from poultry, red meat, dairy products, and fresh produce (alfalfa sprouts, cantaloupe, tomatoes).[183] Campylobacter jejuni causes 2 million cases of gastroenteritis per year in the United States,[184] and the increasing use of fluoroquinolones in food animals has resulted in a steadily increasing incidence of Campylobacter infections in humans.[185] The ribotypes of vancomycin-resistant eterococci in some human clinical isolates are identical to those in non-human animal sources.[186] Fish and shrimp produced by aquaculture may exceed those collected by captive fishing by the year 2007 and are a source of antibiotic-resistant Salmonella, Vibrio, Aeromonas, Listeria, and various parasites (nematodes, cestods, and hematodes).[187]

The most widely publicized and studied microorganism transmitted to humans in the food chain is enterohemorrhagic E. coli 0157 which may induce bloody diarrhea and, in 5 percent to 10 percent of cases, the hemolytic-uremic syndrome (microangiopathic hemolytic anemia, thrombocytopenia, renal failure) with a 3.5 percent mortality in children and up to 35 percent in the elderly.[189,190] In Japan in 1986, 9,000 documented cases occurred with 11 deaths;[191] and in 1993, 20,000 cases occurred in the United States with 250 deaths.[190] This vero cytotoxin-producing E. coli serotype 0157 was recognized in 1982 as a human pathogen,[192]and the infecting dose can be as low as 50 microorganisms.[193] The primary source of E. coli157:H7 is undercooked beef as 1.6 percent of feedlot cattle and 1.5 percent to 5.7 percent of calves shed the organism.[194]

Since 1986, Sweden has banned antibiotic growth-promoting chemicals and has been able to successfully compete in the European Community marketplace in cattle and hogs.[195] This restriction of antibiotics only to diseased animals has led to a 50 percent decline in the agricultural use of antibiotics in Sweden.[195] Since the ban of avoparcin in Germany in 1995, the percentage of vancomycin-resistant enterococci has fallen from 12 percent to 3 percent in the intestines of human vancomycin-resistant enterococci carriers.[196] In 1969, the Swann Committee in the United Kingdom recommended that no antibiotic be used in farm animals if the same drug is employed in humans and selects for antibiotic resistance.[176] It appears wise some 31 years later to now implement this recommendation before the antibiotic resistant microorganisms in food chain animals and the 1.4 billion tons of animal waste (manure) they annually generate in the United States do any more harm.

Institutional Antibiotic Resistance

Day Care Centers

The transmission of microorganisms at day care centers is endemic via contaminated body fluids (saliva, urine, feces) and fomites (toys, surfaces).[197] The most commonly transmitted diseases are respiratory: rhinitis, sinusitis, pharyngitis, bronchitis, and pneumonia. The offending organisms include adenovirus type II and V, respiratory syncytial virus, parainfluenza virus B, H. influenzae Type B, N. meningitidis, and M. tuberculosis.[197] Diarrhea is the second most common infection and is commonly due to rotavirus, adenovirus, Shigella, Salmonella, E. coli, Y. enterocolitica, Giardia lamblia and Entamoeba histolytica.[197] In day care children younger than 3, 2.6 cases of acute diarrhea occur per year.[167] Other day care center transmitted diseases include otitis media, whooping cough, herpesvirus, and hepatitis A and B.[197]

Significantly, 20 percent to 60 percent of children attending day care centers are carriers of antibiotic resistant S. pneumoniae.167 In a recent Canadian study, 44.3 percent of children attending 59 day care centers were carriers of S. pneumonia with 17 percent of the isolates exhibiting decreased susceptibility to penicillin and 13.7 percent displaying multiple-antibiotic resistance.[198] Antimicrobial use both individually and in the total community is strongly associated with nasopharyngeal carriage of penicillin-resistant pneumococci in children.[199]

In a study of two child care centers, 3 percent of children at one center and 24 percent at the other were carriers of methicillin-resistant S. aureus.[200] The number of children in the community hospitalized with community-acquired methicillin-resistant S. aureus without identifiable risk has increased from 10 of 100,000 hospital admissions in 1988-1990 to 259 of 100,000 hospital admissions in 1993-1995.[201]

The critical factors for disease transmission in day care centers are the age of the child and the size of the facility.[202] Age determines the personal hygiene and immunological maturity of the child while the size of the facility (children attending) and the percent of pre-toilet-trained as opposed to toilet-trained children determines the cleanliness and odds of transmission.[202] In the first and second years of day care, 52 percent to 76 percent of children contract an infection as opposed to 27 percent to 36 percent in the third year and 16 percent at home.[167] In an eight-month study of child care centers, the incidence of antibiotic use was 36 percent in child care centers, 7 percent in child care homes and 8 percent in the child's own home.[203] The annual rate of antibiotic use was 3.6 times greater in child care centers than home and five times longer in duration.167 A symposium on child day care health is available.[204]

Long-Term Care Facilities

There are presently 2.5 million United States residents of long-term care facilities; and infections, primarily pneumonia, are a major cause of morbidity and mortality. Approximated 43 percent of the U.S. population that turned age 65 in 1990 will spend time in a nursing home.[205,206] Antibiotics account for 40 percent of all drugs employed in nursing homes with 50 percent to 70 percent of residents getting at least one antibiotic per year.[206] Between 35 percent and 75 percent of antibiotic use in such facilities is considered inappropriate.[206]

The occurrence rate of nursing home infections range from 1.6 percent to 32.7 percent with most studies showing an occurrence rate of less than 10 percent with an incidence rate of 1.8 to 7.1 per 1,000 resident days.[206] Risk factors include IV lines, indwelling catheters, malnutrition, polypharmacy, chronic disease (dementia, cardiovascular disorders, urinary and fecal incontinence), and altered immunity (T lymphocyte and cytokine function).[205,206] Another major factor is colonization of the oropharynx, external nares, and skin with highly antibiotic-resistant S. aureus, beta-hemolytic streptococci, P. aeruginosa, Enterobacteriaceae, and particularly K. pneumoniae.[205,206]

Antibiotic-resistant pathogens in nursing homes include penicillin-resistant S. pneumoniae, extended-spectrum beta-lactamase-producing gram-negative bacilli resistant to third generation cephalosporins, vancomycin-resistant enterococci, methicillin-resistant S. aureus, coagulase-negative staphylococci,

and vancomycin-intermediate-resistant S. aureus.[205-208] Antibiotic resistance is high due to extensive antibiotic use in nursing homes, selection, and transfer of resistance genes and microorganisms from incoming residents.[206]

In a recent study, 31 of 35 nursing home residents admitted to tertiary care hospitals from eight separate nursing homes were infected with or colonized with ceftazidime resistance in E. coli, K. pneumoniae, or both.[209] It appears that nursing home residents pose a significant risk for introducing highly antibiotic-resistant pathogens into acute-care hospitals with the reverse also possibly true.

Hospital-Acquired Infections

The Centers for Disease Control and Prevention has variously estimated that of the 40 million people hospitalized every year in the United States, 2 million to 4 million experience a nosocomial infection[210-212] resulting in 90,000 deaths.[213] This is likely to be a considerable underestimate.[214,215] This reported death rate from nosocomial infections is likely to be much smaller than the reality as pathologists commonly list causes of death by the general pathologic diagnosis (lobar pneumonia) rather than the causative microorganism (pneumococcus)[214] and multiple cause-of-death data do not allow for the extraction of microbial causation information.[215] If the microbial cause (methicillin-resistant S. aureus septicemia, for example) were listed as the cause of death rather than congestive heart failure, renal failure, and so forth, the nosocomial infection death rate would rise dramatically and would likely make the list of the 10 leading causes of death in the United States.[215,216]

The morbidity/mortality rate from nosocomial infections has been estimated to be 5 percent to 25 percent depending on the given country[217] with a possible 50 percent mortality in surgical intensive care units for nosocomial blood-stream infections.[218] Approximately 50 percent to 60 percent of nosocomial antibiotic-resistant organisms are resistant to several antibiotics and in some intensive care units there is a 27 percent to 70 percent chance of acquiring a nosocomial infection due to one of these microorganisms.[210] Many of these infections are related to invasive devices (catheters, ventilators, central lines) with possibly at least 400,000 annual catheter-related blood-stream infections in the United States.[219]

In a review of more than 10,000 blood-stream infections at 49 hospitals, gram-positive organisms accounted for 64 percent of cases, gram-negatives for 27 percent, and fungi for 8 percent.[220] The most common organisms were coagulase negative staphylococci (32 percent), S. aureus (16 percent) and enterococci (11 percent).[220] Intensive care unit infections were more likely to be Enterobacter, Serratia, coagulase negative staphylococci, and Candida infections while in patients with neutropenia, viridans streptococci were most common.[220] Methicillin resistance was seen in 29 percent of S. aureus and 80 percent of coagulase-negative staphylococci while 3 percent of E. faecalis and 50 percent of E. faecium were vancomycin-resistant.[220] Studies in the Western hemisphere show similar numbers, with 33 percent to 48 percent of all viridans group streptococci resistant to penicillin and 20 percent resistant to the macrolides.[221] New extended-spectrum beta-lactamases have conferred high resistance to third generation cephalosporins in E. coli and K. pneumoniae and increasing resistance is seen in Acinetobacter baumanii, Stenotrophomonas maltophila and P. aeruginosa.[222,223]

The principal infections in pediatric intensive care units are primary bloodstream, pneumonia, and urinary tract infections,[224] while in adult intensive care units, urinary tract infections predominate followed by pneumonia and blood-stream infections.[223] The principal organisms are S. aureus, coagulase-negative staphylococci, enterococci, E. coli, and Candida for blood-stream infections; E. coli, enterococci, K. pneumoniae, and P. aeruginosa for urinary tract infections; S. aureus, H. influenzae, P. aeruginosa, and E. cloacae for respiratory tract infections; and staphylococci, E. cloacae, and P. aeruginosa for skin/wound infections.[222,225-227] All of these microorganisms are highly lethal and multiple-antibiotic resistant.

Patterns of Antibiotic Use

Antibiotics are often employed as "drugs of fear"[228] used to "cover" for errors of omission or commission and thereby "prevent" claims of negligence. Approximately one-half of all antibiotics employed in hospitals are in patients without signs or symptoms of infection, and in many cases are used to prevent infections or to ensure that "all was done" to prevent later criticism.[229] In hospital antibiotic use, approximately one-third are used empirically, one-third for prophylaxis, and one-third with appropriate culture and sensitivity tests.[230] The increasing use of broader spectrum antibiotics may allow hospitals to save the costs of microbial sensitivity tests. Paul Ehrlich's "magic bullet" has been replaced by a shotgun.[231]

Outpatient antibiotic use can be characterized by the 80:80 rule: 80 percent of all antibiotics are used in the community and 80 percent of these are used for respiratory infections.[232] Most of these respiratory infections are viral in nature and are not amenable to antibiotic therapy.[233] Of the 50 percent of people with acute respiratory illness that seek medical treatment, 50 percent to 80 percent will receive an antibiotic; but pneumonia (the only upper respiratory tract infection requiring antibiotic therapy) will account for only 2 percent of these cases.[234] The prescribing of antibiotics can vary 15-fold among physicians, and those that tend to prescribe many drugs tend to do the same with antibiotics.[235] Antibiotics remain the single most abused privilege that physicians have.[236]

The reasons for the inappropriate use of antibiotics are:

- Insufficient training in infectious diseases and proper antibiotic therapy;
- Empirical use;
- Lack of culture and sensitivity tests where appropriate and useful;
- Inadequate diagnostics
- Inappropriate choice of drug, dose, and duration;

- Need of self-assurance;
- Patient demands; and
- Fear of litigation.[232]

A final difficulty with antibiotics comes from a pharmaceutical industry that is beholden to stockholders as well as the health professions: "Clearly it is in the best interests of pharmaceutical companies to promote the wide use of antibiotics to justify research and development costs. This fact, coupled with the willingness of some physicians to prescribe the latest antibacterial, has undoubtedly increased the frequency of resistance."[237] To be fair to the pharmaceutical industry, very significant risks and costs are associated with new drug development, particularly with antimicrobials where: "A single base change (in the nucleotide sequence of a bacterial gene) can render useless a hundred million dollars of pharmaceutical research effort."[238] "Humans should not confuse themselves. This is true biological warfare in which new drugs designed by humans will become obsolete through bacterial mutations, only to be replaced by new drugs and new bacterial mutations in a seesaw battle."[238]

The Control of Antibiotic Misuse

It is generally accepted that a direct causal relationship exists between antibiotic use and the appearance of microbial resistance as:

- Antibiotics select for specific resistance traits;
- A reduction in antibiotic use results in a reduction in antibiotic resistance to that agent;
- Hospital changes in antibiotic use leads to altered antibiotic resistance patterns;
- Nosocomial resistance rates are far greater than those in the community due to more intensive antibiotic use;
- Hospital patients with resistant strains are more likely to have taken prior antibiotics;
- Areas of the hospital with the greatest antibiotic use have the highest resistance rates; and
- The longer the duration of antibiotic use, the more likely colonization with resistant organisms will occur.[239]

The intensity of antibiotic use in a given populationwhether in a hospital or community is the most important factor in the selection of microorganisms for resistance.[240] It follows then that all microbial resistance to antibiotics is local and depends on the patterns of antimicrobial use in the particular geographic locale. What is true in Spain may not be true in England nor in Los Angeles nor New York. It is equally true that any attempts to reduce microbial resistance must begin locally. There are only two ways to prevent the development and spread of resistant microorganisms:

Reduce antibiotic use to reduce the selection of resistant bacteria or the emergence and/or transfer of resistance genes; and

Improve hygiene measures in hospitals to prevent the development and spread of resistant microbial strains.[241]

Attempts to restrict the use of antibiotics in specific locations such as intensive care units and even entire countries is showing promise in the control of resistant microbes. In Finland, the reduction in defined daily doses (the amount of antibiotic taken in one day) from 2.40 to 1.38 per 1000 people per day from 1992 to 1996 has resulted in a decrease in group A streptococcal resistance to erythromycin from 16.55 percent in 1992 to 8.6 percent in 1996.[242] Alarmed by a rise in penicillin-resistant pneumococci from 2.3 percent in 1989 to almost 20 percent in 1993, Iceland restricted the use of penicillin resulting in a decline of these organisms to 16.9 percent in 1994 and a reduction in penicillin-resistant pneumococci in day care centers from 20 percent to 15 percent.[243] Hungary has also experienced a decline in antibiotic-resistant S. pneumoniae from 50 percent to 34 percent with reduced antibiotic use.

An 80 percent reduction in hospital use of cephalosporins between 1995 and 1996 resulted in a 44 percent decrease in ceftazidime-resistant K. pneumoniae infection, and colonization decreased by 70.9 percent in intensive care units.[244] A reduction in the hospital use of cephalosporins, imipenem, clindamycin, and vancomycin resulted in a reduction in patients colonized by methicillin-resistant S. aureus and ceftazidime-resistant K. pneumoniae.[245] These changes in antibiotic use must be closely monitored as there is a tendency to then employ other antibiotics, which leads to different resistance problems.[244,245]

Professional Responsibility to Control Microbial Resistance

Hospitals

A number of suggestions have been made to reduce either the extent of microbial resistance to antibiotics in hospitals or the transmission of strains from patient to hospital staff or vice versa. These include:

- Educate health professionals and the public about microbial resistance to chemicals;
- Decrease antibiotic use by employing proper indications, dosage, and duration of use;
- Restrict the use of new antibiotics;
- Develop a monitoring system for microbial resistance patterns and in-hospital antibiotic use;
- Isolate patients colonized or infected with resistant organisms;
- Decrease the clonal spread of resistant strains by infection control practices;
- Discourage the use of multiple antibiotics unless dictated by culture and sensitivity tests;
- Optimize antibiotic use for surgical prophylaxis and reduce antibiotic prophylaxis to established uses;
- Encourage culture and sensitivity testing instead of broad spectrum antibiotics (a return to the one bug, one drug rule); and
- Improve socioeconomic conditions (crowding, hand washing, feces disposal, clean water).[246,247]
- Other measures that can be useful outside the hospital include:
- Decreased antimicrobial use in agriculture and aquaculture;
- Practitioner resistance to patient antibiotic demands;
- Better diagnosis of upper respiratory viral diseases and cessation of antibiotic use for these conditions;
- Washing of fruits and vegetables;
- Restriction of antibiotics to proper

durations of use;
- Attention to local antibiotic resistance data; and
- Handwashing.[248]

Dentistry

Since dentistry prescribes approximately 10 percent of all the common antibiotics (penicillins, cephalosporins, macrolides, tetracyclines), our contributions to the problems of microbial resistance can be substantial.[233] Antibiotic misuse in dentistry primarily involves the use of antibiotics in inappropriate situations or for too long a period of time. Inappropriate uses include:

- Giving antibiotics after a dental procedure is completed in an otherwise healthy patient to "prevent" an infection, which in all likelihood will not occur anyway (read to "prevent a lawsuit" in many cases);
- Using antibiotics as "analgesics" particularly in endodontics;
- Employing antibiotics for prophylaxis in patients not at risk for metastatic bacteremias;
- Using antimicrobials to treat chronic adult periodontitis, which is almost totally responsive to mechanical treatment;
- Using antimicrobial therapy in lieu of mechanical therapy in periodontitis management;
- Using antibiotics and antimicrobials chronically in periodontitis;
- Using antibiotics instead of surgical incision and drainage of infections; and
- Using antibiotics to "prevent" claims of negligence.

The use of antibiotics to "prevent" post-treatment infections by giving the drugs after the dental procedure is completed violates all the principles of antibiotic prophylaxis (loading dose, drug in the system before surgery begins, only against a single pathogen, only as long as bacteremia persists, proper risk-cost/benefit ratio) and has not been demonstrated to be clinically effective.[249] Antibiotic prophylaxis for the prevention of surgical infections is only effective if the drug is in the system before the procedure begins and then only in clean/clean or clean/contaminated surgery where the drug is discontinued shortly after the surgery is completed.[249] The mouth is one of the most heavily contaminated areas of the body and may not qualify under this scenario. The pharmacokinetics of antibiotics ensures that an antibiotic begun sometime after the dental procedure and without a loading dose may achieve significant blood levels six to 12 hours after the procedure or sometime the next day when the issue of whether an infection occurs has already been decided (in the vast majority of cases against a postoperative infection).[250,251]

The use of antibiotics as "analgesics" to treat postoperative pain is irrational as better drugs are available as analgesics, and most studies indicate that antibiotics do not relieve postoperative edema, pain, and trismus.[249] The proper attention to the established guidelines for antibiotic prophylaxis to prevent metastatic infections as advocated by the American Heart Association for infective endocarditis and the American Dental Association/American Academy of Orthopaedic Surgeons for dental patients with orthopedic prosthetic joints will significantly reduce unnecessary antibiotic prophylaxis in dentistry.[252,253]

The use of antibiotics in the treatment of periodontal disease is only appropriate in the management of acute periodontal infections, primarily periodontal abscesses, and in the management of refractory or rapidly progressive periodontitis, which has failed to go into remission after standard treatment procedures.[254,255] The use of antimicrobials such as low-dose doxycycline as an "adjunct" to periodontal care for extended periods of time or in lieu of periodontal subgingival instrumentation has been discussed above and in a recent review.[256] The risk-benefit ratio for such a practice appears inadequate and, if used instead of competent subgingival instrumentation, violates the cardinal principle of infection control: removal of the source of the infection.

Antibiotics are almost never a substitute for surgical drainage (incision and drainage, extraction, endodontics) of an infected area (the sun should never set on undrained pus) for a number of reasons:

- Antibiotics do not diffuse well into infected areas;
- The blood supply to abscesses is usually compromised;
- Some antibiotics do not work well at the acidic pH of abscesses;
- Microorganisms may be dividing slowly or not at all, particularly in older abscesses thereby negating the effects of penicillins and cephalosporins that act only on dividing organisms; and
- High levels of antibiotic inhibitors (beta-lactamases) may be present in abscesses.[250,251]

Occasionally, an infected area is not amenable to incision and drainage (pericornitis, indurated cellulitis) and antibiotics are the only available treatment, but the exception should not become the rule.

The use of antibiotics as " drugs of fear" to "prevent" lawsuits has never been rational but has been somewhat understandable considering the tort climate today. Such a practice has contributed substantially to antibiotic resistance problems; and it is unknown just how many lawsuits, if any, have been prevented since no study of this problem has ever been performed. A case can be made that the legal profession in the United States has had as much a role in microbial resistance to antibiotics as the health care professions and patient misuse.

The second factor in the misuse of antibiotics in dentistry in addition to inappropriate use is employing the drugs for too long a duration and at too low a dose. Antibiotics should be used aggressively and for as short a time as is compatible with patient remission of disease.[251,252] In infectious diseases that do not rebound (return upon cessation of the antibiotic), such as orofacial infections, the proper duration of the antibiotic is determined by the time it takes for the patient host defenses to gain control of the infection.[251,252] With orofacial infections, the antibiotic is terminated when the infection has resolved or is reasonably certain to resolve. [251,252] The use of antibiotics for too long a duration and particularly at subinhibitory concentrations greatly increases microbial resistance.[6,15,170,257,258]

The duration for antibiotics can vary significantly due to the following factors:

- The ability to incise and drain the infection;
- Host medical status and response to the infection;
- Growth rate and virulence of the infection;
- Ability of the antibiotic to diffuse to the infection site;
- Presence of resistant bacterial strains; and
- Antibiotic choice and dose.[251,252]

Therefore, each infection is unique and a "standard therapy" of the same dose and duration for every infection will lead not only to increased microbial resistance, but also to treatment failures.[251,252]

The old adage that antibiotics should be given for x number of days (five, 10, 14, or whatever) to "kill resistant strains" is an oxymoron since bacteria that are resistant are by definition unaffected by the antibiotic. While it is true that some bacteria may occasionally mutate to resistance in a "stepwise" fashion over several generations and that prolonged antibiotic therapy may kill or inhibit these mutants before they gain full resistance, this does not reflect the reality of how resistance operates today. Virtually all microbial resistance occurs by the transfer of resistance genes via bacteriophages, plasmids, transposons, and integrons from microorganisms already resistant to the antibiotic(s). Prolonged antibiotic use over what is necessary will only select for these often highly resistant strains and pose a much greater risk for human health than failing to inhibit a few isolated mutants.

Lastly, patients are often mandated to "finish the course of the antibiotics" no matter what has happened with the infection. This is reasonable with rebound infections. However it is also predicated on an assumption: that the prescribing health practitioner actually knows beforehand precisely how long the infection will last. This is often unlikely due to the patient and drug variables listed above. Even the experts make this mistake by assuming that the course of the infection is predictable from its outset, that the practitioner knows precisely what the clinical course will be or that the 10-day therapy established for the treatment of streptococcal sore throat fits all infections. The wise practitioner follows the progress of the infection until its termination.

Conclusions

When antibiotics are employed, six things may occur, only the first of which is good:

- The antibiotic may aid the immune system to gain control of the infection; or
- Toxicity or allergy may occur;
- Already resistant microbes may be selected for and a superinfection may result;
- The antimicrobial may promote microbial chromosomal mutations;
- Gene transfer may be encouraged from resistant to nonresistant microbes; and
- Latent resistance genes may be expressed.

Antibiotic treatment failures will continue to increase in medicine as well as in head and neck infections. Dentistry should not be surprised that the future will hold increasing difficulties with penicillin and macrolide resistant viridans group streptococci and beta-lactamase producing Prevotella and Porphyromonas. Nature may hold other microbial resistance surprises for us also. The more we look, the more we will find.

The global problem of microbial resistance to antibiotics is serious not only in its extent but also in the rapidity with which microorganisms are attaining and maintaining resistance. It is not time to panic, but it is time for all to realize that the problem cannot be solved without a concerted effort on the part of all concerned: patients, parents, health professionals, veterinarians, food producers, and governments. We must fully appreciate that: "Penicillin brought more curative power to a barefoot, itinerant care provider in the deepest reaches of Africa than the collective powers of all the physicians in New York City." [259] It is time for us all to become part of the solution and not the problem. After all, our lives depend upon it.

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Global Antibiotic Resistance and Its Impact on the Dental Community

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Crossing That First Bridge

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Do you remember your first clinical bridge? How could you not? Forever verdant in memory, etched on your cerebral cortex like your first pair of long pants, your first kiss or your first set of wheels is that whole episode of the First Bridge.

Actuarially speaking, the trauma of the first bridge shortened every dental student's life by 10 years and reduced his skeletal being to the consistency of jellied consommé. Even today, the memory of it is a moment of nostalgia laced with masochism.

Picture this: **Day One**, *16th and Los Angeles streets in the City of Angels, 1941, in a structure erected by hominoids toward the end of the Pleistocene Period. It has now grown so decrepit, dogs refuse to relieve themselves on it. Within its stygian interior, a white-coated Olympian figure with red-striped sleeves summons a student who, lacking the adroitness to jerk sodas, has espoused a career in dentistry.*

"Number 76," he intones, assuming the voice of James Earl Jones as Darth Vader, "you will commence your first bridge case at morning's light." Having been relieved of my Christian name at the outset of the freshman year, I recognize that my double-digit persona has been addressed.

"Yes, Sir," I gulp, my marrow quietly freezing, my features petrified in the dreadful risus sardonicus. Deep within my thyroid, a shrill whistle gives a long, piercing blast to signalize the close of business, and before I can claw open my 45-button student gown to equalize the pressure, I am a 22-year-old dental student entirely surrounded by floor.

Day Two: Whatever thirst I had for a DDS degree has been effectively slaked, but there is nothing for it now but to forge ahead as if I know what I am doing. With the speed of library paste, I hastily assemble my state-of-the-art armamentarium as delineated in the Junior Crown and Bridge Syllabus. This consists of two green stone points for a contra-angle handpiece; an assortment of steel burs guaranteed by the manufacturer to turn blue after two minutes or 50 revolutions, whichever comes first; a saliva ejector; rubber dam; clamps; and a small flashlight for illuminating the darker recesses of the mouth. The Doriot handpiece -- which redlines at a dizzying 4,000 rpm right up to the moment it throws a belt or suffers pulley seizure – completes the setup.

Days Three to 14: This period is being used to prepare the molar abutment. Although green stones are said to be on the cutting edge, the actual cutting is on a par with sawing through two inches of stainless steel with an emery board. The steel burs are of little assistance, being compounded of equal parts of pig iron and lead. Still, except for a lost week trail-

ing the instructor around in the conga line that was fastened to his backside like a leech, the molar anchor is finally, albeit grudgingly, approved. The little column of smoke that arose from the tooth after two hours of green-stoning will later prove to have been a harbinger of things to come for the pulp, but for the nonce is a matter of signal irrelevancy.

Days 15 to 25: Abutment No. 2 proceeds at an incendiary rate now that I've got the hang of it. Punctuated only by an unfortunate incident wherein the saliva ejector reverses the flow of its contents, the appointment goes well. The patient, who is initially thought to be merely asleep, is discovered to be comatose, possibly related to the 16 liters of procaine he has flowing in his vascular system in lieu of blood. Beginner's luck, or not, the bicuspid anchor is checked off as a "6" on a 1-10 scale.

Fabrication of the temporary crowns is accomplished in just slightly more time than Michelangelo required painting the Sistine Chapel. On the other hand, Michelangelo wasn't obliged to check with the Vatican every time he thought he was finished with an angel's finger or a wing feather. Nor was he constantly harassed by the Pope demanding, "Do it over, Buonarroti!"

During the hiatus wherein the patient is unshackled to celebrate a couple of birthdays and father a child, I am stockpiling hydrocolloid, trays and an uninterrupted water supply in anticipation of Impression Month.

Days 61 to 87: My patient seems to have grown a full beard, which is handy because we are experiencing a shortage of bibs until the advent of the next tuition rise. I effectively use the time between impression retakes waiting for the little blisters to subside by delivering with fetching candor my opinion of what a moron you'd have to be for losing the tooth I'm replacing in the first place.

Days 81 to 104: My patient is only dimly aware -- not only of what he is doing here, but that he is about to receive the best dentistry has to offer: a pontic with the Long Pin Facing. This replacement tooth is so realistic it's scary! Only the gold occlusal, the distinctive gray-green hue of the porcelain, and the extra 3 mm length can give it away.

I have now slaved over this bridge for six months, not counting Spring Break and Christmas, and it looks as if it will go in shortly before the end of the year. My patient is becoming restive. I am able to mollify him by threatening him with a felonious blow on the sconce -- and a fervent promise that I will never touch him again if he will allow me to finish.

Day 216: Polished brighter than a new Buick, the completed bridge warms the cockles of my heart no less than if I had just thrown a span composed of Erector Set girders over the Grand Canyon.

March, 11, 1943: Despite numerous tearful entreaties on my part, my ex-patient refuses to return to the West Coast from Indonesia where he claims to have fled to escape the consequences of my having just a little difficulty seating his new bridge. My explanation that the abutment teeth drifted together a paltry quarter inch during the preparation and it was therefore not my fault, falls on deaf ears.

Apparently he also faults me for a perceived excess of brio in tapping the bridge into place with an orangewood stick and mallet during which the molar abutment disappeared into the maxillary sinus.

There's a lesson to be learned here. That's why I'm going into orthodontics; what could go wrong there?