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COVER STORY

The integration of clinical research into dental therapeutics

The role of the astute clinician

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The evolution from a clinical observation in dental practice to a validated therapeutic innovation in dentistry is illustrated best by the recognition of the link between mottled enamel, drinking water source and the incidence of caries.¹ In 1901, Dr. Frederick S. McKay, a recent dental-school graduate, noted that many of his patients had permanently stained teeth.

The small proportion of validated practices provides ample opportunities for dentists to address problems and propose solutions important to dental practice.

His efforts to learn more about this strange phenomenon attracted the attention of Dr. G.V. Black, who collaborated with Dr. McKay in studying what they termed "mottled enamel." They were the first to suggest a possible link to the source of drinking water. Dr. McKay persisted in his studies and by 1925 noted that children in areas where mottled enamel was prevalent also had less caries. These clinical observations and a report that a diet that included fluoride produced mottled enamel in experimental studies in animals prompted the U.S. Public Health Service, or USPHS, to action in 1931.²

The USPHS charged newly hired dental officer Dr. H. Trendley Dean to study the relationship between fluoride in water supplies and mottled enamel, with the intended outcome of learning how to remove fluoride from water to eliminate the cause of the mottling. Within months of initiating studies to examine

Background. Although productive, traditional research approaches may not always address clinically relevant outcomes or translate into changes that can be made in practice. Conversely, clinical observations often result in therapeutic innovations but require verification of safety before widespread use.

Overview. As a strategy for greater integration of research findings and clinical practice, the authors suggest approaches for clinicians to document clinical observations through best case series as a basis for more controlled clinical trials. The aim is to engage clinicians in the process of therapeutic innovation through clinical research.

Conclusions and Practice

Implications. This approach represents a necessary first step for practitioners to formulate hypotheses for further testing, to identify clinically relevant outcome measures and to contribute to the evidence base for clinical practices in dentistry.

children's teeth,¹ collect water samples and confer with state health officials and local dentists, Dr. Dean detected a link between the mottled enamel and a lowered incidence of dental caries.

Development of more sophisticated methods to quantify fluoride levels in drinking water eventually established that 1 part per million, or ppm, resulted in no evidence of mottled enamel and no detectable toxic effects. By establishing a relationship between the amount of fluoride in drinking water and the incidence of dental caries, Dean provided the level of evidence needed to advance a clinical observation to a prospective clinical trial. This clinical trial was the Grand Rapids fluoridation project, initiated in 1945. This community-based controlled clinical trial confirmed that fluoride in drinking water at 1 ppm significantly lowered the incidence of

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caries without mottled enamel or other signs of toxicity. This example illustrates that a highly successful public health intervention that changed the incidence of dental disease dramatically was based on the clinical observations of an astute clinician.

The hazard of using a seemingly effective therapy in humans without appropriate validation is illustrated by the cases of patients who received temporomandibular joint, or TMJ, implants for the surgical treatment of temporomandibular disorders, or TMD. Teflon (DuPont, Wilmington, Del.) implants were introduced in 1970 as a TMJ implant material without preclinical testing being conducted based on use of this material for soft-tissue defects in plastic surgery. Early published reports consisted of an uncontrolled series of cases reporting short-term clinical success without any signs of toxicity.^{3,4} These implants eventually degraded in most patients when subjected to biomechanical joint forces, which resulted in localized reactions at the joint region, degenerative changes, persistent joint pain and joint dysfunction.⁵⁻⁷ The extent of problems with TMJ alloplastic implants and the characteristics of patients who have had unsuccessful outcomes remain unclear in the absence of epidemiologic studies. Clinical reports, however, indicate that some patients developed chronic orofacial pain, impaired jaw function, fibromyalgia⁸ and further structural changes.⁹⁻¹¹ The introduction of TMJ implants based on clinical observations and uncontrolled case series into dental practices resulted in negative outcomes such as diminished quality of life and altered sensitivity to sensory stimuli for some of these patients. There was little evidence of long-term efficacy to justify the adverse outcomes.

In both of these examples, the initial clinical observations showed promise for addressing a significant clinical problem. Fluoridation of water proved to be one of the most successful public health initiatives of the 20th century, while an untold number of patients continue to experience negative effects owing to the failure of Teflon TMJ implants. What differed with fluoride is that in one case, the observations of an astute clinician were validated through further scientific studies and the safety of the therapeutic intervention was proven through appropriately conducted clinical trials. In the case of the TMJ implants, widespread clinical use followed after a few articles that reported uncontrolled case series were pub-

lished. This case series represents an initial form of scientific evidence,^{12,13} but it should have been validated by controlled trials and demonstrations of safety. Just as we would not want to be unwittingly exposed to an unproven medication or medical device without assurance by a regulatory agency such as the U.S. Food and Drug Administration, or FDA, of the product's effectiveness and safety, we ethically have to hold this same standard for treatments that are used in clinical dental practice. The skill of an astute clinician is based on professional training, powers of observation and clinical experience, but it also requires knowledge of the scientific process and consideration of the ethical imperative to "first, do no harm."

THE SCIENTIFIC FOUNDATION FOR CURRENT CLINICAL PRACTICES

The daily decisions as to what diagnosis is best assigned to a patient, what the most appropriate treatment is and what the likely outcome is often are taken for granted. Ideally, each of these steps in therapy is founded on past basic and clinical research and may be improved in the future with continuing clinical research. The decision about how to treat a patient once the diagnosis has been made usually involves selection from several therapeutic options, an assumption of the outcomes associated with the decision to treat versus allowing the natural history of the disease process to continue, and knowledge of the effectiveness and safety of the various treatments. The treatment of a carious lesion, for example, can range from enameloplasty (to remove incipient caries) to promotion of remineralization to removal of the lesion and placement of an accepted restorative material to an endodontic procedure to extraction of the tooth in the case of gross caries or financial limitations. Better yet, the carious lesion could have been prevented.

Research has permitted the dental profession to evolve from extractions as the traditional approach to treatment of caries in the 1800s to use of restorations with increasingly improved biomechanical properties in the 1900s to use of dental sealants by the turn of the 20th century to current research for specific interventions at the biofilm level or through regeneration of lost structures. Sustained progress in treating and preventing dental disease can be attributed to basic research findings, translational research that validates these findings, and applied research in

humans to demonstrate efficacy and confirm safety of new therapies based on research findings. While the process is imprecise (because the answers are not known until relatively late in the development process) and the length of time from research observation to therapeutic innovation is slow (to maximize safety), the evolution in dental practice rests largely on a foundation of basic, translational and clinical research.

The ability to differentiate among treatment options also is based in part on knowledge of the likely time course of the disease process if the disease is not treated, also known as the natural history of the disease. For example, although advances have occurred in diagnostic methodology for caries and treatment options are more varied than ever, the natural history of caries is predictable and can be gleaned readily from clinical experience, which is a composite of cross-sectional comparisons across patients at varying steps in the disease process, as well as patient observations over time. Clinicians assimilate these factors when selecting a treatment option for a patient.¹⁴ More problematic are areas such as TMD in which many symptoms are self-limited and actually may be exacerbated by treatments that can contribute to development of chronic pain, activate immune processes or produce iatrogenic injury.

Faced with a treatment decision, a practitioner can rely on clinical experience with similar patients, consult expert and peer opinion, or try to sort through the literature to make an informed therapeutic decision. This difficult process often is waived by adopting methods advocated by a well-recognized expert without considering whether the therapeutic procedure has been validated scientifically, is based on an uncontrolled series of patients, or may represent biased case presentations. In the latter two situations, the risks and ethical considerations of using non-validated practices still rest on the practitioner and convey the same potential for adverse outcomes as we described earlier with the injudicious use of TMJ implants.

EVALUATION OF THERAPEUTIC INTERVENTIONS

Novel treatments first described on the basis of initial case reports, case series or poorly controlled clinical trials usually appear to have therapeutic benefit or the results would not be publicized or published. After evaluation of a putative

therapy in well-controlled clinical trials, a number of alternative interpretations often are possible. If several trials indicate that the treatment is effective with an acceptable level of safety, it then is considered to be a validated therapeutic practice. An example is the use of non-steroidal anti-inflammatory drugs, or NSAIDs, for the control of acute orofacial pain. If the treatment is found not to be effective or toxicity becomes evident, the drug is removed from the market in a manner similar to what occurred with zomepirac (Zomax, McNeil Pharmaceuticals, Fort Washington, Pa.) in the 1970s. Another example is labeling restrictions that may be imposed as was done for orally administered ketorolac (Toradol, Roche Pharmaceuticals, Nutley, N.J.) in the 1990s. However, unlike pharmaceutical interventions, which undergo a continuum of evaluation from phase 1 (safety) to phase 4 (population-based adverse events surveillance), few other therapies and products undergo this level of scrutiny.

Most therapies used in dentistry do not fall under the jurisdiction of the FDA as either drugs or devices, and they are not subjected to rigorous examination before being used in humans. Other review processes, such as the U.S. Pharmacopeial Convention, use expert panels to review non-FDA-approved uses for marketed drugs, but they do not address devices or clinical practices. As a consequence, most drugs, devices and therapeutic strategies that are used for dental therapy fall into the category of nonvalidated clinical practices. This does not imply that these treatment modalities do not have some therapeutic value. Rather, they have not been subjected to well-controlled trials that allow the community to determine if they are validated clinical practices whose efficacies exceed the potential for toxicity and are preferable to alternative treatments or, possibly, that their use represents an irrational clinical practice that should not be continued. Again, the hazard of using a seemingly effective therapy in humans without appropriate validation of safety is illustrated by the example of using Teflon implants to treat TMDs. The principles of using clinical interventions in dental practice rests on the same principles that apply to the use of all therapeutic modalities: demonstrated efficacy for the indication, an acceptable incidence and severity of adverse reactions for the condition being treated, and safety when used in large numbers of patients for prolonged periods.

Evidence for the efficacy and safety of dental therapeutics based on clinical experience does provide a level of proof that often is valid and is based on undocumented but successful iterations in clinical practice. Conversely, review of the current status of clinically relevant evidence in dentistry¹⁵ concludes that outcome studies are not available to guide management of caries, periodontal diseases or facial pain—three of the most common problems faced in daily dental practice. Similarly, evidence often is lacking that provides reliable information to patients on the level of pain associated with various dental procedures and that can inform their decisions on which therapeutic option to select.¹⁶ Even in areas in which ample evidence is available from controlled trials that demonstrates the efficacy of a treatment in the context of a relatively small, carefully selected sample of patients, as in the use of NSAIDs for acute pain, data often are scant on the effectiveness of the treatment in the more diverse clinical milieu. Evidence of the adverse gastrointestinal and renal effects of NSAIDs, for example, is now well-documented through rigorous epidemiology studies involving millions of drug exposures, a perspective that is beyond the scope of individual clinicians in practice. Rather than being contrary to clinical experience and intuition, information derived from clinical research serves as a foundation for clinical decision making¹⁷ and provides a framework for validating therapeutic innovations under the real-world conditions of clinical practice. Similarly, observations in clinical practice can serve to inform and guide clinical research.

MOVING FROM 'IN MY HANDS' TO 'IN YOUR HANDS'

The primary justification for basing therapy on the results of controlled clinical research is that clinical trials are the most objective way to obtain a meaningful answer to a therapeutically relevant issue.¹² A successful trial is one that reaches the correct conclusion, not necessarily one that produces a positive result. Ultimately, a therapeutic device, drug or procedure is validated successfully when others can replicate the results of a trial of it under similar circumstances. While replicate controlled clinical trials provide one of the highest levels of scientific evidence,^{12,13} a convincing indicator of how well a new technique performs is when it is tested under the conditions in which it actually will be used. For most dental procedures and devices, the real world consists of

community-based dental practices in which procedures can be evaluated “in my hands” with sufficient numbers of patients and practitioners to judge whether it also can be used successfully in the hands of others. This is where the astute clinician can help integrate therapeutic innovations into clinical practice.

How can this be achieved? Approaches to involve practitioners in clinical research are instructive examples for the dental profession. The Clinical Community Oncology Program of the National Cancer Institute, or NCI, has been a successful approach to community-based clinical research that has evaluated investigational chemotherapy agents and their combinations for more than 20 years.^{18,19} The National Eye Institute uses networks of practice-based collaborative study groups to evaluate new treatments.²⁰ These large studies are conducted with the assistance of data coordinating centers to provide guidance through all steps of the clinical research process.

Another approach to practitioner participation in clinical trials is the referral of appropriately screened patients to academic health centers to serve as subjects in clinical trials that require a greater number of subjects than might be recruited at a single site within a reasonable time frame. This permits confirmation that the patients meet inclusion and exclusion criteria before enrollment, administration of any specialized diagnostic tests that may be available more readily in an institutional setting and an infrastructure for data collection. Study subjects often receive the clinical procedure at discount or no cost, which often is not feasible in a private-practice setting. For example, a clinical trial evaluating an intervention to attenuate the development of persistent pain required more than 100 dentistry-phobic patients seeking oral surgery under general anesthesia who were willing to remain at the clinic for up to six hours postoperatively and to return daily for two days for follow-up data collection.²¹ Subjects were selected from approximately 700 annual patient referrals to a biomedical research facility over a two-year period. The results provide evidence for an intervention that can be used readily by dentists: administration of a long-acting local anesthetic to prevent pain in the immediate postoperative period contributing to the development of prolonged pain.

In another study of patients with TMD, researchers screened a large number of subjects

by phone interview, evaluated their eligibility at a clinical examination and randomized them to one of three groups, including a placebo group, for six weeks of drug administration with follow-up appointments. The study required more than two years to accumulate significant numbers of carefully selected subjects, but it provides the first publishable evidence that NSAIDs have therapeutic value for this common dental condition.²²

These examples illustrate how a novel therapeutic strategy suggested by basic research²³ could be translated into a validated clinical innovation,²¹ as well as how a previously nonvalidated therapy—the use of NSAIDs for TMDs—could be validated. Both were contingent on community referrals to a biomedical research center where the studies could be conducted in a controlled fashion. These approaches contrast with some commercially supported product evaluations conducted in private practices in which controls often are lacking and subjective evaluation of clinical success is used largely as the primary outcome measure.

Increased emphasis is being placed on involving practitioners in clinical research. The National Institute of Dental and Craniofacial Research, or NIDCR, for example, is supporting centers for research on health disparities that emphasize community-based research,²⁴ and initiatives for establishing practice-based networks²⁵ and training in clinical research are under way.²⁶ Support for curriculum development to introduce research and evidence-based practice into dental education is offered by NIDCR.²⁷ Lastly, capturing and sharing information is facilitated by electronic record keeping and access, which now are being incorporated into many clinical practices and educational settings.

THE ROLE OF THE ASTUTE CLINICIAN IN CHANGING CLINICAL PRACTICES

Clinicians can play a role in evaluating standard therapies and fostering therapeutic innovation (Figure). Accepted clinical practices are acted on by a clinician's professional training, clinical expertise and insights to result in a clinical observation. These practices can be reported in the literature as a case report or case series in the context of a review of the relevant scientific literature. This may lead to a prospective pilot study to demonstrate the concept, but safety and efficacy must be validated in properly controlled clinical trials before the concept can be considered

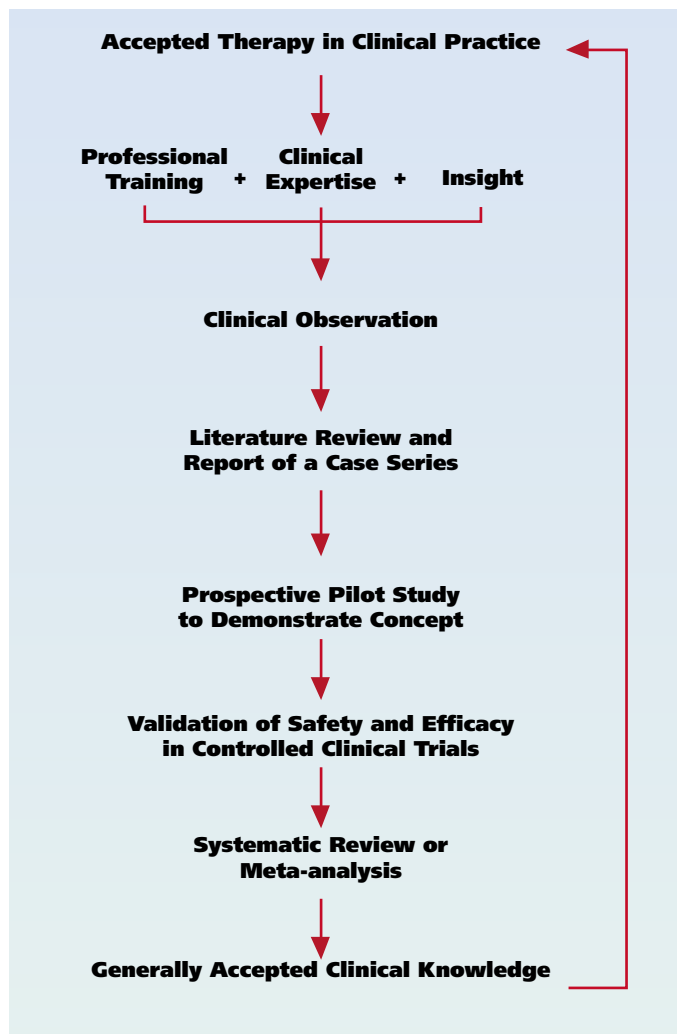


Figure. Role of the astute clinician in evaluating standard therapy and fostering therapeutic innovation.

for widespread use in practice. If a sufficient body of evidence emerges, a systematic review or meta-analysis leads to a revision in generally accepted knowledge on which clinical practice is based, until the process repeats itself to continually improve and expand clinical knowledge and practices. Hence, clinicians become involved not only in the use of evidence but also in generating evidence. For example, the NCI directs a Best Case Series project²⁸ for new cancer treatments based on complementary and alternative medicine modalities. Clinicians can submit a series of cases with evidence to support a new therapeutic approach that then is evaluated critically and may result in the selection of a promising modality for more rigorous evaluation in a controlled clinical trial. Structured collection and reporting of findings, as well as wide dissemina-

tion of these observations, eventually may lead to more definitive, well-controlled proof-of-concept studies.

Slow progress in translating basic and clinical research into practice may be caused, in part, by the difficulty of applying biomedical research findings to clinically relevant questions. Despite enthusiasm for basing clinical practices on the results of clinical trials and other forms of scientific evidence, translation of this concept into changed clinical practices is problematic. However, many converging factors described previously in this article and the emergence of evidence-based health care indicate promise for greater integration of research findings into clinical practice.

CONCLUSIONS

The pioneering efforts of Drs. McKay and Dean, which we described earlier, advanced a clinical observation to a highly successful public health intervention—water fluoridation. This is an example of how astute clinicians played a role in innovating dental therapeutics. The composite of professional training, clinical skills and insight that lead to an observation do, in fact, form the basis for a series of readily achievable steps (figure) leading to therapeutic innovation. Demonstration of evidence in the form of case series can be the first step leading to controlled clinical trials to provide a greater level of scientific certainty. Precedent exists for such approaches, and the small proportion of validated practices provides ample opportunities for dentists to address problems and propose solutions important to dental practice. ■

1. Harris RR. Dental science in a new age: A history of the National Institute of Dental Research. Rockville, Md.: Montross Press; 1989: 42-61.
2. Smith MC, Lantz EM, Smith HV. Cause of mottled enamel, defect of human teeth. Univ Ariz Agr Exp Sta Tech Bull 1931;32.
3. Kent JN, Homsy CA, Gross BD, Hinds EC. Pilot studies of a porous implant in dentistry and oral surgery. J Oral Surg 1972;30:608-15.
4. Kent JN, Lavelle WE, Dolan KD. Condylar reconstruction: treatment planning. Oral Surg Oral Med Oral Pathol 1974;37:489-97.
5. Lagrotteria L, Scapino R, Granston AS, Felgenhauer D. Patient with lymphadenopathy following temporomandibular joint arthroplasty with Proplast. Cranio 1986;4(2):172-8.
6. Bronstein SL. Retained alloplastic temporomandibular joint disk implants: a retrospective study. Oral Surg Oral Med Oral Pathol 1987; 64(2):135-45.
7. Fontenot MG, Kent JN. In vitro wear performance of Proplast TMJ disc implants. J Oral Maxillofac Surg 1992;50(2):133-9.
8. Ta LE, Phero JC, Pillemer SR, et al. Clinical evaluation of patients with temporomandibular joint implants. J Oral Maxillofac Surg 2002; 60:1289-99.

9. Wolford LM, Henry CC, Nikaein A, Newman JT, Namey T. The temporomandibular joint alloplastic implant problem. In: Sessle BJ, Bryant PS, Dionne RA, eds. Temporomandibular disorders and related pain conditions. Seattle: IASP Press; 1995:443-7.

10. Fontenot MG. Temporomandibular devices: past, present, and future. In: Sessle BJ, Bryant PS, Dionne RA, eds. Temporomandibular disorders and related pain conditions. Seattle: IASP Press; 1995:309-22.

11. Milam SB. Failed implants and multiple operations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83(1):156-62.

12. Pocock SJ. Clinical trials: A practical approach. New York: Wiley; 1983:1-13.

13. Sackett DL, Sackett DL. Clinical epidemiology: A basic science for clinical medicine. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1991:187-248.

14. Bader JD, Shugars DA. What do we know about how dentists make caries-related treatment decisions? Community Dent Oral Epidemiol 1997;25(1):97-103.

15. Bader J, Ismail A, Clarkon J. Evidence-based dentistry and the dental research community. J Dent Res 1999;78:1480-3.

16. Bader JD, Ismail AI. A primer on outcomes in dentistry. J Public Health Dent 1999;59(3):131-5.

17. Dodson TB. Evidence-based medicine: its role in modern practice and teaching of dentistry. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83(2):192-7.

18. Williams CJ, Carter SK. Management of trials in the development of cancer chemotherapy. Br J Cancer 1978;37:434-7.

19. National Cancer Institute. Cancer facts: Community clinical oncology program—questions and answers. Available at: "cis.nci.nih.gov/fact/1_3.htm". Accessed Sept. 23, 2004.

20. National Eye Institute. Clinical studies database. Available at: "www.nei.nih.gov/neitrials/index.aspx". Accessed Sept. 27, 2004.

21. Gordon SM, Brahim JS, Dubner R, McCullagh LM, Sang C, Dionne RA. Attenuation of pain in a randomized trial by suppression of peripheral nociceptive activity in the immediate postoperative period. Anesth Analg 2002;95:1351-7.

22. Ta LE, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen. Pain 2004;111(1-2):13-21.

23. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293-9.

24. National Institutes of Health. NIDCR funds Centers for Research to Reduce Oral Health Disparities. Available at: "www.nih.gov/news/pr/oct2001/nidcr-01.htm". Accessed Sept. 23, 2004.

25. National Institute of Dental and Craniofacial Research. Practice based research network. Available at: "www.nidcr.nih.gov/Funding/FundingAnnouncements/RecentlyCleared/PracticeBasedResearch.htm". Accessed Sept. 27, 2004.

26. National Institute of Dental and Craniofacial Research. Clinical research training. Available at: "www.nidcr.nih.gov/Funding/FundingAnnouncements/RecentlyCleared/ClinicalResearchTraining.htm". Accessed Sept. 27, 2004.

27. National Institutes of Health. Oral health research curriculum grants. Available at: "grants1.nih.gov/grants/guide/pa-files/ PAR-02-144.html". Accessed Sept. 23, 2004.

28. Office of Cancer Complementary and Alternative Medicine. Best case series. Available at: "www3.cancer.gov/occam/bestcase.html". Accessed Sept. 23, 2004.



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