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Evidence-based best practices are yet to be established for the management of caries-associated pulpal disease in young permanent and primary teeth. Controversies still remain among practitioners, including pediatric dentists and endodontists, as to which treatment modalities are most predictable in the contemporary practice of pulpal therapy. Many clinicians still remain divided as to whether indirect pulp capping is a viable procedure in primary and young permanent teeth, or whether formocresol remains the medicament of choice for pulpotomies in primary teeth. To begin the process of establishing evidence-based best practices in pulpal therapy as well as highlight some of the future directions in pulpal therapy including pulp regeneration with stem cells and root canal revascularization, the American Academy of Pediatric Dentistry (AAPD) and the American Association of Endodontists (AAE) jointly sponsored “Emerging Insights in Pulp Therapy: New Insights into Dilemmas and Controversies.” The symposium was held on November 2–3, 2007, in Chicago, Illinois.

The convening of this pulp therapy symposium was heralded as a major event in that it was a first-time joint-symposium sponsored by these 2 national specialty organizations. The genesis of the idea for joint sponsorship was the need to examine the shared procedures performed by the 2 specialties. With specialty organizations routinely producing evidence-based practice guidelines that provide the foundation for treatments performed, it is critical that when 2 specialties perform the same or similar treatments, their guidelines are parallel in language and in content. Without these guidelines, confusion and uncertainty will result in clinical practice when a rational treatment plan is required to manage a specific pathologic entity such as caries.

Pediatric dentistry and endodontics share in the important treatment decisions associated with pulpal therapy for the cariously involved young permanent tooth. In addition, endodontists are consultants to and involved in pulp therapy treatment decisions for the cariously involved primary tooth. With the eventual expectation that the 2 organizations could come together and produce practice guidelines that share common goals and language for caries-associated pulpal therapy for primary and young permanent teeth, the decision was made to bring together a panel of world-renowned experts from both specialties to present the current best evidence as a first step in developing the anticipated guidelines.

Individuals identified to be on the planning committee from the AAE were Drs Gerald N. Glickman, Alan Gluskin, and Bradford Johnson. From the AAPD, Drs Suzi Scale, Elizabeth Barr, and James Coll were selected. These individuals met and identified the following areas as appropriate for focus: the nature of the carious lesion of dentin; indirect pulp therapy, including stepwise excavation for both young permanent teeth and primary teeth; primary tooth pulpotomy agents with special emphasis on formocresol and the controversy surrounding its use; and revascularization of young permanent teeth and pulpal regeneration by using stem cells. To that end, a cadre of 9 experts was identified and invited to present evidence for assigned topics. The articles resulting from their presentations appear in this publication.

During the conference Professor Lars Bjørndal discussed the caries process and its effect on the pulp. He applied this information to the dilemma of the deep carious lesion and indirect pulp capping, with special emphasis on the coronal seal. Dr Joe Camp focused on diagnostic dilemmas in vital pulp therapy for young immature teeth. Dr Martin J. Trope spoke on how new trends are changing our understanding of the regenerative potential of the dental pulp, whereas Dr David Wither-}

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The Caries Process and Its Effect on the Pulp: The Science Is Changing and So Is Our Understanding

Lars Bjørndal, DDS, PhD

Abstract
The understanding of the caries process and its effect on the pulp is presented in the context that caries does develop in various rates of progression. Early in the caries process, the pulp reflects changes within lesion activity. Thus, the early pulp response is reversible. Later, the rate of caries progression is reflected by the quality of the tertiary dentin. Slowly progressing lesions create tertiary dentin resembling normal tubular dentin. Rapidly progressing lesions lead to the production of atubular dentin or complete absence of tertiary dentin, as well as pulp necrosis and apical pathology. Finally, the nature of the untreated deep carious lesion is an ecosystem that might undergo significant changes. The untreated lesion is temporarily converted from an active and closed lesion environment into one that is open and slowly progressing. The analysis of untreated carious lesions has transformed the treatment philosophy of deep carious lesions. (J Endod 2008;34:S2-S5)

Key Words
Dental caries, dental pulp, dentin, indirect pulp treatment, stepwise excavation, tertiary dentin

Can We Obtain Consensus on Caries Pathology?
Caries can be compared with a train that passes through many stations. Imagine that each station represents a specific stage of caries progression. The first station represents the initial surface etching at the outer enamel layer, leading to the dull white appearance of the active progressing enamel lesion. The last station represents the deepest layer of the carious tooth, with a necrotic, infected root canal system and the presence of apical pathosis. Investigators, clinicians, and researchers who enter the “caries train” have typically focused on only a few stations. They might also have different understandings and opinions about how to treat dental caries. Their opinions have developed from a mixture of clinical empirical tradition and an understanding from research. These opinions could be named the cariologist opinion, the operative opinion, and the endodontic opinion.

Some Opinions about the Approach to Dental Caries
The classic cariologist opinion is focused on the prevention of caries and further progression of the established lesion. The initial focus is on the white spot lesion, whose histologic picture is visualized in the laboratory via transmitted or polarized light. Treatment philosophies here are typically related to nonoperative and preventive approaches. If caries has progressed into the dentin, with demineralized dentin being visible on the x-ray or, at most, extending through half the thickness of the dentin, excavation procedures are planned to avoid pulp exposures.

The operative opinion is typically initiated when caries has progressed into a clinical breakdown of the enamel surface and with carious dentin exposure. Without focusing on specific details about caries pathology, the cavity needs to be “drilled and filled.” A lesion means an exposure of the pulp, and this might be avoided by leaving carious dentin behind. The operative opinion also tends to be a two-edged sword, because sometimes the design of the cavity overrides the fact that the caries lesion might not be in need of operative intervention. However, for esthetic or other reasons, the operative intervention is carried out with a minimally invasive approach, even though the actual lesion is dark, discolored, arrested caries.

Finally, the endodontic opinion deals with the prevention of an infected pulp and subsequent apical pathosis; the issue of a lesion mainly concerns this region. Therefore, all carious dentin should be removed, even if the result is a pulp exposure. The existence of these virtual opinions was reflected in a recent practice-based research network to determine dentists' treatment methods for deep caries lesions in which one would expect pulpal exposure (1). The survey findings showed that 62% of the responding dentists would remove all caries (operative opinion), 18% would partially remove caries (cariologist opinion), and 21% would initiate endodontic treatment (endodontic opinion). Differences in decision making for treating deep carious lesions in primary molars have also recently been reported (2).

Actually, this topic is not new, as shown in the following quotations: “It is better that a layer of discolored dentin should be allowed to remain for the protection of the pulp rather than run the risk of sacrificing the tooth” (3). In contrast, Black (4) wrote: “...it will often be a question whether or not the pulp will be exposed when all decayed dentin overlaying it is removed...It is better to expose the pulp of a tooth than to leave it covered only with softened dentin.”

It is necessary to remain within the historical perspective to understand how these different opinions have justified various treatment concepts. The endodontic opinion advocating an invasive pulp treatment in relation to caries might very well have gained
inspiration from pulp studies carried out on animal models by using standardized test cavities in sound dentin, in which the pulp reacts very early to the influx of various external stimuli. These stimuli might include samples of plaque or soft carious dentin (5, 6). In this context, the study by Brännström and Lind (7) has been a key reference, showing that the early enamel lesion in human teeth could also lead to odon-to-blast alterations and signs of pulpal infiltration. This is a key reference because in this symposium presentation it is hypothesized that these findings have been used as evidence for the early onset of irreversible pulpal inflammation caused by caries progression. Taken together, it is tempting to suggest that the observation of the “early influx pulp data” might have led to the clinical interpretation that irreversible pulp inflammation is also reached relatively early in relation to caries. Therefore, radical interventions have been advocated. A recent Cochrane review of pulp management in extensive caries deals with clinical studies in which deep lesions without clinical symptoms were treated (8). One could question why a pulp-preserving treatment was not an option.

In contrast, the cariologist opinion, and to some extent the operative opinion, can be traced back decades to Massler (9). Massler, among others, integrated a sophisticated and advanced biologic understanding of caries into caries treatment. He described acute and chronic caries on the basis of clinical criteria and histologic descriptions. Consequently, different pulpal reaction patterns were to be expected that could lead to differing means of treating caries as opposed to only a radical approach.

With the metaphor of the caries train in mind, it is too much to force everyone to get on and off at all the stations, but during a symposium such as this, a natural goal would be to reach a consensus of understanding caries in between these group opinions. Therefore, when entering a caries discussion aiming to cross invisible lines of dental subspecialities, it is necessary to be clear and precise with the use of well-defined terms. Why? Because the interpretation of the very same clinical situation even today might reflect completely different treatment (1, 2), and misunderstandings might very well occur in communication between clinicians and researchers. Let us update our understanding of caries pathology by considering that the caries train might use more than one track. This reflects the understanding and importance of caries as a disease that can progress at varying rates.

What is the sequence of the various zones in carious dentin, beginning with early lesions? When and how does the pulp begin to produce extradentinal matrix and tertiary dentin? What is the spreading pattern of caries? When will microorganisms invade the demineralized dentin? Can we say something about the prehistory of caries, when viewing the histologic picture of tertiary dentin? Why do we sometimes find tertiary dentin produced during caries, whereas at other times it is difficult to detect? Is knowledge about lesion activity important?

**An Update of Caries Pathology: The Non-cavitated Enamel Lesion Complex—Understanding the Early Pulp-Dentinal Response to Caries**

The proximal white spot lesion is triangular when viewed in 2 dimensions and conical when viewed in 3 dimensions. On the basis of quantitative data related to the degree of porosity in the enamel lesion, the lesion comprises a multitude of many microlesions following the direction of the enamel rods. Hence, the topography of the lesion reflects the acidogenic potential of the cariogenic biofilm at the enamel surface. The central lesion area is the oldest part and shows the deepest penetration, whereas the peripheral parts represent “new beginners” following the direction of the rods (10).

In short, the shape of the enamel lesion represents a transmission of stimuli from the enamel surface that can be related to time and provides the possibility for understanding the subjacent pulpal-dentinal response in relation to time. Thus, the deepest penetration of the entire caries lesion complex can also be seen as the oldest lesion area along the dentin-pulp interface following the direction of the dentinal tubules. Consequently, the peripheral areas represent younger and less progressed areas along the dentin-pulp interface, guided by the cariogenic biofilm covering the surface of the enamel lesion. The morphology of reactionary dentinogenesis, defined as tertiary dentin produced by primary odon-to-blasts, has been described by using this concept (11). I will return to this subject later.

**Examples of Improved Laboratory Methods That Have Created a Better Understanding**

One approach that has improved our understanding from the histologic findings of Brännström and Lind (7) was the use of thin, undemineralized tooth sections in the examination of well-defined carious lesions. The normal structural relationships between enamel, dentin, and the pulp were preserved with this new histologic method. Therefore, it was possible to describe new histologic changes in the enamel and the subjacent pulp-dentinal organ within the same section (12). Also, the application of immunohistochemistry has improved our understanding of the underlying molecular events (13), as well as reactions leading to reactionary and reparative dentinogenesis (14).

**The Sequence of the Carious Development in the Tooth**

Morphologic changes in odon-to-blasts have been found in well-defined enamel lesions of freshly extracted third molars (14). Moreover, morphologic and molecular features in the odon-to-blast cells leading to the production of extradentinal matrix can also be detected (15, 16). During our daily clinical practice we might only recall the early odon-to-blast response from the library, but when we experience the pulp in relation to caries, it is during a very late stage of lesion progression as we consider whether pulp exposure should be avoided.

How should we interpret the early pulp response? An updated interpretation and understanding would be that the pulp response follows the caries lesion from the very beginning. However, it should not be considered as a “station” along the track of irreversible pulp inflammation, hence a “point of no return.” Some observations even indicate that the pulp might react to the signals passing through the enamel even before histologic caries reactions can be observed in the dentin (14).

The first visible histologic change in the dentin subjacent to an enamel lesion is the formation of hypermineralized dentinal tubules. This reaction is seen in the dentin before any signs of demineralization. The reaction might represent activity of the odon-to-blasts, and it might very well resemble the age-related intratubular physiologic sclerosis (17). When the enamel lesion reaches the dentinoenamel junction (DEJ), dentin demineralization is initiated. Note that the initial dentin demineralization takes place not in unaffected sound dentin but in dentin with a decreased permeability as a result of the presence of the hypermineralized dentin.

After the dentin begins the process of demineralization, the advancing front of demineralization also reflects the dynamic nature of the cariogenic biofilm, expressed as different pH gradient creating either dissolution or reprecipitation of dentin mineral. Thus, the hypermineralized dentin is probably the result of physiologic activity from the odon-to-blast, but it also contains reprecipitation of previously dissolved dentin crystals. However, this topic requires additional study (18).

No serious microbial invasion takes place in the dentin as long as the highly organized enamel layer (even though being demineralized) separates the biofilm from the dentin. The bacteria are not able to
penetrate through the enamel rod structure (19). The microbial invasion is related to the gradual structural breakdown of the enamel layer (20).

Another important change in our understanding is the misinterpreted concept of caries spreading along the DEJ subjacent the non-cavitated enamel lesion (21). The extent of the demineralized dentin is restricted to the histologic enamel lesion contact, and no spreading of demineralized hard tissue is noted undermining sound enamel. The lateral spread of demineralized dentin and enamel is related to the total breakdown of the enamel layer and therefore describes a relatively later stage of tissue destruction than previously believed.

During the stages of dentin exposure a completely different situation is created under heavy bacterial invasion. A moist, soft, disintegrated, demineralized, and necrotic zone is observed. At this active stage the carious dentin can easily be separated from the enamel. The outflux of mineral has been extensive, and as the moisture is decreased, eventually the dentin shrinks, and a clinically visible gap develops between the enamel and dentin (Fig. 1a). Subsequently, the cariogenic biofilm gains improved growth conditions along the lateral spread of caries or retrograde caries (23). If the carious tooth is left untreated, further tissue breakdown occurs. Eventually the caries process will bring about irreversible changes in the pulp, leading to necrosis and pulpal infection with apical pathosis. This worst case scenario is often what we find in many textbooks. It also represents what takes place several times a week with apical pathosis. This worst case scenario is often what we find in many textbooks. It also represents what takes place several times a week with apical pathosis.

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The pulpal response in lesions with a conversion of lesion activity might appear (27). As the lesion progresses, the enamel breaks down (Fig. 1b), and at the same time the growth conditions change for the cariogenic biofilm. The cavitated lesion transforms from a closed ecosystem into an open ecosystem (Fig. 1c). Different rates of progression can therefore be present within one tooth. After the enamel breakdown, the occlusal part of the tooth has no heavy plaque accumulation, as the degree of protection of the biofilm has decreased. The subjacent dentin discloses the clinical signs of slowly progressing caries by its brownish discoloration (Fig. 2a). In contrast, the peripheral parts are protected, and accumulations of cariogenic biomass are apparent. On the basis of these observations, pulp vitality is not necessarily maintained, but it indicates that deep exposed dentin lesions are not unconditionally related to an irreversible pattern of pulp pathology, as traditionally taught in textbooks advocating invasive pulp treatments (28). Of course, if nothing is done with the deep lesion even though it might be temporarily arrested, eventually the caries activity in the peripheral parts of the lesion leads to the breakdown of the tooth (Fig. 2b, c).

The pulpal response in lesions with a conversion of lesion activity can be reflected by the presence of reparative dentinogenesis, defined as the combination of fibroductin and new tubular dentin produced by new odontoblast-like cells. It appears that this takes place in the same manner as the primary odontoblast cells, with finger-like projections but into the reactionary dentin (16). Very little attention has been given previously to the potential capacity of the primary odontoblast to be part of tertiary dentin formation.

Also within deep carious lesions (Fig. 1), large variation in lesion activity might appear (27). As the lesion progresses, the enamel breaks down (Fig. 1b), and at the same time the growth conditions change for the cariogenic biofilm. The cavitated lesion transforms from a closed ecosystem into an open ecosystem (Fig. 1c). Different rates of progression can therefore be present within one tooth. After the enamel breakdown, the occlusal part of the tooth has no heavy plaque accumulation, as the degree of protection of the biofilm has decreased. The subjacent dentin discloses the clinical signs of slowly progressing caries by its brownish discoloration (Fig. 2a). In contrast, the peripheral parts are protected, and accumulations of cariogenic biomass are apparent. On the basis of these observations, pulp vitality is not necessarily maintained, but it indicates that deep exposed dentin lesions are not unconditionally related to an irreversible pattern of pulp pathology, as traditionally taught in textbooks advocating invasive pulp treatments (28). Of course, if nothing is done with the deep lesion even though it might be temporarily arrested, eventually the caries activity in the peripheral parts of the lesion leads to the breakdown of the tooth (Fig. 2b, c).

The pulpal response in lesions with a conversion of lesion activity can be reflected by the presence of reparative dentinogenesis, defined as the combination of fibroductin and new tubular dentin produced by new odontoblast-like cells (29). The presence of fibroductin or interface dentin indicates that all primary odontoblasts have died. After the change in caries activity, the pulp might respond with reparative dentin resembling the dentin-bridge formation after a direct pulp capping procedure (16).
Understanding of Caries Pathology Creates the Treatment Philosophy Related to Deep Caries

In the past, the following have all been clear justification for the performance of radical operative intervention: (1) early microbial invasion of carious dentin, (2) early spreading along the DEJ that undermines sound enamel, and (3) the early onset of an irreversible pulp response. Even though textbooks often illustrate the worst case scenario, this does not mean that we should wait for it to happen! We should be motivated to understand the lesion activity and use this information in the treatment of caries. Instead of accepting that there is a steady progression through the tooth leading toward the same results if left untreated, it might be more appropriate to understand that caries activity constitutes many different rates of progression, each of them leading to different pulp reactions. Perhaps with the appropriate clinical intervention we can reduce the rate of caries progression, perhaps even arresting the subjacent pulpal inflammation. Only well-designed clinical trials will answer this question, given that we do not yet have noninvasive tools for the measurement of the severity of the inflamed pulp. Therefore, the clinical discussion of reversible or irreversible development of pulps will continue to be controversial in relation to the actual state of pulp pathology. However, when diagnosing deep carious lesions, we must make a choice on the basis of our knowledge of the caries process and its effect on the pulp and on the basis of existing diagnostic methods. The noninvasive pulp treatment of deep caries lesions will be the focus of my second presentation.

References


Figure 2. The pattern of untreated deep lesions might involve a decrease in lesion activity (a), but it might be temporary because the enamel margins will obtain protection for the cariogenic process (b). Eventually the entire crown breaks, leaving remnants of roots behind (c). Red zones indicate plaque. Reprinted with permission from Blackwell Munksgaard from Bjørndal L. Dentin and pulp reactions to caries and operative treatment: biological variables affecting treatment outcome. Endodontic Topics 2002;2:10–23. (22)
Diagnosis Dilemmas in Vital Pulp Therapy: Treatment for the Toothache Is Changing, Especially in Young, Immature Teeth

Joe H. Camp, DDS, MSD

Abstract
The literature is almost devoid of scientific studies of diagnosis of pulpal pathology in primary and permanent teeth with open apices. Most reports are empirical or retrospective studies without adequate prior knowledge of preexisting conditions or histologic findings leading to the necessity of pulpal procedures. Appropriate diagnostic tests and their effectiveness are documented for both groups. This article reviews the available literature and current techniques of indirect pulp therapy, pulp capping, and pulpotomy for primary teeth and permanent teeth with open apex. The apical barrier with mineral trioxide aggregate followed by root strengthening with bonded composite is reviewed. (J Endod 2008;34:56-512)

Key Words
Diagnosis, pulp, pulp capping, pulpotomy

D

dagnosis in primary and young, permanent, immature teeth varies greatly from that in fully formed permanent teeth. Most of the diagnostic tests used in conventional endodontic therapy are of very little or no value in primary teeth and of limited value in permanent immature teeth. While admittedly poor for diagnosing the degree of inflammation in this group of teeth, diagnostic tests must be performed to obtain as much information as possible before arriving at treatment options.

Diagnostic literature based on scientific studies is almost nonexistent. Most outcome reports are supported by empirical treatment and anecdotal case reports (1). Many outcome studies are conducted retrospectively on the basis of clinical signs and symptoms and make assumptions regarding the pulpal status before treatment without histologic or bacterial data to support the preoperative diagnosis. Without histologic examination an accurate determination of the extent of inflammation is impossible (2).

Correlation between clinical symptoms and histopathologic conditions is poor and complicates diagnosis of pulpal health in exposed pulps of children (3).

Many of our treatments are based on our diagnosis of the root development stage. Consequently, to properly diagnose and treat primary and young permanent teeth, it is necessary to have a thorough knowledge of normal root formation and the differences between developing and fully formed teeth. The decision to render conservative vital treatment to allow root formation completion or more radical treatment such as root canal therapy might hinge on our diagnosis of root development.

According to Orban (4), the tooth root’s development begins after enamel and dentin formation has reached the cemento-enamel junction (CEJ). Hertwig’s epithelial root sheath is formed by the epithelial dental organ, with one tube for each of the future roots. As root formation proceeds apically, each root is wide open, diverging apically and limited by the epithelial diaphragm. Each root’s internal surface is lined by odontoblasts. Once root length is established, the sheath disappears, whereas dentin deposition is continued until root formation is completed.

Depending on each root’s external anatomy, differentiation into multiple canals might occur. During this formative stage, communication exists between the canals in the form of isthmuses. As growth continues, the opposing walls meet and coalesce, and islands of dentin are formed, which eventually expand to divide the root into separate canals. Continued dentin deposition narrows the canals, and the apex is eventually closed with dentin and cementum, creating apical convergence. Isthmuses and fins extending toward the root’s center might persist in fully formed teeth.

In permanent teeth, root formation is not completed until 1–4 years after eruption into the oral cavity. Because of the shorter roots of primary teeth, root formation is completed faster than for permanent teeth. Because the faciolingual width of most roots and canals is greater than the mesiodistal width, apical closure cannot usually be determined radiographically. The x-ray beam is exposed in the faciolingual plane, but the radiograph is read mesiodistally. Because of this anatomy, with the exception of the maxillary central and lateral incisors and some single canal lower premolars, radiographs cannot determine apical closure. Therefore, the clinician must rely on time to determine root closure in all other teeth to prevent treatment protocols that cannot be successfully completed without apical convergence (5).

During this formative period, treatments should be oriented toward maintenance of vitality to allow completion of root formation. Further deposition of dentin will strengthen the roots’ thin dentinal walls and help diminish future root fracture.
The root canals of primary teeth differ greatly from those of permanent teeth, and treatment is complicated by apical resorption to allow for eruption of the succeeding teeth. At the time of root length completion, the root canals roughly correspond to the external anatomy's form and shape. At this time, resorption of the roots begins and, combined with additional dentin deposition internally, might significantly change the number, size, and shape of the canals within the primary roots. Continued physiologic, apical resorption of the roots makes the teeth progressively shorter. In addition, resorption on the roots' internal surfaces adjacent to the forming permanent tooth might open other communications with the periapical tissues. These factors complicate establishment of working lengths if root canal therapy is necessary.

In the primary anterior teeth (incisors and canines), the permanent tooth buds lie apically and lingually near the primary roots. Resorption is initiated on the primary root's lingual surface. This causes the apical foramen to move coronally, resulting in a difference in the apical foramen and the anatomic apex and complicating determination of root canal length. One study demonstrated that half of the primary incisor's root might be resorbed lingually before it becomes obvious on a radiograph (6). Primary anterior teeth have one simple root canal and rarely have lateral or accessory canals.

The primary molar teeth normally have the same number and position of roots and root canals as the corresponding permanent teeth. At root length completion, most roots have only 1 canal, but continued deposition of dentin might divide the root into 2 or more canals (7–9). During this time, communication exists between the canals in the form of isthmuses or fins (Fig. 1). Secondary dentin deposition contributes to this change in morphology (10, 11). Like the permanent molars, most variations occur in the mesial roots of mandibular molars and facial roots of the maxillary molars. Also, these variations are usually in the facial to lingual plane and cannot be visualized on radiographs (7, 9).

Accessory and lateral canals and apical ramifications of the pulp are common in primary molars (8). In addition, other communications between the pulp and the periapical tissues are formed by physiologic resorption of the internal surfaces of the roots adjacent to the permanent tooth buds.

### Diagnosis of Pulpal Status in Primary Teeth

As with any dental procedure, a thorough medical history must be completed, and any implications related to treatment must be considered. A child with systemic disease might necessitate different treatment than a healthy one.

The examination should begin with a thorough history and characteristics of any pain, because these are often important in helping to determine pulpal status and eventual treatment. Whereas pain usually accompanies pulpal inflammation, extensive problems might arise without any history of pain. If possible, a distinction between provoked and spontaneous pain should be ascertained. Provoked pain that ceases after removal of the causative stimulation is usually reversible and indicative of minor inflammatory changes. Stimuli include thermal, chemical, and mechanical irritants and many times are due to deep caries, faulty restorations, soreness around a primary tooth nearing exfoliation, or an erupting permanent tooth.

Spontaneous pain is a constant or throbbing pain that occurs without stimulation or continues long after the causative factor has been removed. In a well-controlled histologic study of primary teeth with deep carious lesions, Guthrie et al. (12) demonstrated that a history of spontaneous toothache is usually associated with extensive degenerative changes extending into the root canals. Primary teeth with a history of spontaneous pain should not receive vital pulpal treatments and are candidates for pulpectomy or extraction.

The clinical examination might produce evidence of pulpal pathology. Redness, swelling, fluctuance, severe dental decay, defective or missing restorations, and draining parulis might indicate pulpal involvement. Percussion sensitivity might be valuable to the diagnosis, but it is complicated by the reliability of the child's response because of the psychological aspects involved. Tooth mobility might be present normally because of physiologic resorption, and many pulpally involved teeth have no mobility.

Electric pulp tests are not valid in primary teeth (1). Laser Doppler flowmetry might be of greater help in determining vitality, but this equipment has not been perfected, and the price is prohibitive (13).

Thermal tests are usually not conducted on primary teeth because of their unreliability (1, 5).

After the clinical examination, radiographs of good quality are essential. Like permanent teeth, periapical radiolucencies appear at the apices in primary anterior teeth. In primary molars, pathologic changes are most often apparent in the bifurcation or trifurcation areas. Consequently, bite-wing radiographs are often best to observe pathologic changes in posterior primary teeth. Pathologic bone and root resorptions are signs of advanced pulpal pathosis that has spread into the periapical tissues and is usually treatable only with extraction.

Mild, chronic pulpal irritation such as seen in caries might stimulate the deposition of tertiary reactionary dentin over the pulp (5). With acute or rapid onset as the disease reaches the pulp, calcified masses might form away from the exposure site. Such calcified masses are always indicative of advanced pulpal degeneration extending into the root canals (14). Primary teeth with such calcified masses are candidates for only pulpectomy or extraction (Fig. 2).

Internal resorption in primary teeth is always associated with extensive inflammation (12). Because of the thinness of the primary molar roots, if internal resorption can be seen radiographically, a perforation usually exists, and the tooth must be extracted (Fig. 3).

Interpretation of radiographs of primary teeth is always complicated by the presence of the succedaneous tooth and surrounding follicle. Misinterpretation of the follicle can easily lead to an erroneous diagnosis of periapical pathology. Superimposition of the permanent tooth might obscure visibility of the furca and roots of the primary tooth, causing misdiagnosis. Added to this is the normal physiologic resorption process.

Radiographs might also reveal evidence of: previous pulpal treatment; calcification changes in pulp chambers and root canals; oversized

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**Figure 1.** Silicone models of the pulps of 2 primary mandibular second molars. Note the communication between the facial and lingual canals in the mesial roots.
canals indicative of cessation of root formation and pulpal necrosis; and after trauma, root fractures, bone fractures, displacement of teeth, imbedded tooth fragments, or foreign bodies in soft tissues.

The size of a pulpal exposure and the amount and color of hemorrhage have been reported as important factors in diagnosing the extent of inflammation under a carious lesion. Although all carious exposures are accompanied by pulpal inflammation, the larger the exposure, the more likely it is to be widespread or necrotic.

Excessive (2, 5, 14, 15) or deep purple (15) colored hemorrhage is evidence of extensive inflammation, and these teeth are candidates for pulpectomy or extraction. Hemorrhage that cannot be controlled within 1–2 minutes by light pressure with a damp cotton pellet at an exposure site indicates more extensive treatment is necessary. The same is true after removal of tissue when doing a pulpotomy. A pulpectomy or extraction would then be indicated.

In addition to the aforementioned tests and observations when dealing with traumatic injuries to the primary teeth, other factors must be considered.

Studies have shown that 1 in 3 children receive traumatic injuries to the primary dentition (16, 17). Because of the less dense bone and shorter roots as compared with permanent teeth, most injuries are displacements rather than fractures. Such injuries might heal normally without sequelae by formation of an amorphous diffuse calcification histologically resembling osteodentin, formation of a partial or complete obliteration of the canal (18, 19), or result in pulpal necrosis.

In a study of 545 traumatized primary maxillary incisors, Borum and Andreasen (20) found that 53% of subjects developed pulpal necrosis, and 25% developed pulp canal obliteration. The factors found to influence development of pulp necrosis were age of the patient, degree of displacement and loosening, and concurrent crown fracture. Calcific obliteration of the canal was influenced by tooth displacement and amount of root resorption. Crown fracture decreased canal obliteration. They also pointed out that no well-established treatment guidelines exist concerning healing processes and complications in primary teeth.

It has been suggested that the proximity to the succedaneous tooth is an important factor when deciding on treatment for the injured primary tooth. The treatment least likely to damage the permanent tooth should be chosen (1, 20). Conflicting data exist regarding treatment of primary injuries. Studies have shown no relationship between treating injured primary teeth compared with extraction regarding disturbance of the permanent teeth (16, 21). Others have shown a tendency toward more extensive disturbances in the mineralization when injured primary teeth were retained (22).

Near universal agreement exists that avulsed primary incisors should not be replanted because of the possibility of danger to the permanent tooth bud (1).

Roughly half of traumatized primary teeth presenting for treatment develop transient or permanent discoloration. These colors vary from yellow to dark gray and usually become evident 1–3 weeks after trauma. Primary teeth with yellow discoloration frequently have radiographic signs of pulp canal calcification and have a low incidence of pulpal necrosis (20, 23).

Injured primary teeth with dark gray discoloration are reported to have necrotic pulps in 50%–82% of the cases. Conversely, necrosis of the pulp occurred in teeth with no discoloration in approximately 25% of injured primary incisors (20, 23–25). Attempts to correlate discoloration to pathologic, radiographic, and histologic changes in the pulps of injured primary incisors present mixed findings. Color change of the tooth alone without other findings is not a reliable indicator of pulpal health (26). Diagnosis of pulpal necrosis in primary incisors is primarily based on dark gray color change and radiographic evidence of periapical pathology or lack of root formation (1) (Fig. 4). Schroder et al. (25) reported development of periapical osteitis in 82% of gray discolorations within 1 month. Andreasen and Ris (27) have shown that pulp necrosis and periapical inflammation of 6 weeks' duration did not lead to developmental disturbances of permanent teeth. Thus, when diagnosis cannot be established, it is justifiable to wait for further developments.

### Diagnosis of Pulpal Status in Permanent Immature Teeth

In teeth with incomplete root formation, correct pulpal and periapical diagnosis is of paramount importance before proceeding with any endodontic treatment because of the devastating result of loss of vitality. Every attempt should be made to preserve the vitality of these immature teeth until maturation has occurred. Loss of pulpal vitality before completion of dentin deposition leaves a weak root more prone to fracture as a result of the thin dentinal walls.

In a 4-year study, Cvek (28) noted a significant increase in cervical root fractures in treated immature teeth compared with those with completed roots. In immature teeth, the frequency of fractures was dependent on the stage of root development, ranging from 77% in teeth with the least to 28% in teeth with the most developed roots (28). Thus, even if treatment is successful, prognosis for prolonged retention of the tooth should not be replanted because of the possibility of danger to the permanent tooth bud (1).

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is greatly diminished. Loss of vitality before completion of root length will lead to a poorer crown-to-root ratio, with possible periodontal breakdown as a result of increased mobility. Therefore, all treatments in this group of teeth are oriented toward vital procedures. If these more conservative procedures fail, the tooth can still be treated with apexification, apical barrier techniques, or conventional root canal treatment.

Although numerous scientific studies have been reported on the treatment of permanent teeth with immature apices, the literature is almost devoid in the area of diagnosis of pulpal status in this group of teeth.

The diagnosis begins with a thorough medical history and any implications related to the anticipated treatment. The dental history and characteristics of associated pain might be helpful in determining pulpal status. History of any traumatic injury to the facial area should be explored in depth and recorded for future medical, dental, legal, and insurance purposes.

The nature, type, length, and distinction between provoked and spontaneous pain are recorded. Provoked pain caused by thermal, chemical, or mechanical irritants usually indicates pulpal inflammation of a lesser degree and is often reversible. Spontaneous pain, on the other hand, is usually associated with widespread, extensive, degenerative, irreversible pulpal inflammation or necrosis.

The medical and dental histories are followed by a thorough clinical examination. Any areas of redness, swelling, fluctuance, tissue tenderness, dental decay, defective or missing restorations, or fractured or mobile teeth are noted. Presence of discolored crowns or a parulis might indicate pulpal necrosis. The alignment of the teeth, including any infrapositioned or suprapositioned teeth, might provide valuable information.

Electric pulp tests and thermal tests are of limited value because of the varied responses as roots mature. In addition, invalid data might be obtained as a result of the often unreliable responses from children because of fear, management problems, and inability to understand or communicate accurately. Consequently, most diagnoses are made on observation of clinical symptoms and radiographic evidence of pathosis.

Numerous studies (29–32) have reported the unreliability of electric pulp tests in permanent teeth with open and developing apices. Inconsistent results ranging from 11% in 6- to 11-year-olds with completely open apices (29) to 79% in older children (31) have been reported. It is also possible to obtain a false-positive in teeth with liquefaction necrosis (33). Thus, electric pulp tests are of little value during the period of root formation, because the data are not reliable.

Electric and thermal tests were shown to be unreliable after traumatic injury to a tooth, and no response might be elicited even after circulation has been restored (34, 35). The potential for healing is greater with incomplete root development than in fully formed teeth.

Laser Doppler flowmetry has been reported to be very reliable for diagnosing pulpal vitality (13, 36, 37). In a very detailed histologic and radiographic study of revitalization of dogs’ teeth after reimplantation, Yampiset et al. (36) were able to make a correct diagnosis 84% of the time. In nonvital pulps, the histologic study proved to be accurate in 95% of cases, whereas in vital ones the data were correct 74% of the time. This significant difference in readings was observed at as early as 4 weeks. Although the authors pointed out the validity of determining nonvital teeth, they cautioned against relying solely on this test and would only initiate pulpal therapy after observing other signs of pathology.

It has also been shown that blood pigment within a discolored tooth crown interferes with laser light transmission (38). This limitation is significant, because discoloration after trauma is frequent. Also, this equipment has not been perfected for routine dental diagnosis and is cost-prohibitive for the practicing dentist.

Figure 4. The dark gray discoloration of the crown of this primary maxillary central incisor is indicative of pulpal necrosis.

Figure 5. The dark gray discoloration of the crown of this permanent maxillary central incisor indicates pulpal necrosis.
Thermal tests with heat in permanent teeth with developing apices are of limited value because of inconsistent responses \((32)\) and are rarely performed.

Radiographic examination and interpretation are key elements in the diagnosis of pulpal pathology in teeth with developing apices. Good quality periapical radiographs of any involved teeth are used to assess root development and discover periapical rarefaction and root resorption. After traumatic injury, radiographs are essential to determine the presence of fractured bone and roots, displaced teeth, and imbedded foreign objects.

In posterior teeth, bite-wing radiographs are also necessary to detect caries, proximity of lesions to the pulp, previous pulpal treatments, and quality of any restorations.

**Figure 6.** Apical barrier with MTA and strengthening of the thin root with bonded composite. (A) Preoperative radiograph of permanent maxillary left central incisor. The pulp is necrotic, and the apex is open. (B) 4-mm plug of MTA placed at the apex. (C) Remainder of canal restored with bonded composite resin. (D) Two-and-a-half-year follow-up showing covering of MTA with cementum and healing of a periapical lesion.
Discoloration of a tooth crown after trauma is a common sequela and one of the foremost diagnostic indicators (40–42). Yellow discoloration is usually indicative of pulp space calcification, and a gray color usually signifies pulpal necrosis (40) (Fig. 5).

Transient coronal discoloration has been reported (42) in 4% of teeth after luxation injuries as a result of vascular damage and hemorrhage immediately after injury. In these cases, it was speculated that pulpal healing depends on the bacterial status. With bacterial infection, healing is unlikely. In this group of teeth, determination of bacterial status could not be ascertained on the basis of coronal discoloration, loss of pulpal sensibility, or periapical rarefaction (42).

Transient apical break down occurs after displacement injuries and might lead to misdiagnosis (42, 43). The development of transient periapical radiolucency—together with coronal discoloration, negative electric pulp test, and cold response up to 4 months—was shown to subsequently regain the original color and normal pulpal responses (43). Transient apical breakdown apparently is linked to the repair process in the pulp and periapical tissues and returns to normal when healing is complete (42). Bone loss, which produces the radioluency, eventually heals with new bone.

Universal agreement exists that immature teeth have the greatest potential to heal after trauma or caries, particularly when the apical foramen is wide open. This group of teeth also has the greatest chance of misdiagnosis and mistreatment. To avoid mistakes, treatment must not be undertaken on the basis of negative responses to pulp testing. Radiographic and symptomatic assessment is currently the principal diagnostic criterion. The following factors are key in making the diagnostic determination: symptoms of irreversible pulpitis or apical periodontitis; clinical signs of periangular infection including swelling, tenderness to percussion, mobility, or parulis formation; radiographically detectable bone loss; progressive root resorption; and arrested root development compared with other adjacent teeth (44).

If doubtful, do not start treatment. Keep the patient under close observation and continue to reassess the diagnostic criteria until a definitive diagnosis can be established.

The treatment of primary and young permanent teeth has changed dramatically in recent years as new materials have been developed and researched. The use of calcium hydroxide (for decades the standard for pulp protection), pulp capping, and pulpotomy procedures in permanent teeth is being replaced with composite resins (45, 46) and mineral trioxide aggregate (MTA) (ProRoot; Dentsply Tulsa Dental, Tulsa, OK). Pulp capping with resin composites in monkeys produced the lowest incidence of bacterial microleakage, pulpal inflammation, and incidence of pulpal necrosis when compared with calcium hydroxide and glass ionomer cement (46).

When compared with calcium hydroxide, MTA produced significantly more dentinial bridging in a shorter time with significantly less inflammation and less pulpal necrosis (47–49). MTA has been shown to be cementoconductive, with attachment of cementoblasts to the material (49). Sarkar et al. (50) studied the interactions of MTA, a synthetic tissue fluid, and dentin of extracted teeth. They concluded that calcium from the MTA reacted with phosphate in tissue fluid, producing hydroxyapatite. The sealing ability, biocompatibility, and dentinogenic activity of the material occur because of these physiochemical reactions.

Once considered taboo, vital pulpal treatment of symptomatic per-

timely completion of apexification and have eliminated the use of calcium hydroxide, except as a temporary canal disinfectant. The use of MTA as an apical barrier has become the standard for treatment of the open apex pulpless tooth (Fig. 6). The development of bonded composite techniques now allows strengthening of these weak roots to levels of intact, fully formed roots and has virtually ended root fractures (53–56) (Fig. 6C).

Revascularization of teeth with necrotic infected canals has been reported by using combinations of antibiotics (57, 58). The canals are accessed and disinfected with copious irrigation of sodium hypochlo-

tite. The canals are not instrumented. A paste of metronidazole, cipro-

floxacin, and minocycline is placed in the canals and left for 1 month. The tooth is re-entered, and endodontic files are inserted through the apices to stimulate bleeding to produce a blood clot at the level of the CEJ. After clotting, MTA is placed over the blood clot, and a permanent external seal is placed. The clot is then revascularized, producing thickening of the canal walls and apical closure.

Stem cell research holds great hope for the future, with the aim of healing impaired dental tissues including dentin, pulp, cementum, and periodontal tissues. By stimulating the body’s intrinsic capacities, we will be able to regenerate tissues, allowing further development of teeth and bone or possibly the formation of new teeth to replace those ravaged by decay or lost to traumatic injuries.

References


Regenerative Potential of Dental Pulp

Martin Trope, DMD

Abstract
The regenerative potential of dental pulp, particularly in mature teeth, has been considered extremely limited. However, our improved understanding of pulpal inflammation and repair and improved dental materials and technologies make vital pulp therapy a viable alternative to root canal treatment. This article explores our knowledge in this regard and the future potential of saving or even regenerating the pulp as a routine dental procedure. (J Endod 2008;34:S13-S17)

Key Words
Pulp, regeneration, revascularization, vital

The Importance of Vital Pulp
Although it is easy to understand the value of a vital pulp when the tooth is immature and underdeveloped, it is also important to understand its value in a fully formed tooth. Endodontic disease is apical periodontitis, and as such, the biologic rationale for endodontics is the prevention or treatment of apical periodontitis. For apical periodontitis to be present, the root canal must contain a necrotic infected pulp (1). Therefore, the vital (noninfected) pulp ensures no apical periodontitis. Thus, maintaining the vital pulp prevents apical periodontitis, and the potential to regenerate an injured or necrotic pulp would be the best root filling possible.

The Pulp’s Regenerative Potential

The Unexposed Pulp
The inflamed pulp unexposed by caries or trauma always has the potential to be repaired. Although our diagnostic ability to differentiate a vital from a necrotic pulp is good, differentiating between reversibly and irreversibly inflamed pulp remains an educated guess at best (2). We do know, however, that the younger the pulp, the better its repair potential.

The Exposed Pulp
Treatment of the exposed pulp remains quite controversial, with different approaches endorsed by different dental specialties. Vital therapy (ie, pulp capping, partial or full pulpotomy) on traumatically exposed pulps is very successful (3), whereas vital pulp therapy on the cariously exposed tooth is not nearly as successful (4). The difference in success rates is explained by the status of the pulp at the time of the procedure (Fig. 1). Capping the healthy pulp gives very high success rates, whereas capping the inflamed pulp results in lower and less predictable success (Fig. 2) (5, 6, 7). On the other hand, with a carious exposure the area and depth of inflammation are very unpredictable, and pulp capping at the superficial exposure site is popular. Thus, it is very likely that we would be capping an inflamed pulp, and more failures (necrotic pulps) would result.

Another extremely important factor in the success of treating a vital exposure is the coronal seal after the pulp capping/pulpotomy (8). Cox et al. (8) showed that the pulp can withstand the toxicity of most dental materials, and that what was previously interpreted as toxicity was, in fact, due to the material not sealing adequately. Therefore, it is considered essential that a well-sealed coronal seal be placed over the vital pulp therapy. This is considered much more important than the material used on the vital pulp.

Approaches to Treatment of Carious Exposure in the Immature Tooth

Pediatric Dentistry
Because the young vital pulp has such good potential for repair, it is considered reasonable to perform an indirect or direct pulp cap on a carious exposure as long as a good coronal restoration can be placed (9). The rationale for this approach is that most young pulps can heal as long as the coronal restoration does not allow leakage of additional inflammatory stimulants or microorganisms.

Endodontics
Pulpal inflammation is usually superficial and is unlikely to extend past the canal orifices, and the healing potential is good if a healthy pulp is treated. Hence, the optimal approach is to perform a full pulpotomy (thus removing the coronally inflamed pulp) and treating the presumably healthy pulp at the canal orifices. When the root canal has
developed thick dentinal walls and the apices are closed, a full pulpectomy can be performed (Fig. 3).

**Revascularization of Infected Pulp Space**

**Pulp Revascularization**

Revascularization of an immature necrotic tooth has many potential advantages.

It has been shown that under certain conditions revascularization can be achieved in young teeth that have been traumatically avulsed, leaving a necrotic but uninfected pulp. Skoglund et al. (10) demonstrated that in extracted dog teeth, pulpal revascularization started immediately after reimplantation and was completed after approximately 45 days (Fig. 4). It is important to understand the biologic features permitting revascularization in young avulsed teeth, so that we might attempt to reproduce these unique conditions when the pulp space is infected. The immature avulsed tooth has an open apex, short root, and intact but necrotic pulp tissue. Therefore, the new tissue has easy access to the root canal system and a relatively short distance for proliferation to reach the coronal pulp horns. It has been experimentally shown that the apical portion of a pulp might remain vital and proliferate coronally after reimplantation, replacing the necrotized coronal portion of the pulp (11–15). The speed with which the tissue completely revascularizes the pulp space is important because bacteria from the outside are continually attempting to enter the pulp space, and the presence of vital pulpal tissue greatly slows or prevents the bacterial penetration into this tissue compartment. The ischemically necrotic pulp that is unique to an avulsion injury acts as a scaffold into which the new tissue grows, and the fact that the crown is usually intact (rather than carious or with an access cavity) slows bacterial penetration because their only access to the pulp is through cracks (14) or enamel defects. Thus, the race between proliferation of new tissue and infection of the pulp space favors the new tissue.

Revascularization of the pulp space in a necrotic, infected tooth with apical periodontitis was attempted by Nygaard-Ostby and Hjortdal (15) in the 1960s but was mostly unsuccessful. However, the materials and instruments available 40–50 years ago were probably not sufficient to create an environment similar to the avulsed tooth, ie, a canal that is free of bacteria, containing a scaffold for new tissue to grow and to be largely resistant to further bacterial penetration. With currently available technologies it could be possible to effectively disinfect an infected pulp, artificially place a scaffold, and then effectively seal the access cavity to resist subsequent infection.

A recent case report by Banchs and Trope (16) has reproduced results in cases reported by others, indicating that it might be possible to replicate the unique circumstances of an avulsed tooth to revascularize the pulp in infected necrotic immature roots (11–13). Our case (Fig. 5) described the treatment of an immature second lower right premolar with radiographic and clinical signs of apical periodontitis with the presence of a sinus tract. The canal was disinfected without mechanical instrumentation but with copious irrigation with 5.25% sodium hypochlorite and the use of a mixture of ciprofloxacin, metronidazole, and minocycline (17), mixed as described in Fig. 6.

A blood clot was produced to the level of the cementoenamel junction to provide a scaffold for the ingrowth of new tissue followed by a double seal of mineral trioxide aggregate in the cervical area and a bonded resin coronal restoration above it. Clinical and radiographic evidence of healing was observed as early as 22 days. The large radiolucency had disappeared within 2 months, and at the 24-month recall it was obvious that the root walls were thick, and the development of the root below the restoration was similar to the adjacent and contralateral teeth.

The antibacterial effectiveness of the triantibiotic paste reported by Hoshino et al. (17) was confirmed by our group in a dog model with infected immature roots (18). In addition, our group demonstrated in dogs that the potential for revascularization does exist (Fig. 7), and that the blood clot was essential as a scaffold (19). At this point, we are unsure of which factors in the blood clot are important. When these factors are isolated, they can be incorporated into a synthetic scaffold that will be easier to for clinicians to manipulate compared with a blood clot.

The procedure described in this section can be attempted in most cases. If no signs of regeneration are present after 3 months, then more traditional treatment methods can be initiated.

**Carious Exposure**

Figure 2. Carious exposure caused by caries. The underlying inflamed pulp is removed, and a partial pulpotomy is performed on the remaining healthy pulp with calcium hydroxide (Courtesy Dr. Francisco Banchs).
Figure 3. In this case a full pulpotomy was performed (thus removing the coronally inflamed pulp) and treating the presumably healthy pulp at the canal orifices. When the root canal has developed thick dentinal walls and the apices are closed, a full pulpectomy can be done (Courtesy Dr. Francisco Banchs).

Figure 4. Revascularization of immature dog teeth during period of 45 days. The teeth were extracted and immediately replanted. During the course of 45 days the blood supply moves into the pulp space.
Figure 5. Immature tooth with a necrotic infected canal with apical periodontitis. The canal is disinfected with copious irrigation with sodium hypochlorite and triantibiotic paste. After 4 weeks the antibiotic is removed, and a blood clot is created in the canal space. The access is filled with a mineral trioxide aggregate base and bonded resin above it. At 7 months the patient is asymptomatic, and the apex shows healing of the apical periodontitis and some closure of the apex. Reproduced with permission from Banchs F, Trope M. Revascularization of immature permanent teeth with apical periodontitis: new treatment protocol? J Endod 2004;30:196-200.

Figure 6. Composition and mixing instructions for the triantibiotic paste (adapted from Hoshino et al. (17)).

3Mix MP
- Antibiotics (3Mix)
  - Ciprofloxacin 200mg
  - Metronidazole 500mg
  - Minocycline 100mg
- Carrier (MP)
  - Macrogol ointment
  - Propylene glycol

Protocol for preparation
- Antibiotics (3Mix) – be sure to not cross-contaminate
  - Remove sugar coating from tablets with surgical blade, crush individually in separate mortars
  - Open capsules, crush in individually in separate mortars
  - Grind each antibiotic to a fine powder
  - Combine equal amounts of antibiotics (1:1:1) on mixing pad
- Carrier (MP)
  - Equal amounts of macrogol ointment and propylene glycol (1:1)
  - Using clean spatula, mix together on pad
  - Result should be opaque
- Separate out small portions of 3Mix and incorporate into MP using the following:
  - 1.5 (MP:3Mix) ➞ creamy consistency
  - 1.7 (standard mix) ➞ smears easily but does not crumble
  - If result is flaky or crumbly, then too much 3Mix has been incorporated

Storage
- Antibiotics must be kept separately in moisture-tight porcelain containers
- Macrogol ointment and propylene glycol must be stored separately
  - Discard if mixture is transparent (evidence of moisture contamination)
There has been a great deal of discussion as to the correct terminology for what has been called pulp revascularization in this article. Some have used the cases shown as examples of pulp regeneration and the beginning of stem cell technology in endodontics. It is clearly not apexification because not only the apex is closed, but the canal walls are thicker as well. Apexogenesis accomplishes a closed apex and thicker dentinal walls but by definition uses remaining vital root pulp to attain this goal, which is not the case here. Guided tissue regeneration has been used in periodontics and has some merit. However, guided tissue regeneration in periodontics assumes regeneration of periodontal structures, yet this is not the case for pulp. In the present cases, we must distinguish between revascularization and pulp regeneration. Presently, we can only say with certainty that the pulp space has returned to a vital state. On the basis of research in avulsed teeth and a recent study on infected teeth, however, it is more likely that the tissue in the pulp space is similar to a periodontal ligament than to pulp tissue (19). It appears that there is approximately a 30% chance of pulp tissue reentering the pulp space (20). Future research will need to be performed to stimulate pulp regeneration from the pluripotential cells in the periapical region (21).

**References**


**Figure 7.** Revascularization of an immature dog tooth with apical periodontitis. The root was artificially infected, producing apical periodontitis. After treatment similar to that described in Fig. 5, revascularization has occurred.
Vital Pulp Therapy with New Materials for Primary Teeth: New Directions and Treatment Perspectives

Anna B. Fuks, CD

Abstract

Vital pulp therapy aims to treat reversible pulpal injury and includes 2 therapeutic approaches: (1) indirect pulp treatment for deep dentinal cavities and (2) direct pulp capping or pulpotomy in cases of pulp exposure. Indirect pulp treatment is recommended as the most appropriate procedure for treating primary teeth with deep caries and reversible pulp inflammation, provided that this diagnosis is based on a good history, a proper clinical and radiographic examination, and that the tooth has been sealed with a leakage-free restoration. Formocresol has been a popular pulpotomy medication in the primary dentition and is still the most universally taught pulp treatment for primary teeth. Concerns have been raised over the use of formocresol in humans, and several alternatives have been proposed. Controlled clinical studies have been critically reviewed, and mineral trioxide aggregate and ferric sulfate have been considered appropriate alternatives to formocresol for pulpotomies in primary teeth with exposed pulps. In most of the studies reviewed, the caries removal method has not been described. The use of a high-speed handpiece or laser might result in an exposure of a “normal” pulp that would otherwise not be exposed. (J Endod 2008;34:S18-S24)

Key Words

Ferric sulfate, formocresol, mineral trioxide aggregate, primary teeth, pulp therapy

The aim of vital pulp therapy is to treat reversible pulpal injuries in both permanent and primary teeth, maintaining pulp vitality and function (1). In addition to these, in primary teeth it is important to preserve the tooth until its natural exfoliation time, thus preserving arch integrity (2). Vital pulp therapy includes 2 therapeutic approaches: indirect pulp treatment (IPT) in cases of deep dentinal cavities and direct pulp capping (DPC) or pulpotomy in cases of pulp exposure (1).

Advances in biomedical research open avenues for the design of new methods of dental treatment, aiming at regeneration of the dentin-pulp complex. New approaches have been based on the understanding of the molecular and cellular mechanisms regulating dentinogenesis during dental tissue repair and their potential for clinical exploitation (1).

The dental pulp possesses the ability to form a dentin-like matrix (tertiary dentin) as part of the repair in the dentin-pulp organ (3). Vital pulp therapy aims to treat reversible pulpal injury in cases in which dentin and pulp are affected by caries, restorative procedures, or trauma. Whenever the dentin-pulp complex is affected by injury, 3 different physiopathologic conditions might be observed at the dentin-pulp border:

1. In the case of mild injuries as in noncavitated enamel caries or slowly progressing dentinal caries, the odontoblasts might survive, and the odontoblastic layer is stimulated to form a tertiary dentin matrix beneath the injury (reactionary dentin). Reactionary dentin shows many similarities to the primary and secondary dentin and can effectively oppose exogenous destructive stimuli to protect the pulp (4).

2. With severe dentinal injuries without pulp exposure as in rapidly progressing carious lesions or in severe tissue damage caused by cavity preparation, odontoblasts are destroyed subjacent to the affected dentin (5, 6). In an appropriate metabolic state of the dentin-pulp complex, a new generation of odontoblast-like cells might differentiate and form tubular tertiary dentin (reparative dentinogenesis) (3, 7). It must be emphasized that under clinical conditions, the matrix formed at the pulp-dentin interface often comprises reactionary dentin, reparative dentin, or fibrodentin formation. It is impossible to distinguish these processes at the in vivo level, and the process might also be indistinguishable from a biochemical and molecular point of view.

3. In the case of pulp exposure, the amputated pulp can be repaired by itself or after application of capping materials (8–10). Pulp exposure caused by caries shows very limited potential for pulp recovery as a result of bacterial infection of the pulp for a substantial period of time, which compromises the defense reaction (11). As part of the wound healing process in the repairing pulp, the dentinogenic potential of pulp cells can be expressed. Proliferation, migration, and differentiation of progenitor cells can give rise to a new generation of reparative dentin-forming cells (odontoblast-like cells), reconstituting the lost continuum at the pulp-dentin border (12, 13).

Indirect Pulp Treatment

After this brief review of the cellular changes during tooth development and how they are mimicked during tissue repair, we are able to assess the biologic validity of the various vital pulp treatments. In this light, IPT, contrary to what was believed in the past, can also be an acceptable procedure for primary teeth with reversible pulp inflammation, provided that the diagnosis is based on a good history and proper clinical and
radiographic examination, and the tooth has been sealed with a leak-age-free restoration (2).

In a recent systematic review on complete or ultraconservative removal of decayed tissue, Ricketts et al. (14) concluded that “in deep lesions, partial caries removal is preferable to complete caries removal to reduce the risk of carious exposure.”

Several articles reported the success of this technique in primary teeth (15–19). On the basis of the biologic changes previously described and the growing evidence of the success of IPT in primary teeth, we can recommend IPT as the most appropriate treatment for symptom-free primary teeth with deep caries, provided that a proper, leakage-free restoration can be placed. This issue will be discussed in greater detail further in this symposium.

Direct Pulp Capping

DPC is carried out when a healthy pulp has been inadvertently exposed during an operative procedure. The tooth must be asymptomatic, and the exposure site must be pinpoint in diameter and free of oral contaminants. A calcium hydroxide medicament is placed over the exposure site to stimulate dentin formation and thus “heal” the wound and maintain the pulp’s vitality (20).

DPC of a carious pulp exposure in a primary tooth is not recommended but can be used with success on immature permanent teeth. DPC is indicated for small mechanical or traumatic exposures when conditions for a favorable response are optimal. Even in these cases, the success rate is not particularly high in primary teeth. Treatment failure might result in internal resorption or acute dental alveolar abscess (20).

Presently, DPC should still be looked on with some reservations in primary teeth. This treatment, however, could be recommended for exposed pulps in older children 1 or 2 years before normal exfoliation. In these children, a failure of treatment would not imply the need for a space maintainer after extraction, as it would in younger children.

In a recent article, Caicedo et al. (21) demonstrated good pulp response in primary teeth after DPC or pulpotomy with MTA and concluded that MTA might be a favorable material for pulp capping and pulpotomy in primary teeth.

Pulpotomy

Pulpotomy is still the most common treatment for cariously exposed pulps in symptom-free primary molars. The aim of this treatment is to preserve the radicular pulp, avoiding pain and swelling, and ultimately to retain the tooth, preserving arch integrity (2). Formocresol (FC) has been a popular pulpotomy medicament in the primary dentition for the past 70 years since its introduction by Sweet in 1932, and it is still considered the most universally taught and preferred pulp treatment for primary teeth (22–24). Concerns have been raised over the use of FC in humans, mainly as a result of its toxicity and potential carcinogenicity (25–32).

The International Agency for Research on Cancer classified formaldehyde as carcinogenic for humans in June 2004, leaving the profession to look for other alternatives to FC (31). On the basis of the information available, an expert working group has determined that there is now sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans, a rare cancer in developed countries, limited evidence for cancer of the nasal cavity and paranasal sinuses, and “strong but not sufficient evidence” for leukemia.

There has been a significant amount of discussion in the dental literature about the appropriateness and safety of using aldehyde-based products in pediatric dentistry (29). FC is no longer used in some countries, mainly as a result of safety concerns.

Milnes (33) published an extensive and detailed review of the more recent research on the metabolism, pharmacokinetics, and carcinogenicity of formaldehyde and concluded that formaldehyde is not a potent human carcinogen under conditions of low exposure. He concluded that extrapolation of these research results to pediatric dentistry suggests an inconsequential risk of carcinogenesis associated with formaldehyde use in pediatric pulp therapy.

In a case-control study in which FC pulpotomies were performed in 5- to 10-year-old children, blood samples were taken before (control) and after treatment to observe the mutagenic potential of FC on lymphocytes cultures. No statistically significant differences could be observed in the cultured lymphocytes. FC was mutagenic for one patient, however, leading the authors to raise doubts about the desirability of using this technique in children (34).

No correlation between FC pulpotomies and cancer has ever been demonstrated. Nevertheless, several studies have reported that the clinical success of FC pulpotomies decreases with time, and the histologic response of the primary pulp is “capricious,” ranging from chronic inflammation to necrosis (35).

Presently, there are several pulp dressing medications that have been proposed to maintain radicular pulp vitality that are equal to, if not better than, FC and can be used as alternatives to pulpotomies in primary teeth. The pulp dressing materials and techniques proposed include: electrosurgery (36, 37), laser (38, 39), glutaraldehyde (GT) (40–44), calcium hydroxide (CH) (45–47), freeze-dried bone (48), bone morphogenetic protein (49), osteogenic protein (50), ferric sulfate (FS) (51–56), mineral trioxide aggregate (MTA) (24, 57–59), and sodium hypochlorite (60).

Although a considerable number of clinical trials and laboratory animal studies have been published on this subject, the Cochrane review found that evidence is lacking to conclude which is the most appropriate technique for pulpotomies in primary teeth (61). The Cochrane review assessment is extremely rigorous, and with the exception of 3 articles, none of the articles evaluated could meet the criteria and were excluded.

Evidence-Based Analysis of Pulpotomy Literature

Loh et al. (62) published an evidence-based assessment of FC versus FS by using a different sieving system including all suitable clinical trials, not only randomized ones. They concluded that both materials were likely to produce similar clinical/radiographic success.

Following Cochrane’s criticism regarding the paucity of appropriately designed, statistically assessed investigations and the lack of long-term outcomes, many studies have been reported, and several others have begun to contribute to the literature (32).

Fukas and Papagiannoulis (63) assessed the relevant articles that have appeared after the aforementioned reviews by using the clinically based criteria listed by Curzon and Tountza (64). In this review, the MEDLINE search used generated a total of 358 citations, and the sieving of these articles was conducted by examining the article title and assessing its relevance (62).

All articles were graded according to the aforementioned criteria and classified as A if the article met 90% or more of the criteria; B1 if an article scored from 75%–89%; B2 if it scored between 60%–74%; and C if it scored 59% or less, which meant that it had to be excluded. Even with different weights attributed to the evaluated articles, no conclusion could be reached as to the optimum treatment or technique for pulpally involved primary teeth. In a meta-analysis to compare the clinical and radiographic effects of MTA with FC, Peng et al. (65) reported that MTA was superior to FC. These authors claimed that MTA induces less undesirable responses and might be a suitable replacement for FC.
In another meta-analysis that included clinical trials and randomized clinical trials, Deery (66) concluded that pulpotomies performed with either FS or FC were likely to produce similar results.

Although meta-analysis generally pools data from randomized clinical trials, they are regarded as observational studies of evidence (67–69). Usually the reviewer identifies the relevant studies from the literature and decides whether to include or exclude them. Therefore, the strength of conclusions drawn from a meta-analysis might only be comparable to that drawn from observational studies, which are open to various forms of bias. Problems, including publication bias and the variable quality of the primary studies, can threaten the validity of meta-analysis (70). Another limitation of meta-analyses is that they all search for relevant articles in electronic databases and are limited to the English language. Most databases date only from 1965. For this reason articles that could have been relevant, particularly on CH or FC pulpotomies, were not included. Language bias can also occur because researchers whose native language is not English are more likely to publish nonsignificant results in non-English journals and significant results in English journals (70).

One of the aims of evidence-based dentistry is to reach an evidence-based conclusion and then translate it into a clinical decision that would result in a better treatment outcome. With these points in mind, this article will consist of critically assessing the randomized and non-randomized human clinical trials that resulted from a MEDLINE search. This search generated a total of 358 citations, as described by Fuks and Papagiannoulis (63), with the addition of the relevant studies published after that date. Duplicate publications of the same study were excluded. The articles assessed will be limited to the comparisons of FS, MTA, and FC, formocresol.

**Studies Comparing MTA With FC**

**Cuisia et al. (2001)** A randomized, clinical trial compared MTA with FC in 120 molars of 24 children. Only restorable molars without clinical and/or radiographic evidence of pulp degeneration were included. Pulpotomies were performed in 60 molars by 1 pediatric dentist using a local anesthetic and restored with a stainless steel crown, but there was no mention of the use of a rubber dam. The results were assessed by 2 pediatric uncalibrated dental residents at 6-month follow-up; the clinical success rate was 93% for FC and 97% for MTA, whereas the radiographic success was 77% for FC and 93% for MTA.

**Agamy et al. (2004)**

This randomized, clinical trial compared gray MTA, white MTA, and FC in 72 molars of 24 children. Only restorable molars without clinical and/or radiographic evidence of pulp degeneration were included. Each child had at least 3 molars with severe carious involvement and received pulpotomies with all 3 medicaments. An additional 15 carious teeth planned for serial extractions after 6 months were selected for the histologic part of the study. All pulpotomies were performed by the same pediatric dentist, and outcome assessment after 12 months was done by 2 “blinded” pediatric dentists. Four children (12 molars) dropped out, and of the remaining 60 teeth in 20 patients, 1 (gray MTA) exfoliated normally, and another 6 teeth (4 white MTA and 2 FC) failed as a result of abscesses. The remaining 53 teeth appeared to be clinically and radiographically successful. In the histologic study, both types of MTA formed thick dentin bridges, but the gray MTA appeared to be better than white MTA and FC as a pulp dressing, because it presented the closest to normal pulp architecture.

**Jabbarifar et al. (2004)**

This randomized, clinical trial compared MTA with FC in 64 molars assigned to 2 groups by the toss of a coin. The number of pediatric dentists who performed the treatments was not specified, rubber dam isolation was not reported, and all the teeth were restored with SSCs. Outcome assessment of 64 molars remaining at 12 months was done by 2 “blinded” pediatric dentists. The number of molars treated at the baseline and the number of dropouts were not reported. Clinical and radiographic success for MTA was 94% and for FC was 91%.

**Farsi et al. (2005)**

This randomized, clinical trial compared MTA with FC in 120 molars of 100 children assigned to 2 groups by the toss of a coin. Only restorable molars without clinical and/or radiographic evidence of pulp degeneration were included. Pulpotomies were performed in 60 molars by 1 pediatric dentist using a local anesthetic and restored with a stainless steel crown, but there was no mention of the use of a rubber dam. The results were assessed by 2 pediatric uncalibrated dental residents at 6-month follow-up; the clinical success rate was 93% for FC and 97% for MTA, whereas the radiographic success was 77% for FC and 93% for MTA.

**Articles Comparing Directly FS and FC**

<table>
<thead>
<tr>
<th>Direct comparison articles: MTA × FC</th>
<th>Molars, FC (n)</th>
<th>Molars, FS (n)</th>
<th>Success (clinical), FC n (%)</th>
<th>Success (clinical), MTA n (%)</th>
<th>Success (x-ray), FC n (%)</th>
<th>Success (x-ray), MTA n (%)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuisia et al. (2001)</td>
<td>30</td>
<td>30</td>
<td>28 (93)</td>
<td>29 (97)</td>
<td>23 (77)</td>
<td>28 (93)</td>
<td>6</td>
</tr>
<tr>
<td>Agamy et al. (2004)</td>
<td>20</td>
<td>19</td>
<td>18 (90)</td>
<td>19 (100)</td>
<td>18 (90)</td>
<td>19 (100)</td>
<td>12</td>
</tr>
<tr>
<td>Jabbarifar et al. (2004)</td>
<td>32</td>
<td>32</td>
<td>29 (91)</td>
<td>30 (94)</td>
<td>29 (91)</td>
<td>30 (94)</td>
<td>12</td>
</tr>
<tr>
<td>Farsi et al. (2005)</td>
<td>36</td>
<td>38</td>
<td>35 (97)</td>
<td>38 (100)</td>
<td>31 (86)</td>
<td>38 (100)</td>
<td>24</td>
</tr>
<tr>
<td>Holan et al. (2005)</td>
<td>29</td>
<td>33</td>
<td>24 (83)</td>
<td>32 (97)</td>
<td>24 (83)</td>
<td>32 (97)</td>
<td>74</td>
</tr>
<tr>
<td>Naik and Hegde (2005)</td>
<td>23</td>
<td>24</td>
<td>23 (100)</td>
<td>24 (100)</td>
<td>23 (100)</td>
<td>24 (100)</td>
<td>6</td>
</tr>
</tbody>
</table>

In English journals (70).

**TABLE 2. Articles Comparing Directly FS and FC**

<table>
<thead>
<tr>
<th>Direct comparison articles: FC × FS</th>
<th>Molars, FC (n)</th>
<th>Molars, FS (n)</th>
<th>Success (clinical), FC n (%)</th>
<th>Success (clinical), FS n (%)</th>
<th>Success (x-ray), FC n (%)</th>
<th>Success (x-ray), FS n (%)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fei et al. (1991)</td>
<td>27</td>
<td>29</td>
<td>26 (96)</td>
<td>29 (100)</td>
<td>22 (81)</td>
<td>28 (97)</td>
<td>12</td>
</tr>
<tr>
<td>Fuks et al. (1997)</td>
<td>37</td>
<td>55</td>
<td>31 (84)</td>
<td>51 (93)</td>
<td>27 (73)</td>
<td>41 (93)</td>
<td>35</td>
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<tr>
<td>Aktoren and Gencay (2000)</td>
<td>24</td>
<td>24</td>
<td>21 (88)</td>
<td>21 (88)</td>
<td>19 (80)</td>
<td>20 (84)</td>
<td>24</td>
</tr>
<tr>
<td>Papagiannoulis (2002)</td>
<td>60</td>
<td>73</td>
<td>58 (97)</td>
<td>66 (90)</td>
<td>47 (78)</td>
<td>54 (74)</td>
<td>36</td>
</tr>
<tr>
<td>Ibrevic and Al-Jame (2003)</td>
<td>80</td>
<td>84</td>
<td>78 (97)</td>
<td>81 (96)</td>
<td>75 (94)</td>
<td>77 (92)</td>
<td>42–48</td>
</tr>
<tr>
<td>Huth et al. (2005)</td>
<td>48</td>
<td>49</td>
<td>46 (96)</td>
<td>49 (100)</td>
<td>43 (90)</td>
<td>42 (86)</td>
<td>24</td>
</tr>
<tr>
<td>Markovic et al. (2005)</td>
<td>33</td>
<td>37</td>
<td>30 (91)</td>
<td>33 (89)</td>
<td>28 (85)</td>
<td>30 (81)</td>
<td>18</td>
</tr>
</tbody>
</table>

FC, formocresol; FS, ferric sulfate.
Degeneration were included. The number of pediatric dentists who performed the treatments was not specified, rubber dam isolation was not reported, and all the teeth were restored with SSCs. At 24 months, 46 molars (38%) were lost, leaving 74 molars for evaluation. All the MTA-treated molars were successful clinically and radiographically (100%). For the FC, clinical and radiographic success was 97% and 86%, respectively.

Holan et al. (2005)24

This randomized, clinical trial compared MTA with FC in 64 molars of 35 children assigned to 2 groups by the toss of a coin. The number of operators was not specified, and in 56 molars SSCs were placed, 1 molar received a composite restoration, and the other 7 teeth were restored with amalgam. Clinical outcomes were assessed by 1 pediatric dentist without “blinding.” Radiographs were assessed by 3 “blinded” pediatric dentists using a standardized evaluation form for calibration (complete agreement for all cases). Internal resorption was considered a failure only when it reached the bone. Arrested internal resorption, calcific metamorphosis, and pulp canal obliteration were not considered failures. At 74 months, 2 molars (3%) were lost, leaving 62 molars for evaluation. Clinical and radiographic success was 97% for MTA and 83% for FC, respectively.

Naik and Hegde (2005)56

This randomized, clinical trial compared MTA with FC in 50 molars assigned randomly (method not specified) to 2 groups. The inclusion criterion was “asymptomatic deep carious lesion with no frank exposure.” Pulpotomies were performed by a postgraduate dentist under local anesthesia and rubber dam. It was not clear whether preoperative radiographs were taken and SSCs were placed 24 hours later. Three teeth were lost to follow-up (2 FC and 1 MTA), and all the remaining teeth were clinically and radiographically successful at the 6-month follow-up.

Studies Comparing FS With FC

Fei et al. (1991)51

This randomized, clinical trial compared FS with FC in 83 molars in 62 children assigned by a table of random numbers to 2 groups. Only restorable molars without clinical or radiographic signs of pulpal degeneration were included. Teeth with pulpal hemorrhage persisting after 2 applications of FS or FC were eliminated. A pediatric dentistry postgraduate student performed all pulpotomies, and 2 pediatric dentists were “blinded” and calibrated before radiographic assessment. At 12 months, 27 molars were lost, leaving 56 molars for assessment. Clinical success for FC was 96% and for FS was 100%; radiographic success was 81% for FC and 97% for FS.

Fuks et al. (1997)52

This randomized, clinical trial compared FS with FC in 96 molars in 72 children assigned to 2 groups by a toss of a coin. Only asymptomatic and restorable molars without clinical and radiographic signs of pulpal degeneration were included. Three pediatric dentists performed the pulpotomies under a local anesthetic and with a rubber dam, but outcome assessors were not reported. Molars with pulp canal obliteration (PCO) were not considered failures. The dropout rate was 4% (4/96 molars) after 6–34 months. Clinical success for FC was 84% and for FS was 93%; radiographic success was 80% for FC and 93% for FS. No statistical difference was observed between the 2 groups.

Aktoren and Gencay (2000)73

This randomized, clinical trial compared FS, FC, and GT. Only asymptomatic and restorable molars without clinical and radiographic signs of pulpal degeneration were included. Clinicians performing the pulpotomies and outcome assessors were not described. At 24 months, clinical success rates for 72 molars were reported to be 88% for both FC and FS, and radiographic success was 80% for FC and 84% for FS.

Papagiannoulis (2002)74

This randomized, clinical trial compared FS with FC in 133 molars in 90 children assigned to 2 groups by a toss of a coin. Only asymptomatic and restorable molars without clinical and radiographic signs of pulpal degeneration were included. Pulpotomies were performed by 3 pediatric dentists; most molars were restored with SSCs, and a few received composite resin restorations. Outcomes were assessed by a separate “blinded” pediatric dentist. Molars with PCO or nonprogressive internal resorption were not considered failures. Clinical success was 97% for FC and 90% for FS, and radiographic success was 78% for FC and 74% for FS.

Ibrevic and Al-Jame (2003)54

This randomized, clinical trial compared FS with full-strength FC in 194 molars in 70 patients allocated alternately to 2 groups. Only restorable molars without clinical and radiographic signs of pulpal degeneration were included. Pulpotomies were performed by 1 pediatric dentist, and most molars were restored with SSCs; a few molars were restored with amalgam. Clinical outcomes were assessed by the operator, but radiographic outcomes were assessed by both the operator and another “blinded” evaluator. Calibration was not reported, but both assessors reached consensus on radiographic outcomes. Ten patients (30 molars) dropped out after 42 months. Clinical success rates were 97% in the FC group and 96% in the FS group. The radiographic success rate was 94% in the FC group and 92% in the FS group. No statistical differences were found between the radiographic assessments of both pulpotomy agents.

Huth et al. (2005)47

This randomized, clinical trial compared FS, FC, CH, and laser in 107 children. A power calculation estimated the numbers of molars required to achieve statistical significance. Randomization was done by casting a concealed lot from a box of 4 × 50 lots, such that 200 molars were allocated to 4 groups. Only asymptomatic restorable molars without clinical and radiographic signs of pulpal degeneration were included. The molars received SSCs or composite resin restorations. Two pediatric dentists performed the pulpotomies under local or general anesthesia and rubber dam, and 2 other “blinded” experienced dentists per-

### TABLE 3. Articles Directly Comparing CH and FC

<table>
<thead>
<tr>
<th>Direct comparison articles: FC × CH</th>
<th>Molars, FC (n)</th>
<th>Molars, CH (n)</th>
<th>Success (clinical), FC (n %)</th>
<th>Success (clinical), CH (n %)</th>
<th>Success (x-ray), FC (n %)</th>
<th>Success (x-ray), CH (n %)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waterhouse et al. (2000)</td>
<td>44</td>
<td>35</td>
<td>37 (84)</td>
<td>27 (77)</td>
<td>37 (84)</td>
<td>27 (77)</td>
<td>To exfoliation</td>
</tr>
<tr>
<td>Huth et al. (2005)</td>
<td>48</td>
<td>38</td>
<td>46 (96)</td>
<td>33 (87)</td>
<td>43 (90)</td>
<td>25 (66)</td>
<td>24</td>
</tr>
<tr>
<td>Markovic et al. (2005)</td>
<td>33</td>
<td>34</td>
<td>30 (91)</td>
<td>28 (82)</td>
<td>28 (85)</td>
<td>26 (76)</td>
<td>18</td>
</tr>
</tbody>
</table>

FC, formocresol; CH, calcium hydroxide.
formed outcome assessments. Intraexaminer and interexaminer reproducibility was optimal (κ = 1.0). The dropout rate was 8% (16/191 molars), and the remaining participants were examined after 24 months. Clinical success rate was 96% for FC and 100% for FS, and radiographic success was 90% for FC and 86% for FS.

Markovic et al. (2005)58

This randomized, clinical trial compared FS, FC, and CH in 104 molars in 104 children assigned randomly to 3 groups. Vital carious-exposed molars with no radiographic signs of pulp degeneration were included. Pulpotomies were performed by 3 pediatric dentists, and outcomes were assessed by a separate evaluator. The intraexaminer agreement was moderate (κ = 0.70). The number of molars at baseline and the number of dropouts were not reported. The clinical success rate at 18 months for FC was 91%, for FS was 89%, and for CH was 82%. The radiographic success was 85% for FC, 82% for FS, and 76% for the CH group. These differences, however, were not statistically significant.

Studies Comparing CH With FC

Three articles compared directly CH with FC. Two of them have been summarized previously (47, 56).

Waterhouse et al. (2000)75

This randomized, clinical trial compared FC and CH in 84 molars in 52 children assigned to 2 groups by the toss of a coin. Only healthy children with restorable molars without clinical and radiographic signs of pulp degeneration were included. Pulpotomies were performed by clinicians under rubber dam or cotton roll isolation; SSCs were placed “where indicated” (indications not described), and other molars were restored with amalgam, glass ionomer, or compomer. Outcomes were assessed by a separate pediatric dentist, “blinded” and calibrated in a parallel study (77% interexaminer agreement). At 22 months, 5 molars in 3 patients dropped out, leaving 79 molars in 49 children. Clinical and radiographic success was 84% for FC and 77% for CH.

Studies Comparing Laser With FC

Saltzman et al. (2005)39

This randomized single-blind, split-mouth clinical trial compared a diode laser pulpotomy with MTA with a conventional FC/zinc oxide–eugenol (ZOE) pulpotomy. A total of 26 pairs of teeth from 16 patients between 3–8 years old were selected on the basis of clinical and radiographic criteria. All teeth were followed up clinically and radiographically for 15 months. A total of 7 laser-MTA–treated teeth were radiographic failures, as opposed to 3 FC/ZOE-treated teeth at 15.7 months; however, these results were not statistically significant. The authors suggested that an improved success rate among a larger patient sample and a longer follow-up period would be required for the laser-MTA pulpotomy to be considered a suitable alternative to conventional FC pulpotomy.

Liu JF (2006)66

This clinical study compared the effects of Nd:YAG laser pulpotomy with FC on human primary teeth. Patients without any medically compromised disease were selected from the patient population at a hospital-based dental clinic in Taiwan. Primary teeth that required pulpotomy “because of carious pulp exposure” were selected for this study. Fifty children with an average age of 5 years, 3 months (range, 4–7 years) participated in the study group, and a total of 68 primary molars were treated with the Nd:YAG laser. Forty-four children participated in the control group, and 69 primary molars were treated with dilute FC. Follow-up time was between 6–64 months. In the Nd:YAG laser group, clinical success was achieved in 66 of 68 teeth (97%), and 94% were radiographically successful. In the control group, 85% and 78% achieved clinical and radiographic success, respectively. The success rate of the Nd:YAG laser was significantly higher than that of the FC pulpotomy. The permanent successors of the laser-treated teeth erupted without any complications.

Study Comparing Sodium Hypochlorite With FS

Vargas et al. (2006)60

This prospective randomized, clinical study compared the effectiveness of 5% sodium hypochlorite (NaOCl) with that of FS as a pulpotomy medicament in decayed primary molars. Twenty-three healthy patients between 4 and 9 years old with at least 2 primary molars needing a pulpotomy were included in the study. The teeth were clinically and radiographically examined, and the signs/symptoms were recorded at 0, 6, and 12 months. Six-month results were based on the first 32 teeth in the NaOCl group and 28 teeth in the FS group. Twelve-month results were based on 13 teeth in the FS group and 14 in the NaOCl group. At 6 months, 100% clinical success was found in both the FS and NaOCl groups. Radiographic success for FS was 68%, with internal resorption being the most common finding. The NaOCl showed 91% radiographic success. At 12 months, FS had 85% clinical success and 62% radiographic success. NaOCl had 100% clinical success and 79% radiographic success. The authors concluded that preliminary evidence showed that NaOCl can be used successfully as a pulpotomy medicament.

Summary

From this review of the randomized, clinical trials, one can observe that all the studies comparing MTA with FC showed that MTA presented better results, even though in some of them there was no statistical difference as a result of the small number of teeth tested. FS was also better than FC in some studies and similar to FC in others, whereas the 3 studies with CH showed inferior outcomes. It should be emphasized, however, that in most of the studies the method of caries removal has not been described. The use of a high-speed handpiece or laser might result in an exposure of a “normal” pulp that would otherwise not be exposed and not need a pulpotomy or that could be alternatively treated by IPT.

As previously mentioned, one of the aims of evidence-based dentistry is to reach an evidence-based conclusion and then translate it into a clinical decision that would result in a better treatment outcome. It should be kept in mind, however, that improving patient care requires the consideration of other factors including the cost and technique sensitivity of the new medicament.

From the studies previously presented, MTA showed better results in all cases and should be recommended as an alternative to FC. One of the drawbacks of this material, however, is its high cost, and its use in pediatric dentistry practice can become almost prohibitive in some circumstances. Hence, FS can still be considered a valid and inexpensive solution for pulpotomies in primary teeth (2).

A recent preliminary evaluation of sodium hypochlorite showed promising results when compared with FS. The follow-up time, however, is only 1 year. Longer follow-up and more clinical studies are needed to confirm these results.

References


Vital Pulp Therapy with New Materials: New Directions and Treatment Perspectives—Permanent Teeth

David E. Wittherspoon, BDS, MS

Abstract

Pulp necrosis in immature teeth subsequent to caries has a major impact on long-term tooth retention. The aim of vital pulp therapy is to maintain pulp vitality by eliminating bacteria from the dentin-pulp complex and to establish an environment in which apexogenesis can occur. A complicating factor in treating immature teeth is the difficulty predicting the degree of pulpal damage. The ability of the clinician to manage the health of the remaining pulp tissue during the procedure is paramount. Currently, the best method appears to be the ability to control pulpal hemorrhage by using sodium hypochlorite. Mineral trioxide aggregate (MTA) currently is the optimum material for use in vital pulp therapy. Compared with the traditional material of calcium hydroxide, it has superior long-term sealing ability and stimulates a higher quality and greater amount of reparative dentin. In the medium-term clinical assessment, it has demonstrated a high success rate. Thus, MTA is a good substitute for calcium hydroxide in vital pulp procedures. (J Endod 2008;34: S25-S28)

Key Words
Apexogenesis, direct pulp cap, mineral trioxide aggregate, pulpotomy

Dental caries is one of the greatest challenges to the integrity of the developing tooth. It can result in irreversible pulpal damage, eventually causing necrosis of the pulpal tissues and associated arrested development of the tooth root. Ultimately, abnormal root development will impact the long-term prognosis for tooth retention (1–4). Thus, the primary goal when treating immature permanent teeth should be to maintain pulp vitality so that apexogenesis can occur (5–8). Direct pulp caps and pulpotomies in teeth with incomplete root formation promote normal development of the root complex. There are long-term prognostic advantages of this treatment outcome over apexitification treatment. The tooth structure formed is of a great quantity, and its composition appears to have greater structural integrity (3). The result is that the fully developed tooth is more resistant to vertical root fractures (4).

The classic study by Kakehashi et al. (9, 10) eloquently established the role of bacteria in pulpal health and necrosis. In a germ-free environment, the pulp demonstrated the ability to heal and deposit additional dentin material. In the presence of bacteria, pulpal demise was inevitable. This fundamental premise is integral to the success of all vital pulp procedures. Thus, the basic principle of vital pulpal treatment can be broken down into 2 broad phases. The initial phase involves removing the diseased and bacterially contaminated tissue. The second phase involves establishing an environment that will prevent any further and future bacterial contamination. The principal procedures aimed at maintaining pulpal vitality include direct pulp caps and pulpotomies. By removing the affected coronal pulp tissue and leaving the unaffected radicular pulp tissue in situ, sealed from the oral environment, normal root development can take place.

Historically, a number of materials (11–13) have been advocated to induce normal root development. To date, the material of choice has been calcium hydroxide (Ca(OH)₂) (14–20). Most recently, an alternative material, mineral trioxide aggregate (MTA), has become available for use in pulpal procedures. Several properties are necessary when choosing a material to be used in vital pulp treatment. These include the ability of the material to kill bacteria, induce mineralization, and establish a tight bacterial seal. The ideal material for vital pulp treatment should be able to resist long-term bacterial leakage and stimulate the remaining pulp tissue to return to a healthy state, promoting the formation of dentin. The early data for MTA suggest that it is the optimum material for fulfilling these goals when vital pulp therapy is the treatment of choice.

MTA’s Physical and Chemical Properties

MTA is composed of tricalcium silicate, bismuth oxide, dicalcium silicate, tricalcium aluminate, and calcium sulfate dihydrate. MTA might also contain up to 0.6% insoluble residue, including free crystalline silica. Other trace constituents might include calcium oxide, free magnesium oxide, potassium, and sodium sulfate compounds (21). Hydration of the powder results in the formation of a finely crystalline gel of the hydrated forms of the components, with some Ca(OH)₂ also being formed. This solidifies to a hard structure in less than 3 hours (22). It has a compressive strength equal to intermediate restorative material (IRM) and Super-EBA IRM but less than that of amalgam. MTA has been shown to have an antibacterial effect on some of the facultative bacteria and no effect on strict anaerobic bacteria (23). This limited antibacterial effect is less than that demonstrated by Ca(OH)₂ pastes. MTA’s ability to resist the future penetration of microorganisms appears to be high. In in vitro leakage studies (24, 25), MTA has resisted leakage predictably and repeatedly. MTA frequently performs better...
than amalgam IRM or Super EBA (26–30). Compared with composite resins placed under ideal conditions, MTA’s leakage patterns are similar (31, 32). Furthermore, the presence of blood has little impact on the degree of leakage (29, 33). It is commercially available as ProRoot MTA (Dentsply Tulsa Dental, Tulsa, OK) and has been advocated for use in vital pulp therapy (34–38).

**Mineralization**

MTA has demonstrated the ability to induce hard tissue formation in pulpal tissues when used as either a direct pulp capping or pulpotomy material (34, 36, 39–45). MTA promotes rapid cell growth in vitro (46). Compared with Ca(OH)₂, in animal studies, MTA consistently induces the formation of dentin at a greater rate with a superior structural integrity. It develops more complete dentin bridges and demonstrates an improved ability to maintain pulp tissue integrity (34, 39). Histologic evaluation in animal and human studies has shown that MTA stimulates reparative dentin formation, with thick dentinal bridging, minimal inflammation, and nominal hyperemia. The net result is that vital pulp therapy with MTA produces negligible pulpal necrosis (34, 41–43, 47).

MTA also appears to induce the formation of a dentin bridge at a faster rate than Ca(OH)₂ (48). In 1 case report (52) partial pulpotomies were conducted on 2 cases of dens evaginatus. After 6 months, the teeth were removed as part of planned orthodontic treatment. Histologic examination of these teeth showed an apparent continuous dentin bridge formation in both teeth, and the pulps were free of inflammation. The process by which MTA acts to induce dentin bridge formation is not known. It has been theorized (49) that the tricalcium oxide in MTA reacts with tissue fluids to form Ca(OH)₂, resulting in hard tissue formation in a similar manner to Ca(OH)₂.

**Clinical Outcomes**

The initial response reported in case reports has been very positive (50–52). Several human clinical studies with MTA for direct pulp capping and pulpotomies have recently been published.

**Direct Pulp Capping**

The clinical data available on MTA pulp capping of cariously exposed permanent teeth are limited to 2 studies. Both of these studies have reported a high rate of success, which ranges from 95%–98% (53, 54). In 1 study (54), 53 teeth with carious exposures that had been diagnosed with reversible pulpitis and normal periradicular tissue were treated with MTA pulp caps. A total of 40 patients between 7 and 45 years old were treated. Briefly, the treatment consisted of caries removal with the aid of an operating microscope and extensive use of caries detector dye. Pulpal bleeding was controlled with 5.25%–6.00% NaOCl applied for up to 10 minutes. After hemostasis was achieved, the pulps were capped with MTA, and the teeth were temporized with unbonded composite Photocore (Kuraray Co Ltd, Osaka, Japan) and a moistened cotton pellet placed directly over the MTA. The teeth were restored with a bonded composite 5–10 days later. Forty-nine of the 53 teeth were available for recall at the 1-year time frame, with an average recall period of 3.94 years.

The maximum period of observation was 9 years. During that time, 98% of the cases presented a favorable outcome, with a normal radiographic appearance, no symptoms, and a normal response to cold testing. In addition, of the 15 teeth in younger patients that were not fully formed at the time of treatment, all subsequently demonstrated continued normal apexogenesis to complete root formation (54). In the second study, a 93% clinical and radiographic success rate was reported at the 24-month recall period. The study used a similar protocol to direct pulp cap 30 young, permanent, cariously exposed asymptomatic teeth with MTA. All the teeth showed signs of vitality and absence of periapical radiolucency, with evidence of continued root growth and no reported symptoms (53).

**Pulpotomy**

The human clinical data available on MTA pulpotomies in cariously exposed permanent teeth have reported high success rates, which ranged from 93%–100%. In a prospective clinical trial comparing success rates of partial pulpotomies with treated cariously exposed permanent molars by using Ca(OH)₂ or MTA, there was no statistically significant difference in the success rate between each group (Ca(OH)₂ = 91%, MTA = 93%). Fifty-one teeth in 34 patients were available for recall. The patients ranged from 6.8–13.3 years old, and the follow-up period was from 25.4–45.6 months, with an average of 34.8 months (55).

When comparing MTA and Ca(OH)₂ pulpotomies within the same patient at the 12-month recall time frame, 2 of the 15 teeth in the Ca(OH)₂ group were considered failures, whereas none of the teeth treated with MTA failed (0 of 15 teeth). Calculis were not evident radiographically in 2 teeth treated with Ca(OH)₂ and in 4 teeth treated with MTA (56).

The use of gray MTA for partial pulpotomy in cariously exposed young permanent first molars diagnosed with reversible pulpitis and normal periradicular tissue has resulted in a very high success rate. Exposed pulp tissue was removed with a diamond bur, and after hemostasis, 2–4 mm of gray MTA was placed against the fresh wound and then covered with a layer of glass ionomer cement. The teeth were restored with amalgam or stainless steel crowns. At the 24-month recall period, 22 of 28 teeth showed no signs of clinical or radiographic failure and responded within normal limits to pulpal vitality tests. Although 6 of 28 teeth did not respond to vitality testing at the final follow-up, the radiographic appearance was within normal limits, and the teeth were asymptomatic. The patients’ ages ranged from 7.2–13.1 years, with an average age of 10 years (57).

In a case series outcomes report that used MTA pulpotomies to treat cariously exposed immature permanent teeth (first or second molars) that had been diagnosed with irreversible pulpitis, a success rate of 92% was reported (58). The key factor in deciding whether to complete a pulpotomy as opposed to a pulpectomy was the ability to control pulpal hemorrhage. In cases in which pulpal hemostasis could be achieved with NaOCl, a pulpotomy was completed. The patients’ ages ranged from 7–15 years, with an average age of 10 years. The recall period ranged from 6–53 months, with an average recall period of 21 months. The single tooth that required nonsurgical root canal treatment had completed normal root development before requiring nonsurgical root canal treatment.

**Technique**

With the vital pulp therapy technique, the patient is anesthetized with a standard local anesthetic protocol. In all cases, a rubber dam is used to isolate the tooth being treated. The affected enamel is removed by using a high-speed bur with copious irrigation. The gross caries can be removed with either a sharp spoon excavator or a large, round, slow-speed tungsten carbide bur. As the pulp is approached, the cavity is flushed with NaOCl to decrease the bacterial load. The remaining affected tissue is removed by using a coarse, high-speed diamond bur with copious irrigation. In the case of a pulpectomy, the pulp is removed to a level where adequate hemostasis can be achieved. Hemostasis is achieved by irrigating with 6% sodium hypochlorite (59) for up to 10 minutes. Care should be taken to avoid the application of pressure to the pulp cap.
Having achieved hemostasis, a layer of MTA should be placed and mixed according to the manufacturer’s recommendations over the exposed pulpal tissue. The thickness of the material should be approximately 2 mm. Once the MTA is in place, a small amount of flowable compomer (or an equivalent light-cured resin or glass ionomer liner) should be applied to cover the MTA material. The remainder of the cavity can then be etched, bonded, and restored (Fig. 1).

Conclusion

The major difficulty in treating permanent immature teeth is the ability to predictably diagnose the state of pulpal health and, therefore, the ability of predicting it to heal. The current tests available to the clinician make it difficult to accurately predict the degree of pulpal degeneration before commencing treatment. Therefore, the clinician’s ability to assess the health of the remaining pulpal tissue during the procedure is paramount. Currently, the best method appears to be the ability to control pulpal hemorrhage with NaOCl.

The current data available on the use of MTA in vital pulp therapy indicate that it is the optimum material and better than the traditionally used material Ca(OH)₂. It has a greater long-term sealing ability and stimulates a high quality and a great amount of reparative dentin. In clinical outcomes evaluation, it has demonstrated a high success rate. MTA is, thus, a good substitute for Ca(OH)₂ in vital pulp procedures.

References

Indirect Pulp Therapy and Stepwise Excavation

Lars Bjørndal, DDS, PhD

Abstract
Various treatment concepts have been suggested to solve the deep carious lesion dilemma. Recent systematic reviews are presented. Their conclusions are based on very few studies, and the main message is that optimal randomized clinical studies are lacking. Observational studies on indirect pulp treatment and stepwise excavation demonstrate that these treatments avoid pulp exposures, but it cannot be said which approach is best. A less invasive modified stepwise excavation approach is described, focusing on changing an active lesion into an arrested lesion even without performing an excavation close to the pulp. In Denmark and Sweden a randomized clinical multi-center trial is currently taking place, the Caries and Pulp (CAP) trial. This trial is investigating the effects of stepwise excavation over 2 visits versus 1 complete excavation of deep caries in permanent teeth. Guidelines for treatment are presented. (J Endod 2008;34:S29-S33)

Key Words
Caries, dentin, indirect pulp treatment, pulp, randomized clinical trial, stepwise excavation, tertiary dentin

Introducing Thoughts about Level of Evidence in Clinical Research
A demanding trend in clinical research is to perform a randomized clinical trial (RCT) to compare 2 interventions. Why is RCT so important, or in particular the randomization? The level of evidence is the short answer to that question. Expert opinion is allocated to the lowest level of evidence, with the next level being observational studies. At the top of the hierarchy is the systematic review of high-quality RCTs. A more extended answer deals with the largest problem in studies that are nonrandomized, which is that of confounding variables. Many factors cannot be controlled for if a simple comparison is made between 2 studies in which the same treatment has been provided. The distribution of prognostic factors might differ between the 2 studies. Are the 2 studies, in fact, treating the very same stage of diseases? With regard to caries, how deep are the lesions? Finally, we cannot exclude the psychological phenomenon that investigators tend to see what they want to see. The perceived effect might in reality differ between the 2 studies.

There is a great deal of difference between RCTs and observational studies, but this does not mean that the thousands of clinical studies that have been carried out with a non-RCT design do not indicate relevance, but they simply do not have the highest level of evidence.

The following is a list of factors that characterize a high-quality RCT:
1. the presence of well-defined inclusion and exclusion criteria;
2. prognostic factors are equally distributed between the 2 interventions that are going to be compared;
3. the number of treatments needed to show a difference between control and experimental groups is calculated;
4. adequate allocation sequences: for example, the randomization of patients to control or experimental groups is generated by a computer;
5. adequate allocation concealment: the randomization is carried out with a central independent unit;
6. follow-up examination is done by an investigator(s) who is blinded as to the patient’s group assignment;
7. ideally, the RCT should be carried out in a number of trial centers.

The Latest Systematic Reviews from the Cochrane Collaboration Regarding Caries Treatment and the Pulp
The Cochrane Collaboration carries out systematic reviews of high-quality clinical studies. The recent reviews of caries and pulp treatments all indicate the lack of RCTs (1, 2). The Cochrane Collaboration has found fewer than 10 studies that could be compared, and they are not all high-quality RCTs.

Within the concept of maintaining pulp vitality, treatment modalities that included indirect pulp treatment (IPT) showed no differences in symptoms at 12 months among studies using Life, Dycal, and Cavitec formulations of calcium hydroxide (2).

In relation to partial caries removal, the following points were addressed in the review (1):

1. Partial caries removal in symptomless primary or permanent teeth reduces the risk of pulpal exposure;
2. No pulpal symptoms were found;
3. Partial caries removal appeared preferable in deep lesions to reduce the risk of carious exposure of the pulp;
4. There is insufficient evidence to show whether it is necessary to re-enter and excavate further in the stepwise excavation technique, but studies that did not re-enter reported no adverse consequences.

Let us add some comments, which in the future might bring these conclusions further up the hierarchy of evidence. One problem has been the definition of the penetration depth of the deep caries lesion. This point has in many studies been defined as a lesion in which one would expect a pulpal exposure if all caries was removed. Among the 4 included studies on which the above conclusions are based, the lesions differed between deep lesions and those extending to half the thickness of the dentin. In 2 of the studies, a stepwise excavation approach was used with lesions defined as deep, whereas the other 2 studies did not re-enter the lesion. The problem in comparing these studies is confounding factors. One of the studies treated less progressed lesions, which might be important when trying to compare the 2 interventions.

We need high-quality RCTs to compare IPT and stepwise excavation. I will return to this later.

How Deep Is a “Deep” Caries Lesion?
The definition of deep caries lesions points toward the potential exposure of the pulp (3). When do clinicians expect that a potential pulpal exposure is close? In a practice-based observational study, general dentists were asked to judge the penetration depth of caries lesions that would pose a risk for pulpal exposure (4). The majority of dentists selected lesions that penetrated to within three fourths of the entire dentin thickness or more as evaluated on x-rays. This judgment was made in one case in which only half of the dentin was demineralized, indicating that this definition varies substantially among practitioners.

Let us adopt the same clinical concern for potential exposures as did the majority of these general practitioners. A deep caries lesion is present when the penetration depth is in the range of three fourths of the entire thickness of the dentin or more when evaluated on an x-ray.

The Biologic Dilemma
On the first day of this symposium, we discussed the understanding of caries, and that the treatment of deep caries lesions has been placed in what one could call “no mans land,” with different schools of opinions as classically given by Tomes (5) and Black (6). Another aspect is that we do not have any reliable or accurate clinical diagnostic device for monitoring the degree of pulpal inflammation. The case selection for a given treatment, whether or not we want to avoid an exposure of the pulp, is still based on indirect diagnostic procedures. We might try to divide a few clinical stages of vital pulp problems, depending on the results from our clinical as well as paraclinical diagnostic procedures, as described in detail by Reit et al. (7). The diagnostic data should be collected from the following 3 areas: (i) the patient’s description of subjective symptoms, (ii) pulp sensibility testing, and (iii) paraclinical examinations (radiographs for exclusion of apical pathosis).

Attempts to divide degrees of pulp pathology seem ambitious, because we do not always know in what direction the pulpal inflammation will turn. It has not been possible to devise an overall applied classification system on this issue. For some practitioners, the clinical diagnosis of the pulp is centered on subjective symptomatic factors, ie, symptomatic or nonsymptomatic pulpitis (8), whereas for others the use of reversible and irreversible pulpitis is applied (9). Within the latter diagnostic dichotomy, the treatments are guided toward either invasive pulp therapy or procedures aiming to maintain the pulp integrity. Thus, the words irreversible and reversible cannot solely be interpreted as the gold standard expression for the actual state of the pulp, but rather they represent our best clinical judgment.

The Dentist Must Handle the Biologic Dilemma!
The clinical use of the irreversible pulpitis diagnosis as well as symptomatic pulpitis is essentially the same; the tooth will be managed with an invasive pulp treatment (9). However, the deep carious lesion might also be a potential reversible pulpitis case, with confirmed pulp sensibility but with no objective signs of apical pathology or subjective symptoms before start of the treatment. Even though the absence of clinical symptoms is not a sign of absence of pulp pathology, this approach provides one more chance to maintain the pulp’s integrity, until the opposite is proved. An important point after treatment of such cases must be the maintenance of pulp sensibility, because the finding of “no clinical symptoms” could be the result of a silently developing pulp necrosis.

A Brief Historical Focus on Excavations Methods in Asymptomatic Deep Caries Lesions
Many pulps have probably been exposed through the years on the basis of the concept that deep caries lesions are always associated with inflammation, and diagnoses such as asymptomatic pulpitis or chronic pulpitis have been made. Various excavation methods have been proposed, such as IPT (10) and the two-stage excavation procedure or stepwise excavation (11). In recent articles and reviews the expression “partial excavation” (1) has emerged to refer to various treatment modalities, but in reality the term has not led to consensus, because it can mean anything from almost no excavation to excavation very close to the pulp. The differences between the 2 methods mentioned above are that the IPT procedure involves almost complete removal of the affected dentin, leaving a thin layer of demineralized dentin. Re-entry is not attempted. In contrast, the stepwise excavation technique involves re-entry at varying intervals. What did these early clinical articles prescribe in terms of clinical procedure?

One of the earliest articles describing a step-by-step approach is by Sowden (12). Carious tissue was removed, and a 1-mm layer of calcium hydroxide was placed followed by a temporary restoration. No final excavation was performed within the first visit. Re-entry and final excavation were then made after 2–3 weeks.

A more rigorous approach was addressed in the article by Magnusson and Sundell (11), who emphasized that a thin soft layer of dentin should remain on the pulpal wall. The authors did not describe in detail what was meant by a thin layer. They most likely excavated as close as possible to the pulp, leaving a thin layer of residual caries. Residual caries, as defined by Kerhove et al. (10), means that if you apply additional pressure to the dentin with the excavator, the pulp will be exposed. Magnusson and Sundell (11) placed a zinc oxide–eugenol cement temporary restoration and performed the final excavation after 4–6 weeks. This stepwise excavation method has been a very common and widespread approach within the Nordic countries. In 1962, Law and Lewis (13) accessed all areas of carious dentin and placed calcium hydroxide and an amalgam restoration. Re-entry was made after 6 months.

Eidelman et al. (14) provided details of the excavation procedures. It is stated that all undermining enamel is removed to gain more easy access to the carious dentin along the enamel-dentin junction. At the pulpal wall approximately 1 mm of carious dentin was left behind. The tooth was re-entered after 1 year, and the final excavation was performed.

For reasons discussed earlier, we cannot make detailed comparisons among these older studies, because each represents its own decade, and there is a great deal of variation among them. For example, in the study by Magnusson and Sundell (11), primary teeth were treated, and no follow-up examination was done after treatment was completed.
Note that it is also difficult to determine whether there are any differences between the classic IPT and the first excavation step as performed in the study by Magnusson and Sundell (11). Thus, the potential risk of creating pulpal exposures following either IPT or during the first step of stepwise excavation might very well be the same.

**Observational Data about Indirect Pulp Treatment**

In a retrospective study AL-Zayer et al. (15) found that IPT in primary posterior teeth is a successful technique and should be considered as an alternative pulp therapy. Recently, Gruythuysen et al. (16) also reported that the IPT technique produces clinical success. Concerning the more detailed treatment procedures, the Cochrane review indicated that variation in base materials did not produce any differences (2). Also, Marchi et al. (17) concluded that IPT in primary teeth arrests the progression of the underlying caries, regardless of the material used as a liner.

**Use the Knowledge from Caries Pathology to Design an Excavation Approach**

The optimal focus on avoiding a pulpal exposure and using caries pathology might be demonstrated by the concept of a less invasive or modified stepwise excavation (Fig. 1) (18, 19). The primary aim of the first excavation is to change the caries environment and not to remove as much carious dentin, eventually reaching the residual level close to the dentin-pulp interface. Microbiologic and clinical studies have shown that it is possible to decrease the number of bacteria and arrest the caries process during a treatment interval (19, 20). The active, soft, yellowish demineralized dentin becomes a darker, harder, and drier demineralized dentin, resembling a slowly progressing lesion. More detailed microbiologic observations also indicate that during a treatment interval the flora becomes a type associated with slow lesion progress in root caries (21). These findings have gained additional support (22). Whether the presence of such flora can remain “inactive” beneath a permanent restoration in a deep cavity needs further investigation.

This aspect of using our knowledge of caries pathology as an integrated part of caries removal is also reinforced in a new textbook chapter (23).

**Is A Two-step Excavation Necessary?**

As shown from a recent survey, 18% of respondents would partially remove caries in a deep lesion in which one would expect that complete caries removal would lead to pulpal exposure (24). I interpret this technique as the IPT with no re-entry. In the United States IPT

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**Figure 1.** Diagrams demonstrating the less invasive stepwise excavation procedure. A closed lesion environment before and after first excavation (a, b) followed by a calcium hydroxide–containing base material and a provisional restoration. During the treatment interval the retained demineralized dentin has clinically changed into signs of slow lesion progress, evidenced by a darker demineralized dentin (c, d). After final excavation (e) the permanent restoration is made (f). Red zones indicate plaque. Reprinted with permission from Blackwell Munksgaard from Bjørndal L. Dentin and pulp reactions to caries and operative treatment: biological variables affecting treatment outcome. Endodontic Topics 2002;2:10–23. (27)
has been carried out for years, whereas we in the Scandinavian countries traditionally have applied a stepwise excavation approach. It is difficult to state which treatment approach is better, because no high-quality RCTs have yet been performed to give us the answer.

The clinician’s intention is to avoid a pulpal exposure on the basis of the best possible indications. The main concern is that when excavating to a level close to the pulp, a number of pulpal complications might arise, as indicated within the various stepwise excavation approaches. Clinically, the changes in dentin appearance during the excavation provide the clinician with information regarding the changes in caries activity. This is also true in cases in which the changes in color of the carious dentin are not as clear. The final excavation is safer, because it is easier to remove the remaining dry carious dentin.

The final step of stepwise excavation is 2-fold: (1) to assess the tooth’s reaction and (2) to remove the slowly progressing lesion in slightly infected discolored demineralized dentin before carrying out the final restoration.

A Two-step Approach Might Be the First Way of Changing Clinical Habits

The vast majority of respondents to the aforementioned survey selected an invasive approach in relation to the deep caries case because they presumably did not believe in leaving carious dentin behind (24). If the operator leaves infected dentin, it might stimulate obliteration of the root canals, making future endodontic treatment more difficult. It is important to say that such a hypothesis is relevant, but it has not been proved. In reality, this would favor a second visit. Remember the second aim, which is to remove the slowly progressing caries in slightly infected discolored demineralized dentin before carrying out the final restoration.

However, it is not easy to change a clinical habit from one of removing all carious dentin to one of leaving caries permanently. One way to accomplish this would be to experience the strategy of “changing the local caries environment” by performing a 2-step procedure next time a deep caries lesion presents in your practice.

A High-quality RCT Concerning Deep Caries Treatment: The Caries and Pulp (CAP) Trial

The aim of the CAP trial has been to investigate the beneficial and harmful effects of stepwise excavation of symptomatic and asymptomatic permanent teeth during 2 visits versus complete excavation of deep caries in 1 visit. The CAP trial is being performed as a multi-center RCT, except for the less invasive first step. This requires the clinician to decide before reaching the pulp whether to perform a stepwise excavation approach before all carious dentin has been removed. Otherwise, the clinician will not promote local changes in the cariogenic environment.

It is Not Just a Matter of Selecting a Proper Clinical Treatment Concept

We do not yet have noninvasive tools for the measurement of the severity of pulpal inflammation. Thus, the discussion of reversible or irreversible development of pulpitis is controversial in relation to the actual state of the pulp. When treating the deep carious lesion, we are forced to make a choice on the basis of indirect diagnostic methods. Consequently, different schools of thought exist. Future high-quality RCTs might reduce this problem. The understanding of clinical treatment concepts also includes knowledge of its limitations. The control and prevention of further pulpal and periapical damage in relation to the restored tooth will, besides a sufficient restoration, include proper oral hygiene procedures for the removal of cariogenic biofilms, which tend to accumulate where the problem began—in the areas of the restored tooth surfaces. In addition, follow-up examinations are mandatory for the evaluation of pulp sensibility and the possible presence of apical pathosis (28).

Clinical Guidelines Based on an Observational Study and a High-quality RCT

Observational studies from dental practice environments have demonstrated the effectiveness of treating deep carious lesions by using a less invasive or modified stepwise excavation. Long-term recall (3.5–4.5 years) has demonstrated a high success rate (92%), indicating that the method can be carried out in clinical practice (26). The placement of high-quality temporary and final restorative materials must be stressed, because failures are most often associated with inadequate restorations (4). Therefore, a 2-step excavation procedure will add to the cost of the treatment. Because of the possibility of asymptomatic development of irreversible pulp degeneration over time, follow-up examinations are required with regard to pulp sensibility and apical conditions. Because readers are already familiar with the guidelines of the IPT, the following presents the stepwise excavation technique (27):

1. Deep lesion considered likely to result in pulp exposure if treated by a single and terminal excavation. Evaluated by x-ray, the dental lesion involves three fourths or more of the dentin thickness.
2. No history of pretreatment symptoms such as spontaneous pain and provoked pulpal pain. However, mild to moderate pain on thermal stimulation is accepted.
3. Positive pulp sensibility tested by an electric pulp tester, thermal stimulation, or test cavity.
4. Pretreatment radiographs that rule out apical pathosis.
5. Finish the peripheral excavation of the cavity followed by a central excavation removing the outermost necrotic and infected demineralized dentin in order that a provisional restoration can be properly placed.
6. Do not excavate as closely as possible during the first step, thereby reducing the risk of pulp exposure.
7. Select a provisional restorative material on the basis of the length of the treatment interval, ranging between 6 and 8 months.
8. The final excavation is often less invasive than expected, as a result of the altered dentinal changes gained during the treatment interval.

References

Indirect Pulp Capping and Primary Teeth: Is the Primary Tooth Pulpotomy Out of Date?

James A. Coll, DMD, MS

Abstract

Formocresol pulpotomy (FP) in the United States is most frequently used to treat asymptomatic caries near the pulp in primary teeth. Indirect pulp therapy (IPT) is also indicated and has a significantly higher long-term success. Pulpotomy is thought to be indicated for primary teeth with carious pulp exposures, but research shows the majority of such teeth are nonvital or questionable for treatment with vital pulp therapy. IPT has a significantly higher success in treating all primary first molars, but especially those with reversible pulpitis compared with FP. The purpose of this article was to review the dental literature and new research in vital pulp therapy to determine the following: (1) Is a pulpotomy indicated for a true carious pulp exposure? (2) Is there a diagnostic method to reliably identify teeth that are candidates for vital pulp therapy? (3) Is primary tooth pulpotomy out of date, and should indirect pulp therapy replace pulpotomy? (J Endod 2008;34:S34-S39)

Key Words
Indirect pulp therapy, pulp exposure, pulpotomy

The guidelines of the American Academy of Pediatric Dentistry (AAPD) on pulp therapy for primary and young permanent teeth state that a pulpotomy is a procedure in which the coronal pulp is amputated, and the remaining radicular pulp tissue is treated with a medicament or electrocautery to preserve the pulp’s health (1). The guidelines state the objective of a pulpotomy is to keep the remaining pulp healthy without adverse clinical signs or symptoms or radiographic evidence of internal or external root resorption. The AAPD guidelines further state that there is only one other choice for vital pulp therapy in primary teeth where caries approach the pulp. This choice is indirect pulp therapy (IPT), because the direct pulp cap in a primary tooth is contraindicated for carious exposures (1). IPT is a procedure in which the caries closest to the pulp is left in place and covered with a biocompatible material, and the tooth is restored to prevent microleakage. The objectives of treatment are the same as for a pulpotomy (1).

For deep caries in primary teeth, the indications for IPT and pulpotomy are identical for reversible pulpitis or a normal pulp when the pulp is judged to be vital from clinical and radiographic criteria (1). The difference occurs when the caries removal process results in a pulp exposure; a pulpotomy is then undertaken. IPT purposely avoids an exposure by leaving the deepest decay in place. IPT is clearly not indicated when the pulp is exposed by caries, but is pulpotomy indicated for a carious pulp exposure? For deep caries with possible radiographic exposures that are asymptomatic, which is the better choice of treatment, IPT or pulpotomy?

The purpose of this article was to review the dental literature and new research in vital pulp therapy to determine the following: (1) Is a pulpotomy indicated for a true carious pulp exposure? (2) Is there a diagnostic method to reliably identify teeth that are candidates for vital pulp therapy? (3) Is primary tooth pulpotomy out of date, and should IPT replace pulpotomy?

Is Pulpotomy Indicated for Carious Exposures?

A primary tooth pulpotomy should be performed on a tooth judged to have a vital pulp (1). After the coronal pulp is amputated, this leaves behind vital radicular pulp tissue that has the potential for healing and repair in 3 general ways, according to Rodd (2). First, the remaining radicular pulp can be rendered inert, such as by using formocresol. It fixes or denatures the vital pulp so it is no longer pulp tissue in addition to its bactericidal properties. Second, the radicular pulp might be preserved through minimal inflammatory insult by using a hemostatic agent such as ferric sulfate to form a clot barrier to preserve the deeper remaining pulp tissue. The third pulpotomy mechanism encourages the radicular pulp to heal and form a dentin bridge by using calcium hydroxide or mineral trioxide aggregate (MTA).

What is the histologic and clinical research that can help dentists determine which teeth with deep caries are vital and, thus, candidates for pulpotomy? Reeves and Stanley (3) found that as long as the advancing edge of the carious lesion was 1.1 mm from the pulp, no significant pathologic changes were evident in permanent teeth. Once the caries approached within 0.5 mm of the pulp and the reparative dentin was involved, then significant pathologic changes were noted. Shovelton (4) examined permanent teeth and showed that as caries approached 0.25–0.5 mm of the pulp, hyperemia and pulpitis were seen.

Regarding the effect of pulp exposures on the pulp’s capacity to repair, Lin and Langland (5) showed that when no pulp exposure occurred from caries, the pulp’s repair capacity was excellent. After a carious exposure, however, it was questionable...
and unpredictable. They also found that in teeth with a history of pain, the pulp chamber would have an area of necrosis often extending into the radicular pulp. Others have stated that the dentist risks displacing infected dentin chips into the pulp when performing total excavation of deep carious lesions, thus increasing the risk of pulpal inflammatory breakdown (6).

Stepwise caries removal in permanent teeth thought to have radiographic pulp exposures has been proposed as a method to minimize pulp exposures and preserve vitality (7, 8). Caries excavation is a 2-appointment procedure. Initially, the lesion’s periphery is made caries-free, while the center of the caries is partially removed to leave moist, soft dentin over the pulp. Then, calcium hydroxide and a temporary filling are placed for 6–12 months. The lesion is then re-entered, and all the caries is removed. Bjorndal et al. (7) found no pulp exposures on re-entry in 31 permanent teeth by using stepwise caries removal. Leskell et al. (8) tested stepwise caries removal versus conventional in 127 permanent teeth with a patient mean age of 10.2 years. After 8–24 months, stepwise removal resulted in approximately 18% pulp exposure versus 40% for conventional caries removal.

Many of these permanent tooth findings likely apply to primary teeth. Rodd (2) stated that carious primary and permanent teeth showed similar neural changes when mounting a pulpal defense to deep caries. Rodd found that primary and permanent teeth have similar vascularity, except in the midcoronal region, and showed a similar degree of vasodilatation and new vessel formation with caries progression.

Eidelman et al. (9) studied severely decayed primary incisors with no pulp pathology in nonrestorable teeth from 20- to 42-month-old children. After fixation, caries was removed with a slow-speed round bur. A sharp explorer was used to evaluate total caries removal and check for a pulp exposure. Teeth without pulp exposures and no total necrosis likely as a result of trauma were histologically diagnosed as treatable with vital pulp therapy in 23 of 26 cases (88%). By contrast, 16 of 24 (67%) of the incisors judged to be nontreatable (total necrosis) or questionable (chronic partial pulpitis) for treatment with vital pulp

Figure 1. Example of using glass ionomer caries control to diagnose reversible pulpitis or food impaction in a mandibular first primary molar with a history of pain to chewing sweets and solid foods for 2–3 weeks. (a) Preoperative view. (b) Preoperative radiograph. (c) View immediately after glass ionomer placement. (d) Two months after caries control. Pain stopped from day glass ionomer placed. No clinical or radiographic sign of irreversible pulpitis. (e) View of IPT with a glass ionomer base. (f) Tooth 16 months after treatment without signs of pain or irreversible pulpitis clinically or on the radiograph.
therapy had a carious pulp exposure, leaving only 33% that were unquestionably vital. Dentists might think they can obtain a 90% level of pulpotomy success in such a case. The simple mathematics of 33% (chance of finding a vital pulp) × 90% (chance of pulpotomy success), however, would equal a 30% chance of a cariously exposed tooth having a successful pulpotomy. From these histologic and clinical findings, the following conclusions can be drawn:

1. Primary tooth pulpotomy requires a vital radicular pulp, no matter what form or type of pulpotomy procedure is used (1, 2). Teeth with a carious pulp exposure have a low likelihood of being totally vital (9) and are, thus, poor candidates for vital pulpotomy.

2. Stepwise caries removal will result in fewer caries exposures than total caries removal performed in 1 visit (7, 8).

3. For teeth without carious pulp exposures, performing a pulpotomy likely increases the chance of displacing infected dentin chips into the pulp and impairing the pulp’s repair capacity (5, 6).

4. The pulp’s repair capacity is excellent when the carious lesion remains 1 mm or more away from the pulp (3).

Is There a Diagnostic Method to Identify Teeth with Deep Caries That Are Symptomless or Questionable, Yet Are Candidates for Vital Pulp Therapy?

Identifying those teeth with deep caries that are vital and treatable with vital pulp therapy leads to this article’s second purpose, which was to describe a new method to reliably diagnose these teeth. Initially placing an intermediate, therapeutic, temporary restoration by using a material such as Fuji IX (GC America Inc, Alsip, IL), Ketac Molar (3M ESPE, St Paul, MN), Voco Ionofil Molar AC (Voco GmbH, Cuxhaven, Germany), or a resin-modified glass ionomer. A matrix band does not have to be used, but the intermediate therapeutic temporary restoration needs to be removed to accomplish this result. Oliveira et al. (15) reported on 32 permanent teeth after minimal caries excavation and temporization for longer time periods. They concluded that total caries removal did not seem essential to stop caries progression.

Regarding the effect of glass ionomer on the subsequent vital pulp therapy, Vij et al. (11) reported that GICC temporization for 1–3 months increased success of the subsequent vital pulp therapy from 79% to 92%. Teeth temporized with zinc oxide–eugenol, however, had a success rate of 67%. They also reported a “drying out” effect of the moist techniques on re-entry after GICC similar to that reported by Bjornal et al. (7) after 6–7 months of stepwise caries removal.

Another recently completed study reported on GICC’s diagnostic success in deeply cavitated carious lesions (16). A group of primary molars had GICC after minimal caries excavation for a mean time of 3.5 months. The GICC intermediate therapeutic temporary restoration had to have remained intact without displacement for 1–4 months. Another group of primary molars had no GICC. Both groups had IPT or formocresol pulpotomy and were restored with an immediate steel crown the day of treatment and were followed for a mean time of more than 3 years. Diagnostic success was based on the vital pulp therapy success, or the tooth was successfully diagnosed with irreversible pulps after 1–3 months of GICC. The GICC group showed a significant increase (P < .001) in the subsequent vital pulp therapy success (98%) versus the non-GICC group’s vital pulp therapy success (75%). There was a subgroup of 18 teeth that presented with pain and/or a questionable diagnosis of their vitality. All received GICC initially for 1–4 months to diagnose the tooth’s vitality. The GICC produced the correct diagnosis for all the teeth in that 7 molars returned with signs of irreversible pulps and were extracted. For the other 11, however, the pain was diagnosed as reversible, and all were treated with vital pulp therapy successfully.

From these microbiologic and clinical studies, the following conclusions can be made on using glass ionomer caries control:

1. Treating primary teeth with deeply cavitated carious lesions after minimal excavation with glass ionomer caries control for 1–3 months initially before instituting pulp therapy causes the bacteria to significantly decrease within the lesion (13, 14). In vital, symptomless teeth with apparent radiographic exposures or near

<table>
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<td>Dean et al. 2002 (18)</td>
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<td>92</td>
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<td>Huth et al. 2005 (19)</td>
<td>1/5 formocresol</td>
<td>85</td>
<td>24</td>
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<td>Formocresol</td>
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<td>Formocresol</td>
<td>70</td>
<td>40</td>
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<tr>
<td>Smith et al. 2000 (21)</td>
<td>Ferric sulfate</td>
<td>74–80</td>
<td>19</td>
</tr>
<tr>
<td>Casas et al. 2004 (22)</td>
<td>Ferric sulfate</td>
<td>67</td>
<td>36</td>
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<tr>
<td>Eidelman et al. 2001 (23)</td>
<td>MTA</td>
<td>100</td>
<td>13</td>
</tr>
<tr>
<td>Jabbarifar et al. 2004 (24)</td>
<td>MTA</td>
<td>94</td>
<td>12</td>
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<tr>
<td>Holan et al. 2005 (25)</td>
<td>MTA</td>
<td>91</td>
<td>38</td>
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NOTE: Internal root resorption was not always considered failure. Peng et al. (20) calculated MTA success at 93%, counting internal resorption.
exposures, treating them with caries control will likely stop caries progression (15).

2. GICC for 1–3 months changes the character of the dentin so that it is drier and harder, and the affected dentin likely remineralizes similar to dentin after stepwise excavation (7, 11, 14).

3. Using GICC as a diagnostic tool for 1–3 months in teeth with symptomless radiographic exposures or ones with pain and questionable vitality will diagnose those that can be treated successfully with vital pulp therapy 98% of the time (16).

Is the Primary Tooth Pulpotomy out of Date for Treatment of Deep Caries and Should IPT Replace Pulpotomy?

Knowing the pulpal diagnosis of primary teeth with deep caries by using GICC should greatly improve the chance of any vital pulp therapy. This leads to the article’s third purpose: Is IPT or pulpotomy the best choice for vital pulp therapy for deeply cavitated carious lesions?

Most pulpotomy success decreases over time from 90% or more initially (6–12 months) to 70% or less after 3 years or more (11, 20, 22) (Table 1, Figure 2). The MTA pulpotomy appears to have a higher long-term success rate (>90%) than other pulpotomy types (23–25). Yet these reports generally are of shorter duration (only one >24 months (25)) and have small sample sizes (<38 teeth) from which to draw strong conclusions. Most of these MTA pulpotomy studies were performed on teeth with symptomless radiographic exposures, and most had immediate steel crowns placed after pulpotomy. The immediate crown should have minimized microleakage and increased pulpotomy success compared with a large amalgam (27), which had been used in other pulpotomy studies (17, 27). A recent meta-analysis of MTA versus formocresol pulpotomy studies suggested that MTA was superior to formocresol as a result of its lower failure rate (26).

IPT usually shows success rates of 90% or greater no matter the technique, medicament, or time periods (Table 2, Figure 2). IPT’s long-term success (3–4 years) surpasses all other pulpotomy studies, with the possible exception of the 1 long-term MTA study (25). There have been various medicaments used for IPT, from calcium hydroxide (28–30), glass ionomer (11, 17), to none (30), all of which did not significantly change IPT’s success rates, as shown in Table 2. Even using dental students of vastly different abilities and likely different techniques, as reported by Al-Zayer et al. (29), did not significantly decrease IPT’s success below 95%. The type of final, immediate restoration did not alter IPT’s success when steel crowns were compared with composite fillings and glass ionomers (11, 30). Even when no medicament was placed for IPT and the composite filling was bonded to the remaining decay and decay-free dentin, Falster et al. (30) reported success greater than 90%.

How are pulpotomy and IPT being taught and practiced in the United States? Dunston and Coll (31) in 2005 surveyed 48 of the 56 pediatric program directors in the U.S. dental schools and 689 of the board-certified pediatric dentists. They found that 76% of the dental schools taught either diluted or full-strength formocresol pulpotomy, whereas the other 24% taught ferric sulfate. Of the 689 pediatric dentists, 81% used diluted or full-strength formocresol, 18% ferric sulfate, and 1% some other type of pulpotomy (electrocautery, MTA, etc.). Formocresol remains the overwhelming choice for pulpotomy, signifying the toxic concerns regarding formocresol do not seem to be a concern for most schools or practicing dentists. The International Agency for Research on Cancer stated in a 2004 press release that formaldehyde causes nasopharyngeal cancer (32). Milnes (33) in 2006 disputed the cancer concern by stating that the amount of formocresol in a pulpotomy was likely such a small amount that formocresol pulpotomy was a low-exposure condition. Zazar et al. (34) found that when studying the white blood cells after formocresol pulpotomy in 20 children, 1 child showed a 6-fold increase in white blood cell chromosomal abnormalities. From a statistical standpoint, they believed formocresol was not mutagenic, but further studies were needed to verify this.

The 2005 survey (31) also had a clinical scenario question regarding deep caries removal in a primary second molar in a 5-year-old. Seventy percent of the program directors and more than 80% of the pediatric dentists reported that a pulpotomy was the treatment of choice over IPT. It appears that IPT is not emphasized in U.S. dental schools as a method to treat deep asymptomatic caries, and most dentists practice the way they were taught. In addition, most pediatric dentists believe it is best to enter the pulp and do a formocresol pulpotomy, even though long-term formocresol pulpotomy success is significantly lower than IPT (11, 17, 20, 30). Other factors need to be considered when choosing IPT or pulpotomy for deep caries in primary teeth. Vij et al. (11) studied IPT and pulpotomy success treating molars with reversible pulpitis pain. They

| Table 2. IPT Studies Show Success Rates of 90% or Greater over Time with Differing Techniques and Medicaments |
|-----------------|-----------------|---------------|-----------|
| IPT medicaments | Success (%)     | Time (mo)     | Sample (N) |
| Nirschl and Avery 1983 (28) | Calcium hydroxide | 94 | 6 | 33 |
| Al-Zayer et al. 2003 (29) | Calcium hydroxide | 95 | 14 (median) | 187 |
| Falster et al.* 2002 (30) | Glass ionomer | 90t | 24 | 44 |
| Vij et al. 2004 (11) | Glass ionomer | 94 | 40 | 108 |
| Farooq et al. 2000 (17) | Glass ionomer | 93 | 50 | 55 |

*aAdhesive resin alone without a liner or calcium hydroxide liner and adhesive resin.
†Combined success of both groups.
reported that in 20 first primary molars with such pain, IPT success was 85%, which was significantly better ($P = .04$) than the 53% in 19 first primary molars treated with formocresol pulpotomy. They also found that there was significantly ($P = .04$) low success (61%) when first primary molars were treated with formocresol pulpotomy compared with the 92% success with IPT in these molars. When the data of Holan et al. (27) were tested with $\chi^2$ analysis, it also showed a significantly lowered success for formocresol pulpotomy in primary first molars.

Another concern in the choice of using IPT or pulpotomy is the early exfoliation of pulpotomized teeth. More than 35% of formocresol pulpotomies exfoliate significantly earlier (>6 months) than nonpulpotomized teeth, whereas IPT-treated teeth exfoliate normally (11, 17). In addition, pulpotomies cost more than 2.3 times more than IPT, on the basis of published dental insurance reimbursement for the 2 procedures (35, 36). In the United States, however, most dental insurers do not cover IPT for primary teeth, which might result in less utilization. For a tooth with deep caries 1 mm away from the pulp, IPT or pulpotomy can be performed. The pulpotomy could be more painful, because profound anesthesia is always needed for a pulpotomy, whereas the IPT requires no pulpal entry and, therefore, is potentially less painful.

When performing IPT and leaving residual decayed dentin, what are the concerns of leaving this decay after a 1-visit IPT? Aponte et al. (37) reported performing indirect pulp capping with calcium hydroxide followed by amalgam restorations in 30 primary molars. After 6–46 months (mean, 29 months), the amalgam and calcium hydroxide were removed, and the carious dentin that had been left behind cultured. In 28 of 30 teeth (93%), the residual carious dentin was sterile. Oliveira et al. (15) studied 32 permanent teeth judged by radiographs to have a pulp exposure. From digitized radiographs taken 6–7 months after partial caries removal followed by temporary fillings, there was mineralized improvement in the carious dentin over time. Finally, the 10-year prospective study by Mertz-Fairhurst et al. (38) conclusively showed that in 85 teeth after obvious occlusal caries was successfully sealed from microleakage, after 10 years in vivo, there was no progress of the caries in permanent teeth.

The following conclusions on choosing IPT or pulpotomy can be drawn from these studies:

1. Formocresol and ferric sulfate pulpotomy have a significantly lower long-term success for treatment of deep caries compared with IPT (11, 17, 20, 30). Most U.S. pediatric dentists currently choose to use formocresol pulpotomy over IPT (31).
2. IPT has been shown to have a significantly higher success rate for teeth with reversible pulps compared with formocresol pulpotomy (11).
3. IPT shows higher long-term success rates than any pulpotomy other than possibly MTA (Tables 1 and 2). MTA pulpotomy has not been shown to be effective in treating teeth with reversible pulps.
4. IPT is less expensive, has fewer potential side effects, and does not exhibit early exfoliation as pulpotomy does (11, 17, 35, 36).

Conclusions

Controversy persists as to the best way to perform vital pulp therapy, and additional research is needed to see whether MTA pulpotomy performs as well as IPT. From the present review of the literature and research, the following conclusions can be made:

1. Do not treat carious exposures in primary teeth with pulpotomy or direct pulp caps. Consider pulpectomy or extraction because of the high chance of irreversible pulpitis and failure of vital pulp therapy after a carious pulp exposure.
2. For deep caries approaching the pulp, the choice of IPT or pulpotomy is up to the treating dentist.
3. Use glass ionomer caries control for deep cavitated lesions to diagnose the status of the pulp with or without history of pain to attain the highest success for vital pulp therapy. Stay out of the pulp by using IPT for a higher long-term chance of success compared with formocresol and ferric sulfate pulpotomy.
4. IPT has been shown to have a lower cost, higher success long-term, better exfoliation pattern, and better success treating reversible pulps than pulpotomy.

References


Is Formocresol Obsolete? A Fresh Look at the Evidence Concerning Safety Issues

Alan R. Milnes, DDS, PhD

Abstract
Concern has been expressed about the safety of formocresol use in pediatric dentistry. Formaldehyde, a primary component in formocresol, is a hazardous substance and is considered a probable human carcinogen by the International Agency for Research on Cancer, Health Canada, the Agency for Toxic Substances and Disease Registry in the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency. Humans inhale and ingest formaldehyde daily, however, and produce formaldehyde during cellular metabolism. The human body is physiologically equipped to handle formaldehyde through multiple conversion pathways. The resultant single carbon atom released during metabolism is deposited in the "1-carbon pool," which, in turn, is used for the biosynthesis of macromolecules including DNA and RNA. Reevaluation of earlier research that examined potential health risks associated with formaldehyde exposure has shown that this research was based on flawed assumptions, which resulted in erroneous conclusions. The purpose of this review was to examine more recent research about formaldehyde metabolism, pharmacokinetics, and carcinogenicity. These results indicated that formaldehyde is probably not a potent human carcinogen under low exposure conditions. Extrapolation of these research results to pediatric dentistry suggests an inconsequential risk associated with formaldehyde use in pediatric pulp therapy. (J Endod 2008;34;540-546)

Key Words
Carcinogens, chemistry, formaldehyde, formocresol, pulpotomy, toxicity

The suggestion has been made recently that formocresol use in pediatric dentistry is unwarranted because of safety concerns, and consequently, formocresol use in pediatric pulp therapy is obsolete. As a result, numerous investigations for alternatives to formocresol, some of which have shown efficacy equivalent to formocresol, have been completed. There can be no doubt that a reparative, biologic approach to pediatric pulp therapy is preferable to the absolutist, devitalization approach of formocresol pulpotomy or primary tooth pulpectomy, and research into alternatives is not only welcome but absolutely essential. This commentary will demonstrate, through a thorough review of the relevant literature, however, that the “evidence” for banning this medicament because of safety concerns has been either misinterpreted or replaced by better science.

Ubiquity of Formaldehyde

Daily formaldehyde exposure is a fact of life. Formaldehyde is found in the air we breathe, the water we drink, and the food we eat (1). The World Health Organization (WHO) (2) has estimated that daily consumption of formaldehyde approximates 1.5–14 mg/day (mean, 7.8 mg/day), although daily intake from food is difficult to evaluate. Owen et al (3) estimated that North Americans eating a typical North American diet ingest 11 mg/day. There are other numerous sources of formaldehyde exposure, which are summarized in Table 1. In unpopulated areas, outdoor air contains approximately 0.2 parts per billion (ppb) formaldehyde. In populated areas with truck and automobile traffic, however, air concentrations range between 10 and 20 ppb. There have also been instances of high concentrations of formaldehyde in the air inside homes. In 2002–2003, Health Canada (5) found formaldehyde levels of 2–81 ppb in homes in Prince Edward Island and Ottawa, Canada. Second-hand cigarette smoke might contain up to 0.4 ppm of formaldehyde (6). The National Institute for Occupational Safety and Health (7) in the United States has stated that formaldehyde is immediately dangerous to health and life at concentrations of 20 parts per million (ppm) and higher.

Assuming a contribution of 9.4 mg/day from food, 1 mg/day from inhalation, and 0.15 mg/day from water, an adult takes in 10.55 mg of formaldehyde per day (1). At present, there are no estimates of pediatric exposure, although it is likely that children are exposed to lower amounts because of lesser food intake.

The estimated formaldehyde dose associated with 1 pulpotomy procedure, assuming a 1:5 dilution of formocresol placed on a no. 4 cotton pellet that has been squeezed dry, is approximately 0.02–0.10 mg.

Given the environmental ubiquity of formaldehyde and the recognized daily intake by humans, it is highly unlikely that the elimination of the microgram quantities of formaldehyde associated with formocresol pulpotomy will have a significant impact on a child’s daily exposure.

Pharmacokinetics of Formaldehyde

Humans produce endogenous formaldehyde as part of normal cellular metabolism. Hileman (8) has shown that endogenous levels of metabolically produced formaldehyde range from approximately 3–12 ng/g tissue. Amino acid metabolism, oxidative demethylation, and purine and pyrimidine metabolism have all been shown to produce formaldehyde (9). Importantly however, human cells are physiologically equipped to manage this exposure through multiple pathways for oxidation of formaldehyde to formate and incorporation into biologic macromolecules via tetrahydrofolate-depen-
A concentration of 1.9 ppm formaldehyde (a concentration that is considered virtually identical. In rhesus monkeys, Casanova et al (18) reported
they showed that the blood concentrations of the 2 groups were
concentrations in Fischer 344 rats exposed to a very high formaldehyde
concentration (14.4 ppm for 2 hours) and in unexposed controls.

Immediately after exposure by inhalation. Heck et al (16) used gas chro-
nating and chromatography, mass spectrometry to measure blood formaldehyde concentrations in Fischer 344 rats exposed to a very high formaldehyde concentration (14.4 ppm for 2 hours) and in unexposed controls. They showed that the blood concentrations of the 2 groups were virtually identical. In rhesus monkeys, Casanova et al (18) reported that the formaldehyde concentrations in the blood after prolonged exposure to a high concentration of inhaled formaldehyde (6 ppm for 6 hours per day, 5 days per week for 4 weeks) had no significant effect on the formaldehyde concentration in blood relative to pre-exposure levels.

Human experiments have also provided compelling evidence that inhaled formaldehyde has virtually no impact on blood concentrations of formaldehyde. Heck et al (16) exposed 6 human volunteers for 40 minutes to 1.9 ppm formaldehyde (a concentration that is considered slightly irritating to the nasal and conjunctival membranes), but the concentrations before exposure were not significantly different from those measured immediately after exposure. The average formaldehyde concentration in the blood of rats, monkeys, and humans was 2.70 ± 0.15 μg/g (mean ± standard error) or approximately 0.1 mmol/L. In dermal studies, formaldehyde was absorbed less readily by monkeys than by rats or guinea pigs (19).

The half-life of formaldehyde molecules in monkey blood is about 1.5 minutes after intravenous infusion (20). A concurrent rise in formic acid levels occurs, indicating formaldehyde’s metabolism (20). In rats, formaldehyde’s metabolism after administration via the pulp chamber is also rapid, and the majority of conversion reportedly occurs within 2 hours after administration (21). Exogenous formaldehyde has a biologic half-life of 1–1.5 minutes (22) and is quickly cleared from human plasma. In dogs, the conversion of formate to carbon dioxide and water results in a biologic half-life for formalte of about 90 minutes (13). In humans, the liver converts formaldehyde to carbon dioxide at a rate of 22 mg/min (3, 23, 24).

In mice and rats, the metabolites of formaldehyde are eliminated in urine, feces, and expired air, with the relative proportion depending on the route of administration (25, 26). Higher urine concentrations of formic acid were found in 3 of 6 workers occupationally exposed to unspasked concentrations of formaldehyde in air (30.0, 50.5, and 173.0 mg/L, respectively) than in unexposed workers (17 mg/L) (27).

Formaldehyde also acts covalently with amino and sulphydryl groups in target tissues and with DNA, forming unstable hydroxymethyl protein adducts (DNA-protein cross-links [DPX]) and, in a second slower reaction involving recruitment of a second amino group, methylene cross-links (28, 29). In rat and monkey tissues, however, metabolism of formaldehyde and its elimination by pathways other than DPX formation overwhelmingly predominate (30).

Results from dental pulp studies involving rats, dogs, and monkeys showed that formaldehyde labeled with radioactive carbon (14C) was apparently distributed among the muscle, liver, kidney, heart, spleen, and lungs. The number of radiolabeled chemical detected, however, were very small (1% of the total administered dose) (21, 31–33). Myers et al (32) and Pashley et al (33) concluded that [14C]formaldehyde is absorbed systemically from pulpotomy sites. These studies have been widely quoted as evidence that formaldehyde is distributed to distant sites. The investigators in these studies, however, did not determine whether the labeling of tissues occurred by metabolic incorporation of the [14C] moiety of the labeled formaldehyde into macromolecules after the labeled formaldehyde molecule had been metabolized or by covalent binding (formation of protein adducts) by radiolabeled formaldehyde molecules.

In an unrelated study, Casanova-Schmitz et al (34) sampled the venous blood of rats after injecting either [14C]formaldehyde or [14C]formate into the tail vein. They verified that labeling of proteins and target tissues was due to metabolic incorporation of the radiolabeled metabolite of formaldehyde, 14C, and not covalent binding. The profiles of radioactivity in the blood after these injections were similar, regardless of whether [14C]formaldehyde or [14C]formate was the source of 14C. These results excluded the possibility that the labeling of macromolecules is due to formation of protein adducts by formaldehyde, because only [14C]formaldehyde is capable of forming protein adducts, whereas both [14C]formaldehyde and [14C]formate are precursors for macromolecular synthesis by the 1-carbon pool. Hence, it appears that the claims of systemic distribution in dental publications have been overstated and are, in fact, false.
Pharmacokinetics of Cresol

The second active ingredient in formocresol, cresol, has received little attention in the debate about formocresol safety or in investigations of formocresol efficacy. Cresol has poor solubility, and because of this, it has been assumed that it does not enter systemic circulation (35). Cresol is highly lipophilic, however, and has been shown to completely destroy cellular integrity, which presumably would allow for deeper tissue fixation by the formaldehyde component of formocresol (35, 36). No data exist regarding cresol metabolism or elimination in humans or other mammals, and there is virtually no information about environmental sources of cresol to which humans might be exposed. Last, no human studies have been published that have examined plasma concentration after exposure to cresol.

A recent clinical study in Colorado has reexamined the issue of systemic distribution of formocresol (37). Blood samples were drawn preoperatively, intraoperatively, and postoperatively from 30 children, each of whom received comprehensive dental treatment including at least 1 pulpotomy under general anesthesia. Blood samples were examined for formaldehyde and cresol content using gas chromatography and mass spectrometry detection. Neither formaldehyde nor cresol was detected in any blood sample. Benzyl alcohol, however, a by-product of tricresol oxidation (38), was detected in microgram quantities in a dose-response fashion in blood samples collected after placement of formocresol-containing pellets.

Benzyl alcohol is present as a bacteriostatic preservative in many multidose intravenous drugs and solutions (39). It also occurs naturally in many plants, including raspberries and tea, and is an essential ingredient in many essential oils (39). Benzyl alcohol is oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. It has no carcinogenic or mutagenic potential, and the allowable daily intake, as established by WHO, is 5 mg/kg (39, 40).

Mutagenicity, Genotoxicity, and Cytotoxicity

Exposure of cells to formaldehyde leads to the formation of DPX (41). The most common types of DNA damage induced by formaldehyde are clastogenic lesions, including sister chromatid exchanges (SCEs), micronuclei and chromosomal aberrations (42), and deletions (43). Levels of formaldehyde-induced DPX are considered to represent a good molecular dosimeter of formaldehyde exposure at sites of contact and are frequently used for risk modeling and prediction of formaldehyde carcinogenicity for different species (44–46). DPX have been shown to occur only at the site of initial contact in the nasal mucosa of rats and in the upper respiratory tract of monkeys exposed to formaldehyde (45, 46).

It has also been proposed that formaldehyde could induce the development of DPX at distant sites, but no convincing evidence has been obtained from in vivo experimental studies. The outcomes of these studies have included the following:

1. lack of detectable protein adducts or DPX in the bone marrow of normal rats exposed to formaldehyde labeled with radioactive hydrogen ($^3$H) or carbon ($^{14}$C) at concentrations as high as 15 ppm (34);
2. lack of detectable protein adducts or DPX in the bone marrow of glutathione-depleted (metabolically inhibited) rats exposed to $[^1H]$formaldehyde and $[^14C]$formaldehyde at concentrations as high as 10 ppm (22, 47);
3. lack of detectable DPX in the bone marrow of rhesus monkeys exposed to $[^14C]$formaldehyde at concentrations as high as 6 ppm (46); and
4. failure of formaldehyde to induce chromosomal aberrations in the bone marrow of rats exposed to airborne concentrations as high as 15 ppm (41) or of mice receiving intraperitoneal injections of formaldehyde at doses as high as 25 mg/kg (48).

Casas et al (49) have been critical of formocresol use in pediatric dentistry. They have regularly cited 2 studies as evidence of the genotoxic and mutagenic effects of formaldehyde (50, 51). Those published articles, in fact, represent the same study, however, with the first article reporting interim results of nasal tumor development in rodents (50) and the second (3 years later) (51) reporting the final results for the same study. Although Kerns et al (51) discussed the formaldehyde’s mutagenic potential in their animal model, they did not report results pertaining to mutagenicity, as was stated by Casas et al.

More recent research by Heck and Casanova (52) has revealed that the development of DPX in the nasal tissues of rats and the upper respiratory tracts of primates is associated only with exposure to high doses of formaldehyde. At ambient concentrations consistent with environmental exposures, DPX are unlikely to occur. Furthermore, Quievryn and Zhitkovitch (53) have shown that DPX do not persist in tissues for more than a few hours and undergo either spontaneous hydrolysis or active repair by proteolytic degradation of cross-linked proteins. This calls into question the role of DPX in formaldehyde-induced carcinogenesis.

Cytogenetic studies (54) of lymphocytes from rodents after formaldehyde inhalation with exposures ranging from 0.5–15 ppm for 6 hours per day for 5 days failed to detect either chromosomal aberrations or SCEs at any of the formaldehyde concentrations. The authors attributed their negative results to formaldehyde’s pharmacokinetics.

In vitro experiments with a Chinese hamster cell line (45) found that DPX and SCE, as a result of formaldehyde exposure, were associated with cytotoxicity, not mutation (55). In addition, no mutagenesis occurred in cultured human lymphocytes below a formaldehyde threshold of 5 μg/mL in the culture medium (56).

Dental studies have not supported the contention that formaldehyde, as used in dentistry, is mutagenic. Zarzar et al (57) performedformocresol pulpotomy on 20 children by using Buckley’s original formula (19% formaldehyde and 35% cresol in a solution of 15% glycerin and water). Peripheral venous samples were collected from each child immediately before and 24 hours after the pulpotomy, and lymphocytes were collected from each blood sample for cell culture and cytogenetic analysis. No statistically significant differences were found between the 2 groups in terms of chromosomal aberrations, chromatid breaks, or chromatid gaps. Also, Zarzar et al concluded that formocresol is not mutagenic. The authors observed chromosomal aberrations in 1 (5%) of the 20 patients but were unable to determine whether formocresol or other variables accounted for this finding.

Ribeiro et al (58, 59) reported 2 studies that assessed the mutagenic potential of formocresol as well as several other chemicals commonly used in dentistry. With a mouse lymphoma cell line, cultured human fibroblasts, and a series of formocresol dilutions similar to clinical doses, these authors found that formocresol did not produce detectable DNA damage and should not be considered genotoxic.

Laboratory investigations of root canal sealers containing formaldehyde, which are used in endodontic procedures, have demonstrated cytotoxicity (60). For several reasons, however, these investigations are not comparable to formocresol pulpot studies. A larger quantity of formaldehyde is released from root canal sealers than during pediatric formocresol pulpotomy because of the large quantity of sealer used. Moreover, contact of formocresol with vital pulp tissue during pulpotomy is restricted to only a few minutes, whereas root canal sealer remains in the root canal and forms part of the final restoration, with the potential for further release of formaldehyde.
In summary, DPX’s development has been demonstrated only after prolonged exposure to formaldehyde at specific contact sites such as the nasopharynx. Hence, the argument that the microgram quantities of formaldehyde applied to pediatric pulp tissue for a few minutes will induce distant-site genotoxicity is not supported by the available evidence.

Carcinogenicity

It is indisputable that cancer develops in experimental animals after inhalation of air with high concentrations of formaldehyde. These cancers occur as a result of long-term, direct contact between the formaldehyde and susceptible tissues. The resultant toxic effects at these initial contact sites include ulceration, hyperplasia, and squamous metaplasia and “are considered to contribute to the subsequent development of cancer” (61). These high-dose responses, however, are unlikely to occur at sites distant from the point of initial formaldehyde contact (such as the bone marrow). This is because, according to a large body of undisputed evidence, formaldehyde is not delivered to these distal sites. Those who have argued against the continued use of formocresol in pediatric dentistry on the basis that “formaldehyde causes cancer” have failed to recognize this very important distinction.

Those opposed to formocresol use in pediatric dentistry have cited the work of Swenberg et al (50) and Kerns et al (51) to support their argument about carcinogenicity. These 2 studies are, in fact, the same study, with Swenberg et al reporting interim results after 18 months and Kerns et al reporting final results for the same study after 30 months. This group of researchers showed that nasal squamous cell carcinoma developed in Fischer 344 rats exposed to formaldehyde gas at concentrations of 6 ppm and higher for 6 hours per day, 5 days per week for 24 months. The formaldehyde concentrations that resulted in cancer, however, were more than 1000 times the typical human environmental exposure and 8 times the U.S. occupational exposure limit (0.75 ppm) (62). Therefore, they are not representative of human experience. Moreover, the experimental conditions that resulted in nasal cancers in rodents in no way resemble the conditions associated with a 5-minute exposure to microgram quantities of formaldehyde, as experienced by a child undergoing formocresol pulpotomy.

Until recently, formaldehyde was classified as a “probable human carcinogen” by Health Canada (63, 64), the International Agency for Research on Cancer (IARC) (65, 66), the Agency for Toxic Substances and Disease Registry (ATSDR) (62, 67) in the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency (USEPA) (68). Although they lacked sufficient evidence to demonstrate the development of cancer in exposed humans, these regulators (Health Canada, ATSDR, and USEPA) and advisory agency (IARC) predicted the cancer risk posed by low-dose exposure by extrapolating from the laboratory animal data previously cited.

Various researchers, however, have recognized that significant anatomic and physiologic differences between humans and other animal models have confounded extrapolation of animal data to humans (29, 69–71). Researchers at the Chemical Industry Institute for Toxicology Centers for Health Research (CIIT) (70, 71) developed dynamic 3-dimensional airflow models that accurately depicted both airflow and regional deposition of formaldehyde on mucosal surfaces of rodents, monkeys, and humans. The improved understanding garnered from this research allowed the researchers to improve the accuracy of computer-generated predictions of the uptake and absorption of formaldehyde in each animal model. The CIIT researchers also developed a biologically motivated computational model, on the basis of combined rodent and primate data from the computer-generated nasal cavity airflow models, cell proliferation data, and DPX data. This model allowed them to mathematically evaluate the cancer risks associated with formaldehyde inhalation (71).

Finally, with input from the USEPA, Health Canada, and peer reviewers, the CIIT researchers published a thorough evaluation of potential cancer risk from formaldehyde, integrating toxicologic, mechanistic, and dosimetric data (55). These new experimental data, derived from sophisticated mathematical models, replaced the inaccurate default assumptions that had been used by the regulatory authorities.

On the basis of these investigations (55, 71), CIIT suggested that cancer risk is negligible until formaldehyde exposure reaches the levels associated with cytotoxicity (in the range of 600–1000 ppm). The resulting estimates of cancer risk are many orders of magnitude lower than the 1987 and 1991 USEPA estimates (55, 71). The model developed by CIIT overcomes problems associated with the standard risk assessment methods cited by the USEPA and the IARC.

A 2004 IARC press release (66) reclassified formaldehyde from a “probable” to a “known” human carcinogen and has been cited as evidence that formaldehyde should be eliminated from pediatric dentistry (49). Some clarification of the press release is required, however, or readers will be left with the impression that the IARC classification is definitive and binding. The IARC classification is not an assessment of risk but merely an attempt to answer the question of whether, under any circumstances, a substance could produce cancer in humans. Clearly, for formaldehyde the answer to this question is yes. In fact, the author requested clarification from the head of the IARC Monographs Programme regarding a threshold dosage for carcinogenicity of formaldehyde. Dr Vincent Cogliano responded “the evaluations at IARC Monograph meetings concern only whether an agent can increase the risk of cancer at some dose. We do not undertake dose-response analyses, consequently, we did not discuss a possible threshold” (personal communication, August 5, 2005).

Thus, the IARC classification serves as a hazard identification, the first step in a multilevel risk assessment process. More importantly, the IARC reclassification was based primarily on the results of a single National Cancer Institute (NCI) study (44) among workers in formaldehyde industries. That study included many workers at several plants, but only a small number of people working at a single plant were found to have a rare form of cancer. Clearly, confounding variables might have affected the results. Recognizing these uncertainties, the NCI has agreed to update the study.

Health Canada has stated that it considers the CIIT dose-response model (71) “to provide the most defensible estimates of cancer risk, on the basis that it encompasses more of the available biological data, thereby offering considerable improvement over default” (72). The Organization for Economic Cooperation and Development has stated, on the basis of the CIIT research models, that “taking into account the extensive information on its mode of action, formaldehyde is not likely to be a potent carcinogen to humans under low exposure conditions” (73). Pediatric pulp therapy with formocresol as recommended would be considered a “low exposure condition.” The USEPA Office of Air Quality Planning and Standards has stated, “The dose response value in the EPA Integrated Risk Information System (for formaldehyde) is based on a 1987 study and no longer represents the best available science in the peer-reviewed literature. We believe that the CIIT modeling effort represents the best available application of mechanistic and dosimetric science on the dose-response for portal of entry cancers due to formaldehyde exposure” (74).

The possibility that inhaled or ingested formaldehyde might induce cancers at sites distant from the respiratory or gastrointestinal tracts has been investigated in numerous long-term toxicity studies performed in rodents (61). Leukemia was not observed in any of 7 long-term inhalation bioassays in rodents, and it was not observed in 3 drinking water...
studies in which rodents were exposed to doses as high as 1.9–5 g/L. Leukemia was observed in a single drinking water study (75), in which Wistar rats were exposed to doses as high as 1.5 g/L. That study, however, is regarded by the Cancer Assessment Committee of the U.S. Food and Drug Administration (76) as questionable, and the data are unreliable because of a lack of critical detail and questionable histopathologic conclusions.

Evidence from epidemiologic investigations of industrial workers with exposure to formaldehyde provides weak and inconsistent evidence that such exposure is associated with leukemia. Importantly, the researchers in each instance failed to use recognized epidemiologic criteria to evaluate the hypothesis that formaldehyde exposure leads to cancer. The results of 2 large American studies, one from the NCI (44) and the other from the National Institute of Occupational Safety and Health (77), did not support a strong causal relation between formaldehyde exposure and leukemia. The strength of association—the extent to which a collective body of data indicates a positive association between a disease, in this case leukemia, and a suspected causative agent, in this case formaldehyde—was weak (standardized mortality ratio, 0.86). Moreover, a study of British chemical workers, sponsored by the Medical Research Council Environmental Epidemiology Unit in the United Kingdom (78) and involving the highest chronic formaldehyde exposures and highest peak exposures of all 3 investigations, showed no causal relationship between formaldehyde and leukemia.

Therefore, evidence from both experimental investigations and epidemiologic research does not support the hypothesis that inhaled or ingested formaldehyde might induce distant-site toxicity. The abundant negative evidence mentioned previously is undisputed and strongly suggests that there is no delivery of inhaled, ingested, or topically applied formaldehyde to distant sites. The facts are that formaldehyde occurs naturally throughout the body, there are multiple pathways for detoxification, and only microgram quantities of formaldehyde are applied to pulp tissues during pulpotomy procedures for mere minutes. Considering these facts, the negative findings provide convincing evidence that exposure of children to the formaldehyde component of formocresol during a pulpotomy is insignificant and inconsequential.

**Immune Sensitization**

Despite evidence from dogs that formocresol can produce antigenic activity in dental pulp tissue (79), Rolling and Thulin (80) found no increase in either immune response or allergic reactions in 128 children who had undergone formocresol pulpotomy.

More recent evidence supports the work of Rolling and Thulin (80). A Canadian study (81) of urea formaldehyde foam insulation from products in the homes of asthmatic subjects found that long-term exposure had no effect on immunologic parameters. Doi et al (82) found that the prevalence of immunoglobulin E sensitization to formaldehyde was very low among Japanese children, regardless of whether they had asthma; furthermore, they found no clinical relevance of formaldehyde-specific immunoglobulin E. Hence, the suggestion that formocresol “sensitizes” children has not been supported.

**Where Do We Go From Here?**

On the basis of the evidence presented in this review, it is highly unlikely that formocresol, judiciously used, is genotoxic or immunotoxic or poses a cancer risk to children who undergo one or more formocresol pulpotomy procedures. Definitive data to support this hypothesis are lacking, however, and such evidence is needed before definitive conclusions can be reached.

In keeping with accepted therapeutic principles, pediatric dentists who wish to continue to use formocresol should apply the lowest dose possible for the shortest time possible to obtain the desired effect. To that end, a 1:5 dilution of Buckley’s formocresol is recommended. The dilution should be performed in the local pharmacy to ensure accuracy. Recent research (83) has indicated that a minority of pediatric dentists use diluted formocresol because it is not available commercially, so perhaps it is time for the formocresol product manufacturers to develop and market a 1:5 dilution of this medicament to replace the “full-strength” formulations now available, especially given that the effects of the 2 formulations are equivalent (83).

No data exist to verify the actual amount of formocresol delivered to the pulp during the performance of a formocresol pulpotomy. Results from a yet to be published study in Colorado of systemic formocresol distribution in children receiving at least 1 pulpotomy while under general anesthesia determined that the mean dose of formocresol within a cotton pellet was 0.013 mg (37). This study used full-strength formocresol. Presumably, if a 1:5 dilution had been used, the mean milligram dose per pellet would have been 0.0026 mg. The actual dose that interacts with the pulp tissue is probably much smaller in both cases, however, because most of the formocresol will remain in the cotton pellet. Determining the actual doses delivered to the pulp represents an important area for further investigation. In addition, efforts are needed to disseminate information about dose delivered to both the profession and the public.

Evidence continues to accumulate that supports the successful application of indirect pulp treatment (IPT) procedures to primary teeth as well as the use of mineral trioxide aggregate (MTA) in pulpotomy procedures. A Cochrane systematic review by Nadin et al (84) in 2003 suggested that the paucity of randomized controlled trials in pediatric pulp therapy made it virtually impossible to make recommendations regarding pulpotomy procedures. Nevertheless, numerous randomized controlled trials examining both IPT and MTA have since been published. These investigations have shown that both IPT and MTA have clinical and radiographic results that are equivalent to or better than those produced by formocresol over time. The reader is referred to articles in this issue by Fuks and Coll for more detail about these promising alternatives.

It is important to put this discussion into a broader perspective. Antibiotics are used in dentistry at least as often as formocresol, and each year numerous children and adults are injured or die as a result of allergic or anaphylactic reactions to antibiotics (85), yet there has been no call for the elimination of antibiotics from dental practice. In fact, there is an acceptance that an allergic reaction is both a possibility and a risk in the treatment of dental infection. Peroxides for dental bleaching, bonding agents, and solvents used in adhesive dentistry all demonstrate cytotoxicity in vitro (86), yet they form an important part of every dentist’s restorative armamentarium. These chemicals are used in pediatric dentistry without warnings to parents and patients of the associated risks. Diagnostic radiation is an indispensable component of every dental office, yet irrefutable evidence (87) exists showing that radiation exposure can induce the development of cancers. Singling out one chemical such as formocresol for elimination from practice protocols in the face of a complete lack of human experimental data identifying a clear risk is intellectual tomfoolery.

On the basis of the evidence presented in this review, the risk of cancer, mutagenesis, or immune sensitization associated with the proper use of formocresol in pediatric pulp therapy can be considered inconsequential. Until a superior alternative is developed or there is definitive evidence substantiating a cancer risk, there is no reason to discontinue its use. When used judiciously, formocresol is a safe medicament.
Conclusions

Evidence presented in this review of the literature indicates that formocresol, when used judiciously, is unlikely to be genotoxic, immunotoxic, or carcinogenic in children when used in pulpotomy procedures. Until a biologic and reparative alternative has been identified that is clearly and reproducibly superior to formocresol, there are no scientific or toxicologic reasons to abandon formocresol in pediatric dentistry.

References


"New Age" Pulp Therapy: Personal Thoughts on a Hot Debate

Paula Jane Waterhouse, BDS, PhD

Abstract
This article outlines the counterpoint delivered in the debate “Is Formocresol Obsolete?” It addresses the opinion supporting the need to move away from formaldehyde-containing preparations in the dental care of children. It is suggested that such a move should be made not just because of concerns relating to the possible toxicity of formaldehyde but to reflect a more contemporary, biologic approach to pulp therapy in the primary dentition. (J Endod 2008;34:S47-S50)

Key Words
Formocresol, primary teeth, pulp therapy, pulpotomy

The debate over the use of formocresol solution and other formaldehyde-containing preparations in children’s dentistry continues. This is welcomed and should be regarded as a positive activity that will benefit ultimately those for whom we provide dental care. Discussion at meetings and within peer-reviewed and non–peer-reviewed publications has stimulated both specialist pediatric dentists and general dentists, not only on both sides of the Atlantic but worldwide, to consider their stance over this issue. Should we, as providers of healthcare in the 21st century, continue to use formaldehyde-containing medicaments in endodontic therapy?

This counterpoint will provide my personal thoughts on an undoubtedly controversial topic. These thoughts will be presented within the following sections:

- History: Where were we?
- A perspective from the United Kingdom (UK) on formocresol preparations
- Recent advances in primary tooth pulp biology
- Formocresol: Saint or sinner?
- Treatment
- Evidence-based practice
- The current UK guidelines.

History: Where Were We?

Debate centered on clinical technique is not a product of modern medicine. The varying treatments for the tooth pulp during the last 3 centuries illustrate this clearly. During the 1700s and early 1800s, metal foils were used to cap exposed pulp tissue (1), which would one use, gold or lead? Would you also prefer to cauterize the exposed tissue with a red-hot iron wire before placing the foil?

From the mid-1800s to the early 1900s, the use of medicaments in pulp therapies emerged and involved wide-ranging substances such as asbestos fibers, cork, beeswax, pulverized glass, calcium compounds, and others based on eugenol. Interestingly, even at a relatively early time in medical and surgical knowledge, it is documented that there was great debate between those who believed a pulp was capable of healing and those who did not (2).

During this period of innovation and discovery, the first recorded use of a formaldehyde-containing medicament was published. In 1874, Nitzel applied a tricresol-formalin tanning agent to 8000 exposed pulps (3). The technique appeared to be unpopular until Buckley’s method of treating putrecescent pulps was published in 1904, suggesting the use of equal parts of tricresol and formalin (an aqueous solution of formaldehyde gas equivalent to 38% w/w formaldehyde).

In 1908, the use of a mummifying paste with a preparation including solid formaldehyde was advocated (4). One year later, the International Dental Congress was devoted to the pulp and its treatment, and it was here that Boennecken (5) suggested his preparation of 40% formalin, thymol, and cocaine to be superior to Buckley’s solution in pulp amputation procedures.

By the late 1920s, there was disagreement between clinicians from Europe and the United States of America (USA) on treatment criteria and medicaments. In general, clinicians from Europe favored Gysi’s Triopaste with paraformaldehyde, and in the USA, pulp amputation was followed by application of Buckley’s formocresol solution (1).

In the middle of the last century there were many debates on the merits of different medicaments, and several variations of formocresol existed. The defining time for pulpotomy for the extensively carious primary tooth was the work published during a period of 25 years by Sweet (6, 7). During this time, multiple applications of Buckley’s formocresol were reduced to 2, and an additional application of formocresolized zinc...
oxide—eugenol cement was suggested. Since then, the technique for a single visit, 5-minute application formocresol pulpotomy was developed by using an as effective but weaker strength solution (8, 9). It was reported that the formocresol addition to zinc oxide—eugenol cement could be omitted (10).

It has been suggested that these later developments were driven by the impetus from concerns regarding the safety of formocresol (1).

The UK Perspective on Formocresol Preparations

In the UK, Buckley’s formocresol solution (38% w/w formaldehyde) and other formocresol preparations are not available for purchase on the general market. It is classed as a medicament, but it does not have a medicine license. It is prepared from its raw constituents in hospital-based pharmacy departments. In the late 1990s and early this century fewer and fewer hospital pharmacists were willing to prepare Buckley’s formocresol solution, even in its diluted form.

Compounding this problem, there appears to have been confusion within pharmacy services when preparing the medicament in its dilute form (1). In particular, which formulation should be used to produce a 1:5 dilution? This is reinforced by the Extra Pharmacopoeia stating that “…there is often confusion about the terminology and strength of formaldehyde” (1).

Buckley’s original formula appears to have contained 50% of a 38% solution of formaldehyde (equivalent to 19% formaldehyde). In Newcastle, since 1979 the following formulation has been used: formaldehyde solution BP (formalin), 19 mL; tricresol, 35 mL; glycerol, 15 mL; and water to 100 mL. This contains 19% of a 38% solution of formaldehyde (equivalent to 7% formaldehyde) and is then diluted to 1:5; thus the final product contains 1/13 the concentration of formaldehyde (gas). This is inarguably a small amount of formaldehyde.

The apparent confusion over its formulation might make comparison of studies problematic. Further uncertainty related to shelf life was raised. “Laboratories making up these solutions have not only a certain reticence in handling these relatively toxic materials, but also have difficulty in determining a shelf-life for the product” (1).

Full-strength Buckley’s formocresol solution is considered to have a shelf life of approximately 2 months if stored in brown glass bottles, but in its diluted form it is considered unstable and should be diluted just before use, which is impractical. Despite this, the use of pharmacy-diluted Buckley’s formocresol was effective, even under strict criteria for success (11). I believe that in the UK the move away from Buckley’s formocresol has, in part, been driven by increasing difficulties in obtaining the medicament and the increasing reticence of pharmacy staff to prepare the formulation (1, 12).

Recent Advances in Primary Tooth Biology

Dental pulp is a richly innervated tissue, and recent research has evaluated neuropeptide-containing nerve fibers. Nerves that express substance P have provided insight into pulp nerve function. Studies have shown that within a tooth the nerve fibers are predominantly nociceptive. These have an obvious pain receptive role, but they also play a primary role in immunoregulation and healing (13). Both the permanent and primary dentitions show similar increases in innervation density with caries progression, and Substance P is increased in painful caries cases.

In addition to this, during my own undergraduate days, despite few published data, I was taught that in response to caries, primary tooth pulps present a more pronounced and widespread inflammatory reaction compared with permanent teeth and might have been instrumental in continuing with the amputation procedures (14). This response is refuted by more recent immunohistochemical work that demonstrates equality between dentitions for the degree of vasodilation and angiogenesis in relation to caries insult, with responses predominantly in the region of the pulp horns. Although primary teeth contain more immune cells in both intact and carious states, they appear to localize in a manner similar to permanent teeth (12).

It appears that the primary tooth pulp has good potential for tissue repair and healing. In light of these contemporary findings, we as a collective professional body should be re-evaluating our approaches to pulp therapy in the primary dentition as our colleagues within adult restorative dentistry have already begun to do. We should be directing our research energies toward compiling a sound evidence base for therapies that favor pulp regeneration.

Formocresol: Saint or Sinner?

Despite formocresol’s undoubted clinical record of success and its position as the gold standard medicament in both vital and nonvital pulp therapy techniques in the primary dentition, in a recent British survey of 184 specialists in pediatric dentistry, 54% expressed concern over the safety of formocresol (15).

As clinicians, we all know from our own experience and from the reported literature that a pulpotomy performed with a 5-minute application of a 20% dilution of Buckley’s formocresol has a good prognosis, irrespective of whether the radicular pulp is viable. By virtue of the formaldehyde and cresol moieties, the solution has tissue fixative and antimicrobial properties and will fix and devitalize an irreversibly inflamed radicular pulp.

I agree with other pediatric dentists in that the overall amount of formaldehyde in a working solution is small, but whether that amount might cause problems should be explored further.

How many pulpotomies with formocresol would a child receive in 1 visit? How many pulpotomies with formocresol might a pediatric dentist undertake during the course of 1 day?

According to data sheets and a large base of published evidence for animal and human studies, formaldehyde, a volatile organic compound, is toxic and corrosive, particularly local to the point of contact. Fewer findings appear to be available for cresol, but it too is a known irritant and corrosive substance in its own right (16).

The UK’s Health and Safety Executive (HSE) presently rates exposure limits for formaldehyde for both long-term and short-term periods in the workplace to be 2 ppm or 2.5 mg per cubic meter. There appear to be no data published related to the possible levels of formaldehyde vapor and indeed cresol vapor in the dental working environment. The amount of vapor exposure (ppm) to a child undergoing a formocresol pulpotomy is unknown, and the degree and potential effect of accumulative formaldehyde exposure to dental professionals are unknown.

In the UK in 2005, the HSE’s Working Group on Action to Control Chemicals (WATCH) published findings from an Advisory Committee on Toxic Substances (ACTS) related to the carcinogenicity of formaldehyde (17). In Annex 2 of the report the toxicologic profile of formaldehyde is discussed, and in Annex 3 the carcinogenicity of formaldehyde is presented by a summary of the human epidemiologic data mainly relied on by the International Agency for Research into Cancer (IARC) Working Group in reaching its conclusion relating to formaldehyde exposure and cancer (18).

Formaldehyde is a known and accepted direct-acting irritant. But what happens once it has contacted a tissue? This has been investigated mainly in rats (which are obligate nasal breathers). Formaldehyde will pass into tissues such as mucous membranes rapidly, but uptake into skin is poor. Once within tissues, formaldehyde will react directly with proteins and nucleic acids. To put this into the context of formocresol, tricresol is said to decrease the solubility and diffusion properties of formaldehyde, thus reducing movement out of the root canal (19). However, tricresol has been shown to increase the permeability of cell
Table 1. Overview of Some Alternatives to Formocresol for Vital Pulp Therapy

<table>
<thead>
<tr>
<th>Material</th>
<th>Clinical Success %</th>
<th>Human Clinical Studies</th>
<th>Tested Against Formocresol</th>
<th>Effect (Animal Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPT</td>
<td>94% during period of mean 3.4 y (34)</td>
<td>Yes</td>
<td>Yes</td>
<td>Preservation and remineralization</td>
</tr>
<tr>
<td>Ferric sulphate</td>
<td>92% 4 y (35)</td>
<td>Yes</td>
<td>Yes</td>
<td>Preservation</td>
</tr>
<tr>
<td>MTA</td>
<td>100% 1 y (gray), 84.2% 1 y (white) (36)</td>
<td>Yes</td>
<td>Yes</td>
<td>Preservation</td>
</tr>
<tr>
<td>Calcium hydroxide</td>
<td>77.1% at 22.5 mo (11)</td>
<td>Yes</td>
<td>Yes</td>
<td>Preservation and remineralization</td>
</tr>
<tr>
<td>Lasers</td>
<td>100% 90 days (37)</td>
<td>Yes</td>
<td>Yes</td>
<td>Preservation</td>
</tr>
</tbody>
</table>

IPT, Indirect Pulp Therapy; MTA, Mineral Trioxide Aggregate; y, years; mo, months.
sively decayed primary tooth showed a paucity of acceptable related clinical research but did draw conclusions, despite including only 3 prospective randomized controlled trials (40). From the review it was demonstrated that formocresol, ferric sulfate, electrosurgical pulpotomy, and zinc oxide–eugenol pulpotomy all performed equally well. A recent meta-analysis of formocresol versus ferric sulfate found ferric sulfate to be as effective as formocresol (41).

The Current UK Guidelines

The British Society of Paediatric Dentistry has produced a range of clinical guidelines. The update reflects a shift in treatment modalities away from formocresol, discussing IPT, vital pulpotomy, desensitizing pulpotomy, and pulpectomy (12). However, a 1:5 dilution of Buckley’s formocresol solution remains listed as a medicament within the guidelines. This is an acknowledgment that the debate is far from over.

Summary

In light of the findings presented, I would recommend that pediatric dentists should be engaged in further good quality research and debate relating to vital and nonvital pulp therapy for the primary dentition. This should include studies to increase our awareness of the possible formaldehyde and cresol vapor exposure in the clinical environment. In some instances, however, there might be difficulties obtaining ethical approval for such work in certain countries.

At the beginning of this 21st century, we have greater understanding of the pulp biology, pathophysiology, and its powers of healing; we should reflect this in our approach to clinical management and aim to preserve what pulp we can. This in itself might lead to a natural reduction in the use of formocresol and herald a new age of pulp therapy.

Acknowledgments

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References

Regeneration Potential of the Young Permanent Tooth: What Does the Future Hold?

Kenneth M. Hargreaves, DDS, PbD,* Todd Geisler, DDS,* Michael Henry, DDS, PbD,* and Yan Wang, DDS, PbD†

Abstract
During the last 10–15 years, there has been a tremendous increase in our clinical “tools” (ie, materials, instruments, and medications) and knowledge from the trauma and tissue engineering fields that can be applied to regeneration of a functional pulp-dentin complex. In addition, recent case reports indicate that biologically based endodontic therapies can result in continued root development, increased dentinal wall thickness, and apical closure when treating cases of necrotic immature permanent teeth. The purpose of this review was to summarize these findings and illustrate a path forward for the development and evaluation of regenerative endodontic therapies. (J Endod 2008;34: 551-556)

Key Words
Endodontics, pulp biology, regeneration, revascularization, tissue engineering

T
reatment of the young permanent tooth with a necrotic root canal system and an incompletely developed root is fraught with difficulty. Not only is the root canal system often difficult to fully debride, but the thin dentinal walls increase the risk of a subsequent fracture. Historically, acceptable endodontic results have been achieved through aplication procedures with use of long-term calcium hydroxide. Concerns have been raised, however, that long-term calcium hydroxide therapy might alter the mechanical properties of dentin. Recent treatment strategies include 1-step creation of an artificial apical barrier by using mineral trioxide aggregate (MTA) with or without an apical matrix followed by compaction of obturating material and placement of a coronal restoration. MTA has been shown to produce good sealing effects under these conditions (1, 2). In addition, bonded composite resins have been reported to increase fracture resistance under some (3, 4) but not all experimental conditions (5). Unfortunately, even after treatment, these teeth have an elevated risk for fracture (6).

An alternative approach is to provide treatment under conditions where continued dentin formation is promoted. Several reports document that under conditions where at least some pulp tissue appears vital, a pulp cap treatment permits continued dentin formation, described as either continued root development (maturogenesis) or apical closure (apexogenesis) (7). Although these findings and an emphasis for continued research on vital pulp therapy are important (8), in many clinical cases the dental pulp has already undergone tissue necrosis before specialist consultation. Moreover, conventional endodontic therapy is not expected to result in continued dentin formation in these circumstances. Thus, there is continued need to develop biologically based treatment regimens that offer the potential for continued hard tissue formation of the young permanent tooth with a necrotic root canal system and an incompletely developed root.

Regenerative Endodontic Procedures
Several groups recently have published preclinical research or case reports that offer a biologically based alternative to conventional endodontic treatment of these complex clinical cases. In general, these studies have evolved from the trauma literature, where the following precepts have been established:

1. Revascularization occurs most predictably in teeth with open apices (9–12).
2. Instrumentation with NaOCl irrigation is not sufficient to reliably create the conditions necessary for revascularization of the infected necrotic tooth (13).
3. Placement of Ca(OH)2 in root canal systems prevents revascularization coronal to the location of the Ca(OH)2 (14).
4. The use of the “3 mix-MP” triple antibiotic paste, developed by Hoshino and colleagues and consisting of ciprofloxacin, metronidazole, and minocycline, is effective for disinfection of the infected necrotic tooth, setting the conditions for subsequent revascularization (15–19).

This triple antibiotic mixture has high efficacy. In a recent preclinical study on dogs, the intracanal delivery of a 20 mg/mL solution of these 3 antibiotics via a Lentulo spiral resulted in a greater than 99% reduction in mean colony-forming unit (CFU) levels, with approximately 75% of the root canal systems having no cultivable microorganisms present (19). Taken together, these studies provide a strong foundation level of knowledge from the trauma literature that permits subsequent research to focus on developing clinical methods for regeneration of a functional pulp-dentin complex.
Although the trauma literature has used the term revascularization to describe this treatment’s outcome, the goal from an endodontic perspective is to regenerate a pulpdentin complex that restores functional properties of this tissue, fosters continued root development for immature teeth, and prevents or resolves apical periodontitis. Thus, using the term revascularization for regenerative endodontic procedures has been questioned (20). Therefore, this review will focus on the concept of regenerating a functional pulpdentin complex and will restrict the use of the term revascularization to trauma studies.

It should be appreciated that research on regeneration of a pulpdentin complex has a long history. For example, during the last 30–50 years, Nygaard-Østby and others have reported a series of preclinical studies and case studies on patients attempting to regenerate pulp-like tissue in teeth with either vital or nonvital diagnoses (21–24). Connective tissue was demonstrated to grow as much as several millimeters into the apical portion of the root canal system in teeth with necrotic pulpal diagnoses (23). The results were variable, however, and histologic analysis failed to reveal regeneration of a functional pulpdentin complex. This lack of outcome is not surprising, however, given the level of materials, instruments, and medications and the knowledge base available at the time. Instead, current research in regenerative endodontics uses greatly improved materials, instruments, and medications and applies many principles from the fields of trauma research and tissue engineering (25–28).

In part on the basis of this expanding base of tools and knowledge, several recent case reports have been published describing regenerative endodontic procedures applied to cases of necrotic immature permanent teeth. Key features of these published cases (20, 29–32) are summarized in Table 1.

There are several common factors observed in these cases. First, although structurally weak, it is important to realize that the immature permanent tooth in general has a very wide apical opening that likely is conducive to tissue ingrowth. Second, these patients are young (8–13 years old), and several (33–37), but not all (38), studies suggest that younger ages have greater healing capacity or stem cell regenerative potential. Third, none of the cases used instrumentation of the root canal walls, whereas all of the studies used NaOCl as an irrigant. Fourth, both Ca(OH)_2 paste and combinations of multiple antibiotics have been used in these patients. Outcome differences between these 2 medications might reveal an important aspect of regenerative methods, because many of the reported cases treated with Ca(OH)_2 display intracanal calcifications that appear to impede the continued thickening of the dentinal walls of these immature teeth (20). In addition, other investigators (30) have suggested that the use of Ca(OH)_2 might kill any remaining pulpal cells, including stem or progenitor cells known to be present in dental pulp tissue (39–41), or possibly disrupt the apical papilla (30) and its resident stem cells (42, 43), which is critical for continued root development. Fifth, the formation of a blood clot might serve as a protein scaffold, permitting 3-dimensional ingrowth of tissue. Sixth, nearly all of these studies report continued thickening of the dentinal walls and subsequent apical closure. It should be appreciated, however, that the radiographic finding of continued dentinal wall thickness does not address the cellular nature of this calcified material.

Largely on the basis of preclinical studies, it is possible that the radiographic presentation of increased dentinal wall thickness might be due to ingrowth of cementum, bone, or a dentin-like material (23, 24, 44–48). This diversity in cellular response is not surprising, given that human dental pulp cells can develop odontogenic/osteogenic, chondrogenic, or adipogenic phenotypes, depending on their exposure to different cocktails of growth factors and morphogens (49, 50). One advantage of case reports is that they are based on outcomes observed in actual patients and therefore might have great value in stimulating the development of subsequent treatment methods; indeed, the discovery of fluoride emerged from the keen observations of a practicing clinician. We now recognize, however, the critical importance of subjecting these initial findings to prospective randomized clinical trials to generate objective measures of treatment efficacy and the potential liability for adverse events.

Thus, these and other case reports (51) should be viewed as generating a strong impetus for developing future prospective clinical trials. Taken together, these recent case studies support the hypothesis that the immature necrotic permanent tooth might be particularly responsive to biologically based endodontic therapies. Not only do these treatments provide an important alternative in a clinical situation with an otherwise poor prognosis, but equally important, these cases might serve as an important clinical model to evaluate the application of tissue engineering concepts to the regeneration of a functional pulpdentin complex.

**Application of Tissue Engineering Concepts to Regenerative Endodontics**

The field of tissue engineering has literally exploded during the last decade, and extensive reviews on dental applications are available for the interested reader (25, 26, 52–57). Here we briefly review 3 major components of tissue engineering from the concept of developing regenerative endodontic treatment regimens. Although basic research has applied nearly all of the tools of molecular biology for engineering of dental tissues, including transfections and knockout animals, we will adopt a different perspective. What concepts of tissue engineering are most likely to be available to clinicians when treating their patients with regenerative endodontic techniques? We have used this rather practical perspective to shape our review of this field and to suggest a path forward for developing and evaluating regenerative endodontics.

The first component of tissue engineering is a cell source. Odontoblasts are of mesenchymal origin, and under appropriate conditions, cells from dental pulp, the apical papilla, and possibly other tissues can form odontoblast-like cells (49, 50, 56, 58–61). Controversies exist among several of these studies, because measuring only 1 or 2 characteristics of a cell might not be sufficient to conclusively determine whether the resulting cell is a true odontoblast. Indeed, even among odontoblasts, the phenotype varies in cells located in the apical versus coronal dentin. Recent molecular studies have identified many of the genes selectively expressed in odontoblasts (62, 63), however, and this is likely to aid future studies characterizing the conditions necessary for mesenchymal cells of multiple origins to differentiate into the odontoblast phenotype. To date, the precise cell source(s) supporting the continued root development of the cases described in Table 1 are unknown. It is possible that: residual pulp cells might have remained vital in some of the cases, cells from the apical papilla underwent proliferation, or bleeding-induced angiogenesis might have recruited stem/progenitor cells from apical tissues including the apical papilla. The clinical challenge will be to find a reliable cell source capable of differentiating into odontoblasts, convenient for harvesting, and autogenous to avoid tissue rejection or introduction of foreign pathogens (25). Moreover, a delivery method must be developed that permits controlled application of a known amount of cells into the apical region of the root canal system. Clearly, these are critical areas for future research.

The second component of tissue engineering is a physical scaffold. Tissues are 3-dimensional structures, and an appropriate scaffold is needed to promote cell growth and differentiation. It is known that extracellular matrix molecules control the differentiation of stem cells (64, 65), and an appropriate scaffold might selectively bind and localize cells (66), contain growth factors (67), and undergo biodegradation.
<table>
<thead>
<tr>
<th>Tooth no.</th>
<th>Patient age (y)</th>
<th>Patient sex</th>
<th>Preoperative pulpal diagnosis</th>
<th>Preoperative periradicular diagnosis</th>
<th>Treatment&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Outcome</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>13</td>
<td>Female</td>
<td>Necrosis</td>
<td>Chronic apical abscess</td>
<td>5 weekly visits, no instrumentation, irrigation with 5% NaOCl and 3% H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;. Tooth left open between first and second appointments to permit drainage. Interappointment medicament: metronidazole and ciprofloxacin. 6 weeks later: Broach probed vital tissue in canal. Applied Ca(OH)&lt;sub&gt;2&lt;/sub&gt; paste, glass ionomer cement, bonded composite resin. Sixth appointment: Vital tissue observed 5 mm apical to canal orifice. 15 months: Positive response to electrical pulp test. 30 months: Apical closure with thickening of dentinal walls.</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>29</td>
<td>11</td>
<td>Male</td>
<td>Necrosis</td>
<td>Chronic apical abscess</td>
<td>First appointment: Rubber dam and access. No instrumentation. Deep irrigation with 10 mL 5.25% NaOCl and 0.12% chlorhexidine. Interappointment medicament: metronidazole, minocycline, and ciprofloxacin (Lentulo spiral). Cavit. 1 month: Irrigate 20 mL 5.35% NaOCl. Bleeding initiated with endo explorer. Stopped bleeding 3 mm from cementoenamel junction. MTA, wet pellet, Cavit. 2 weeks later: Composite restoration. 26 days: Vital tissue present 15 mm into canal system. 6–24 months: Gradual apical closure with thickening of dentinal walls. Positive response to pulp cold test.</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>29</td>
<td>10</td>
<td>Male</td>
<td>Necrosis</td>
<td>Acute periradicular abscess</td>
<td>First appointment: Rubber dam and access. No instrumentation. Irrigate with 2.5% NaOCl. Interappointment medicament: Ca(OH)&lt;sub&gt;2&lt;/sub&gt; paste. Caviton/IRM. 2 weeks later: Repeat. 3 months: Replace Ca(OH)&lt;sub&gt;2&lt;/sub&gt;. 11 months: Remove IRM and replace with amalgam. 3 months: Found hard tissue at Ca(OH)&lt;sub&gt;2&lt;/sub&gt; site. Asymptomatic. 11 months: Thickening of dentinal walls. 35 months: Continued thickening of dentinal walls and apical closure.</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>Female</td>
<td>(Partial) pulpal necrosis</td>
<td>Chronic periradicular abscess</td>
<td>First appointment: Rubber dam and access. No instrumentation. Formocresol pulpotomy. 9 days: Rubber dam and access. No instrumentation. Irritate with 2.5% NaOCl. Interappointment medicament: Ca(OH)&lt;sub&gt;2&lt;/sub&gt; paste. 1 month: Replace Ca(OH)&lt;sub&gt;2&lt;/sub&gt;. 2 months later and every 2–3 months for 11 months: Replace Ca(OH)&lt;sub&gt;2&lt;/sub&gt;. 1 month: Found hard tissue at mid-root. 11–54 months: Gradual apical closure, thickening dentinal walls in apical half of root canal system.</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>Female</td>
<td>(Partial) pulpal necrosis</td>
<td>Chronic periradicular periodontitis</td>
<td>First appointment: Rubber dam and access. No instrumentation. Formocresol pulpotomy. 9 days: Rubber dam and access. No instrumentation. Irritate with 2.5% NaOCl. Interappointment medicament: Ca(OH)&lt;sub&gt;2&lt;/sub&gt; paste. 1 month: Replace Ca(OH)&lt;sub&gt;2&lt;/sub&gt;. 2 months later and every 2–3 months for 11 months: Replace Ca(OH)&lt;sub&gt;2&lt;/sub&gt;. 1 month: Found hard tissue at mid-root. 11–54 months: Gradual apical closure, thickening dentinal walls in apical half of root canal system.</td>
<td></td>
<td>20</td>
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<tr>
<td>Tooth no.</td>
<td>Patient age (y)</td>
<td>Patient sex</td>
<td>Preoperative pulpal diagnosis</td>
<td>Preoperative periradicular diagnosis</td>
<td>Treatment 1</td>
<td>Outcome</td>
<td>Reference no.</td>
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<tr>
<td>29</td>
<td>9</td>
<td>Male</td>
<td>Necrosis</td>
<td>Chronic periradicular periodontitis</td>
<td>● Tooth left open for drainage at an emergency clinic. Rubber dam and access. No instrumentation. Irrigate 40 mL 2.5% NaOCl. Interappointment medicament: Ca(OH)₂ paste. ● 2 weeks and 5 weeks: Repeat. ● 5 months: Repeat. ● 36 months: Restore with amalgam to calcified bridge.</td>
<td>5 weeks: Hard tissue found at mid-root. 5–60 months: Gradual development of root length, thickening of dentinal walls, apical closure.</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>Male</td>
<td>Necrosis</td>
<td>Chronic periradicular abscess</td>
<td>● First appointment: Consultation. ● Second appointment: Rubber dam and access. No instrumentation. Deep irrigation with 10 mL 5.25% NaOCl and 0.12% chlorhexidine. Interappointment medicament: metronidazole, minocycline, and ciprofloxacin. Cavit. ● Third appointment: Irrigate with 5.25% NaOCl, induce bleeding with endo explorer. Cotton pellet placed 3 mm below cementoenamel junction for 15-minute control location of a blood clot. MTA, wet cotton pellet, Cavit. ● Fourth appointment: Remove Cavit and place bonded composite.</td>
<td>8 months: Asymptomatic. Apical closure with thickening dentinal walls.</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>Male</td>
<td>Necrotic</td>
<td>Acute apical abscess</td>
<td>● Trauma 2 years previously treated with Cvek pulpotomy procedure. ● Incision for drainage. ● Disinfect tooth surface with Betadine. Rubber dam and access. No instrumentation. Irrigate copiously with 1.25% NaOCl. Interappointment medicament: metronidazole, minocycline, and ciprofloxacin (Lentulo spiral). IRM. ● 11 weeks: Irrigate with 10 mL 1.25% NaOCl and 10 mL sterile water. Induce bleeding with endodontic file inserted beyond the apex. 15 minutes allowed for blood clot to reach cementoenamel junction. Place MTA over blood clot with moist cotton pellet. Remove cotton pellet 1 hour later and place bonded composite.</td>
<td>3 months: Asymptomatic. Diffuse radiopacities noted in root canal system. No response to pulp test (CO₂ ice). 6–12 months: Asymptomatic. Diffuse radiopacities noted in root canal system. No response to pulp test (CO₂ ice). Gradual apical development and closure.</td>
<td>32</td>
</tr>
</tbody>
</table>

IRM, intermediate restorative material; MTA, mineral trioxide aggregate.
over time (68). Thus, a scaffold is far more than a simple lattice to contain cells. From our perspective of focusing on practical clinical applications, we believe that platelet-rich plasma (PRP) satisfies many of these criteria. PRP is autologous, fairly easy to prepare in a dental setting, rich in growth factors, degrades over time, and forms a 3-dimensional fibrin matrix (69–72). Interestingly, the case reports from Table 1 all include formation of a blood clot. The use of PRP as an alternative source for a fibrin clot might have several advantages, including increased concentration of growth factors and removal of erythrocytes that would be expected to undergo necrosis shortly after clot formation. To date, however, no publications have evaluated PRP for scaffold generation in regenerative endodontic applications. This and other potential scaffolds require future research.

The third component of tissue engineering to consider for regenerative endodontics is signaling molecules. Both growth factors and other compounds are capable of stimulating cellular proliferation and directing cellular differentiation. As aforementioned, the observed radiographic thickening of the dentinal walls might be due to production of cementum, bone, or dentin. It is likely that the cell source and the available signaling molecules play major roles in guiding the development of cells in the regenerating tissue. For example, the same cultures of human dental pulp cells can differentiate into cells resembling odontoblasts/osteoblasts, adipocytes, or chondrocytes, depending on the combination of signaling molecules such as dexamethasone (49). Other investigators have shown that dentin or application of a dentin extract rich in growth factors will promote formation of an odontoblast phenotype (50, 62, 73). Extracts of dentin promote growth, because many growth factors are embedded into the dentin matrix during dentinogenesis. Interestingly, ethylenediaminetetraacetic acid (EDTA) very effectively releases growth factors from human dentin (74). It is not yet known, however, whether root canal irrigation with EDTA would promote the development of odontoblast proliferation in a regenerative endodontic procedure. It is likely that intracanal delivery of known signaling molecules or the solubilization of endogenous signaling molecules will promote the formation of dentin in regenerative endodontic methods.

### A Path to the Future

Collectively, there has been a tremendous increase in our clinical tools (ie, materials, instruments, and medications) and knowledge from the trauma and tissue engineering fields during the last decade. Moreover, recent case reports from multiple investigators support the feasibility of developing biologically based regenerative endodontic procedures designed to restore a functional pulp-dentin complex. Although these case reports primarily involve treating the immature permanent tooth, it is quite possible that knowledge gained from this clinical application will have value in developing regenerative endodontic procedures for the fully developed permanent tooth. In short, the question is no longer “can regenerative endodontic procedures be successful?” Instead, the important question facing us is “what are the issues that must be addressed to develop a safe, effective, and consistent method for regenerating a functional pulp-dentin complex in our patients?”

In our opinion, the path to the future should focus on translational research models that simulate likely clinical procedures. For example, although of clear scientific importance in understanding cellular mechanisms, we do not believe that gene transfection is likely to have major application in clinical endodontic procedures. Similarly, if natural tooth development takes several years to occur, then we are not convinced that the growth of artificial teeth with cells of allogenic or even xenogenic origin (42, 75) is likely to have major clinical application. Instead, we believe that research modeling clinical procedures designed to regenerate a functional pulp-dentin complex is likely to have the greatest impact. On the basis of current concepts, one approach would be to focus on methods permitting the delivery of known cells, signaling molecules, and a scaffold such as PRP into the apical 1–2 mm of a root canal system and then “backfilling” the root canal system with a solution of PRP and signaling molecules. Because most cells must be less than 1 mm away from a blood vessel to survive (76), research focusing on the initiation of pulpal regeneration at the apex is likely to have major impact in developing other clinically useful procedures. Cellular proliferation could then occur along the backfill scaffold.

One possible approach is to develop a model system resembling clinical application. For example, the revascularization of root canal systems has been evaluated in human tooth slices after implantation into nude mice (who are immunocompromised, thus avoiding tissue rejection (77)). Similarly, it might be possible to evaluate the initiation of pulpal regeneration after various treatments by implanting the apical 5–10 mm of sectioned human roots into nude mice. This approach has particular advantages, because it permits rapid evaluation of conditions necessary to initiate tissue regeneration and could be extended in future research by evaluating conditions necessary to optimally disinfect necrotic root canal systems before tissue regeneration.

A recent editorial has suggested that “little progress has been made” in the years since the Nygaard-Østby studies on the regrowth of dental pulp (8). From many perspectives, this statement is accurate. We believe, however, that the last decade has produced a critical mass of knowledge and methods that are likely to result in the generation of biologically based endodontic therapies that will answer the challenge issued decades ago.

### References


Contemporary Perspectives on Vital Pulp Therapy: Views From the Endodontists and Pediatric Dentists

N. Sue Seale, DDS, MSD,* and Gerald N. Glickman, DDS, MS†

Abstract
The purpose of this study was to determine the level of agreement between pediatric dentists and endodontists at a pulp therapy symposium jointly sponsored by the American Association of Endodontists (AAE) and the American Academy of Pediatric Dentistry (AAPD) on November 2–3, 2007. Presymposium and postsymposium tests were administered, and respondent answers were compared between pediatric dentists and endodontists. Opinions on 3 areas were sought: pulp therapy for cariously involved primary teeth; indirect pulp treatment (IPT) for cariously involved immature permanent teeth; and innovative treatment options including pulpal revascularization and regeneration. Results were analyzed with $\chi^2$ tests. Comparisons of presymposium and postsymposium responses and between the 2 groups of attendees indicated that the pediatric dentistry and endodontic communities agree that formocresol will be replaced as a primary tooth pulpotomy agent, that mineral trioxide is the first choice to take its place, that IPT in primary teeth holds hope as a replacement for pulpotomy, and that IPT is an acceptable pulp therapy technique for cariously involved young permanent teeth. Both groups believe that pulp revascularization and regeneration will be viable treatment modalities in the future. The AAE and the AAPD are positioned to begin preparation for working together to produce best practice guidelines that share common language and treatment recommendations. Such an outcome would require both disciplines to agree with interpretation of the evidence presented concerning the shared treatments.

Methods
An 8-question pretest was prepared and administered to attendees before the first presentation. The first 3 questions asked for demographic data, including dental discipline, age, and current situation (pediatric or endodontic resident, or academician). Five additional questions used a 5-point Likert scale with the choices of strongly agree, agree, neutral, disagree, and strongly disagree and queried about primary tooth pulpotomy and primary and permanent tooth IPT. Frequency tables of responses to the pretest questions were calculated for all respondents and compared by discipline, age group, and current career position. Additional questions used the Likert scale or allowed the attendees to choose a single best answer from a list of options and patient scenarios. Six questions addressed primary tooth pulpotomy, including medicament choice and opinions about formocresol as a primary tooth pulpotomy agent. Four questions asked for opinions about indirect pulp capping (IPC)/stepwise excavation in primary teeth, and an additional 5 questions asked about the same procedure in permanent teeth. Five questions addressed pulpal revascularization and the potential for stem cell research for pulpal regeneration. Frequency tables of responses to the ARS questions were calculated for all respondents and compared by discipline (pediatric dentist or endodontist) by using $\chi^2$ analysis, with a significance level of $P < .05$.
Results

A total of 376 individuals provided responses, and they were divided as follows: 79 endodontists, 23 endodontic residents, 231 pediatric dentists, 21 pediatric dental residents, and 22 others. The numbers of residents and nonspecialists were small. Therefore, $\chi^2$ analyses were only performed on responses from pediatric dentists and endodontists.

One of the major areas addressed by the speakers was pulpotreatment for the cariously involved primary tooth. Issues covered included the controversy surrounding the use of formocresol as a pulpotomy agent in primary teeth and the level of evidence supporting either discontinuing its use or maintaining it as a viable pulpotomy agent; the status of different pulpotomy agents for primary teeth and the level of evidence that supports them; and the use of IPT as an alternative to pulpotomy for cariously involved primary teeth.

Pretest responses concerning the acceptability of formocresol as a contemporary technique for primary tooth pulpotomy were significantly more positive ($P < .001$) from pediatric dentists, with 80% agreeing or strongly agreeing compared with only 29% of endodontists. Three of the post-seminar ARS questions revisited this issue, primarily concerning formocresol’s safety. When attendees were asked to respond to the statement “formocresol, when used as a primary tooth pulpotomy agent, presents documented danger to the patient,” pediatric dentists (5%) were significantly ($P < .001$) less likely than endodontists (15%) to agree or strongly agree. When asked whether the fact that formocresol is a potential carcinogen should contraindicate its future usage in pediatric pulp therapy, however, 18% of pediatric dentists agreed or strongly agreed, compared with 37% of endodontists. Again, these differences were significant ($P < .001$; Fig. 1). Attendees were asked their opinion about the statement “formocresol will be replaced as a primary tooth pulpotomy agent, not because of its danger to patients, but because there is much controversy about its potential.” Pediatric dentists and endodontists were divided in their opinions, with 78% and 76%, respectively, agreeing or strongly agreeing.

Pulpotomy agents or treatment alternatives for cariously involved primary teeth were addressed in 2 post-symposium ARS questions. Attendees were asked to give their opinions of the best treatment for a reversibly inflamed primary molar with a large carious lesion encroaching on the pulp. They did this by choosing from a list that included an IPT, a pulpotomy with formocresol, ferric sulfate, mineral trioxide aggregate (MTA), or sodium hypochlorite. MTA was the favorite pulpotomy agent, chosen most often by both pediatric dentists (30%) and endodontists (34%), whereas 20% of pediatric dentists and 4% of endodontists chose formocresol. The second question dealt with choices of agents for pulpotomy and asked, “If cost were not an issue, which is the recommended medicament for primary tooth pulpotomy?” IPT was the overwhelming winner, with pediatric dentists and endodontists in agreement, choosing it 85% of the time. Only 15% of pediatric dentists and 3% of endodontists chose formocresol (Fig. 2). IPT in primary teeth was addressed in the pretest by asking attendees whether IPT was an acceptable substitute technique to replace pulpotomy to maintain vitality of cariously involved primary teeth. Endodontists were significantly ($P = .003$) more likely at 47% to agree or strongly agree, compared with pediatric dentists (32%). The post-symposium ARS used 5 questions to further explore opinions of attendees concerning the subject of IPT in primary teeth. IPT was offered as a treatment option in cariously involved primary teeth in a question that asked attendees to choose from a list the best treatment for a reversibly inflamed primary molar with a large carious lesion encroaching on the pulp. Forty-seven percent of pediatric dentists and 58% of endodontists chose IPT (Fig. 3).

A second question asked attendees to respond to the statement “there is convincing evidence that IPT is as successful as a pulpotomy in primary teeth with reversible pulpitis.” Seventy-four percent of pediatric dentists and 70% of endodontists agreed or strongly agreed. When asked to respond to the statement “there is convincing evidence that primary teeth with reversible pulpits should all be treated by step-wise excavation for 3 months and only receive a pulpotomy if exposure occurs on re-entry to remove remaining caries,” attendees were divided...
in their opinions. Forty percent of pediatric dentists and 63% of endodontists agreed or strongly agreed. A scenario question asked what they would do for a 5-year-old child with a second primary molar in which they had removed nearly all of the decay, knowing that if they removed the remaining decay, a pulp exposure would be imminent. More than half of the pediatric dentists (55%) and 71% of endodontists would stop caries removal and do an IPT.

The final question about IPT in primary teeth in the postsymposium ARS asked attendees to choose from a list their main reason for not performing an IPT in a primary tooth with reversible pulpitis. The most frequently chosen answers in descending order by pediatric dentists were “pulpotomy is supported by evidence to have a better, more predictable outcome” (40%), “there is inadequate reimbursement by third party payers for the procedure” (32%), “there is insufficient evidence to support its efficacy and success” (19%), and “I don’t believe IPT is successful in primary teeth” (9%). Endodontists had slightly different rankings of their choices, with “there is inadequate reimbursement by third party payers for the procedure” (35%), “pulpotomy is supported by evidence to have a better, more predictable outcome” (28%), “there is insufficient evidence to support its efficacy and success” (18%), and “I don’t believe IPT is successful in primary teeth” (20%) (Fig. 4).

A second major area addressed by the speakers was management of the carious lesion encroaching on the pulp of an immature permanent tooth, including those with an open apex. Two pretest questions dealt with attendees’ opinions about IPT for these teeth. The first asked for reactions to the statement “indirect pulp capping is an acceptable contemporary technique for maintaining the vitality of asymptomatic, cariously involved young permanent teeth.” Pediatric dentists were overwhelmingly positive and significantly ($P < .001$) at 94% to agree or strongly agree, compared with endodontists (69%).

The second pretest question asked for reactions to the statement “symptoms of reversible pulpitis are contraindications to IPT in young permanent teeth.” Endodontists were significantly ($P = .02$) more likely to agree or strongly agree at 31% than pediatric dentists at 26%. The post-symposium ARS used the exact same question to assess opinions after the presentations, and there was a significant difference in how the attendees responded to this question by the end of the conference. When the endodontists’ pretest responses (31%) were compared with their ARS responses, significantly fewer ($P < .001$) at 7% agreeing or strongly agreeing that symptoms of reversible pulpitis were a contraindication to IPT, compared with their pretest responses (26%) (Fig. 5).

Additional post-symposium ARS questions asked attendees’ opinions of the stepwise, 2-appointment version of IPT in permanent teeth. One question asked about agreement with “step-wise excavation as a practical treatment modality for IPT in young permanent teeth.” Pediatric dentists were significantly ($P < .05$) more likely to agree or strongly agree at 71%, compared with 59% of endodontists. Another question asked attendees to choose from a list their main reason for not performing stepwise excavation in a permanent tooth with an open apex. Pediatric dentists chose in descending order: patient compliance for 2 appointments might be questionable (52%); MTA pulpotomy is supported by evidence to have a better outcome (20%); there is more evidence to support the efficacy of the 1-step indirect pulp cap (18%); and inadequate reimbursement by third party payers for the procedure (10%). Endodontists expressed different preferences for their answers, with their first choice being: MTA pulpotomy is supported by evidence to have a better outcome (61%); patient compliance for 2 appointments might be questionable (27%); there is more evidence to support the efficacy of the one-step indirect pulp cap (6%); and inadequate reimbursement by third party payers for the procedure (6%) (Fig. 6).

Finally, attendees were asked to choose from a list their strongest argument for performing stepwise caries excavation in a young permanent tooth. Responses from pediatric dentists included patient recall to assess symptoms and vitality (41%); patient recall to assess evidence of root maturation (31%); re-entry to ensure dentin remineralization

**Figure 4.** Comparison by specialty of responses to the statement: My main reason for not performing a pulpotomy in a primary tooth with reversible pulpitis.

**Figure 5.** Comparison by specialty of presymposium and postsymposium responses to statement: Symptoms of reversible pulpitis are contraindications to IPT in young permanent teeth with open apices.

**Figure 6.** Comparison by specialty of responses to the question: What is your main reason for not performing stepwise excavation in a permanent tooth with an open apex?
(24%); and provides low-cost treatment for patients needing access to care (4%). Endodontists responded differently, listing in order: patient recall to assess evidence of root maturation (41%); patient recall to assess symptoms and vitality (25%); re-entry to ensure dentin remineralization (25%); payment to practitioner for a second appointment (6%); and provides low-cost treatment for patients needing access to care (3%) (Fig. 7).

Root canal revascularization via blood clotting in necrotic young teeth has been reported in the literature through documented case reports. A major aspect of this technique is usage of disinfecting irrigants such as sodium hypochlorite and chlorhexidine followed by the placement of a special antibiotic mixture. Respondents’ opinions expressed through the ARS indicated that the vast majority of pediatric dentists (87%) and endodontists (86%) agreed or strongly agreed that this will be a viable treatment modality for permanent teeth with apical periodontitis within the next 10 years. When asked to choose from a list their major concerns about the procedures, pediatric dentists gave the following responses in descending order: no major concerns at this time (34%); current evidence is based primarily on case reports (33%); unpredictability (18%); complex case selection criteria (13%); and use of antibiotic paste within the canal (2%). Endodontists gave slightly different ordering to their choices: no major concerns at this time (32%); unpredictability (26%); current evidence is based primarily on case reports (16%); use of antibiotic paste within the canal (14%); and complex case selection criteria (12%). The greatest disagreement between the 2 groups came when asked whether general dentists should perform such procedures if properly educated and trained. Pediatric dentists were favorably inclined, with 74% agreeing or strongly agreeing compared with only 45% of endodontists.

Regeneration of pulp tissue involves tissue engineering therapies by using stem cells, growth factors, and gene therapies. Although this exciting concept is at its early stages of development, the American Association of Endodontists has made regenerative endodontics and revascularization high priority areas for further investigation. ARS questions asked for opinions about whether, from a public health perspective, the future use of stem cells for pulp regeneration in permanent teeth would be an acceptable treatment. Endodontists were more likely to agree or strongly agree at 64%, compared with pediatric dentists at 37%. This question had the highest percentage of uncommitted responders, with 33% of pediatric dentists and 21% of endodontists choosing neutral as a response. Finally, the ARS asked for opinions from an ethical standpoint whether they believed the future use of stem cells for pulp regeneration in permanent teeth would be an acceptable treatment. All of the endodontists (100%) and 96% of pediatric dentists agreed or strongly agreed.

**Discussion**

Evidence of a merging level of agreement between pediatric dentists and endodontists concerning important issues addressed by the presenters was needed for the symposium planning committee’s goal to be met for the collaborative production of pulp therapy guidelines. Pretest responses indicated significant differences in opinions between pediatric dentists and endodontists concerning the acceptability of most of the pulp therapy treatments under consideration. Beginning with primary tooth pulpotomy agents and formocresol in particular, the vast majority of pediatric dentists initially viewed formocresol pulpotomy as an acceptable pulp treatment for cariously involved primary teeth. Although the pretest question did not ask respondents to choose formocresol from among other pulpotomy agents, as did the ARS questions, 80% of the pediatric dentists favored its use at that point. Comparing the large number of positive responses initially to formocresol with the ARS responses appears to indicate a changing attitude by pediatric dentists. In the post-symposium ARS questions, only 20% chose formocresol as the best treatment for a primary tooth with reversible pulpitis, and only 15% chose it as the recommended medication for primary tooth pulpotomy. The way the questions were phrased does not allow direct comparisons between presymposium and postsymposium responses, but these results certainly appear to suggest that formocresol lost popularity. The trend away from formocresol would place pediatric dentists more in agreement with endodontists, who did not favor formocresol either pre- or post-symposium.

There was a different trend apparent when pediatric dentists were asked to comment on the safety of formocresol. Their responses to ARS questions about its documented danger to the patient and whether its potential as a carcinogen should contraindicate its use indicated that they do not believe the case that formocresol is dangerous has been made; only 5% of pediatric dentists and 18% of endodontists agreed. They did appear convinced, however, that it will be replaced because it is too controversial. In that respect, they were in complete agreement with the endodontists. When applying these data to the production of practice guidelines, it is probably most important that the 2 groups be together in their opinions about the need to find and endorse a replacement for formocresol.

Continuing with the issue of primary tooth pulp therapy and with respect to agents used for pulpotomy, post-symposium ARS data indicated that pediatric dentists and endodontists are unified in their overwhelming favor of MTA as the pulpotomy agent of choice. This finding is interesting in light of the fact that there are few well-designed studies examining MTA as a primary tooth pulpotomy agent, even though those studies that are available report positive outcomes in favor of MTA. A second option being examined to replace formocresol pulpotomy as the treatment of choice for cariously involved primary teeth is IPT. Pretest data indicated poor acceptance by the pediatric dentistry respondents, with less than one third agreeing that it was an acceptable substitute technique for pulpotomy. Their post-symposium ARS responses appeared to indicate a marked trend toward a more positive attitude about IPT for primary teeth. More than half would stop caries excavation and perform an IPT rather than a pulpotomy, and 75% agreed that there is evidence that IPT is as successful as pulpotomy in primary teeth. Endodontists started out more positively than pediatric dentists about the procedure for primary teeth and remained that way. The gap between
them narrowed, however, as pediatric dentists more frequently expressed positive opinions in their responses after the symposium.

The issue where pediatric dentists and endodontists have the most potential to both be treating the same kinds of teeth is the management of cariously involved young permanent teeth with immature or open apices. This is also the issue where there has previously been the most divergence of opinion between the 2 groups concerning the appropriateness of IPT for these teeth. The pretest question responses bore out this divergence. Almost all of the pediatric dentists (94%) opined that IPT was an acceptable technique for the “asymptomatic cariously involved young permanent tooth,” compared with only approximately two thirds of the endodontists.

Most pediatric dentists and endodontists, however, agreed to a pretest question concerning reversible symptoms of pulpitis contraindicating IPT. By the end of the conference, their opinions about whether such symptoms were a contraindication to IPT changed dramatically. The post-symposium ARS question was worded exactly the same way as in the pretest. Only 8% of endodontists and 7% of pediatric dentists agreed that symptoms of reversible pulpitis were a contraindication to IPT, indicating agreement on this important diagnostic issue.

The IPT procedure in permanent teeth presented at the symposium was the variant called stepwise excavation. The variant involves 2 appointments and aims to eventually remove all affected dentin rather than leave a small amount in the tooth as is performed in the 1-appointment IPT. The procedure has not received wide exposure in the United States because most of the publications on its use and success have appeared in journals not widely read by the practicing community. The post-symposium ARS questions dealt mainly with the stepwise excavation version of IPT and appeared to indicate similar favorable agreement on its use in permanent teeth by both pediatric dentists and endodontists.

It is this topic of the more conservative, cost-effective treatment modality of IPT for cariously involved young permanent teeth that is the most important issue for which the 2 communities must reach agreement and formulate practice guidelines with common language and intent. Many children and young adults who have the highest risk for caries and lesions and who are candidates for IPT have either no payer sources or sources with limited participation by individuals who perform endodontic treatment (general dentists and endodontists). In fact, many cariously involved teeth in these young individuals have open apices and are simply not candidates for complete endodontic treatment. They need to be treated with the more complex and lengthy procedure of vital pulpotomy to obtain root closure followed by complete root canal treatment. The length of time involved in completing the 2 procedures might make them impractical for patients on some payment programs such as Medicaid, where their eligibility might vary during the time period required. The issue of access to care mandates that the 2 groups be unified in agreeing that IPT is an evidence-based and appropriate pulp therapy modality for young permanent teeth with immature or open apices.

Conclusions

In summary, what do endodontists and pediatric dentists agree on? These survey data appear to indicate that the pediatric dentistry and endodontic communities alike agree that formocresol will be replaced as a primary tooth pulpotomy agent, that MTA is the overwhelming first choice to take its place, that IPT in primary teeth holds hope as a replacement for pulpotomy, and that IPT is an acceptable pulp therapy technique for cariously involved young permanent teeth with open apices. In addition, both the endodontists and pediatric dentists believe that pulp revascularization and regeneration will be potentially new exciting treatment modalities in the near future.