Mechanisms of antimicrobial activity of calcium hydroxide: a critical review

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Abstract


Literature review The primary function of calcium hydroxide as a routine intracanal medicament is to provide antimicrobial activity. However, the mechanisms of antimicrobial activity of calcium hydroxide are not well known. Physicochemical properties of this substance may limit its effectiveness in disinfecting the entire root canal system. In addition, calcium hydroxide is not effective against all bacterial species found in root canal infections. Association with other medicaments may enhance the efficacy of the intracanal medication in eliminating residual bacteria in the root canal system.

Keywords: antimicrobial activity, calcium hydroxide, root canal treatment.

Introduction

Endodontic treatment is essentially directed toward the prevention and control of pulpal and periradicular infections. Given the relevance of microorganisms for the pathogenesis of periradicular lesions, it is clear that the outcome of the endodontic therapy depends on their reduction or elimination. Complete chemomechanical preparation may be considered an essential step in root canal disinfection. However, total elimination of bacteria is difficult to accomplish (Byström & Sundqvist 1981, 1985, Siqueira et al. 1997a). By remaining in the root canal between appointments, intracanal medicaments may help to eliminate surviving bacteria (Byström & Sundqvist 1985).

Since its introduction in 1920 (Hermann 1920), calcium hydroxide has been widely used in endodontics. It is a strong alkaline substance, which has a pH of approximately 12.5. In an aqueous solution, calcium hydroxide dissociates into calcium and hydroxyl ions. Various biological properties have been attributed to this substance, such as antimicrobial activity (Byström et al. 1985), tissue-dissolving ability (Hasselgren et al. 1988, Andersen et al. 1992), inhibition of tooth resorption (Tronstad 1988), and induction of repair by hard tissue formation (Foreman & Barnes 1990). Because of such effects, calcium hydroxide has been recommended for use in several clinical situations (Heithersay 1975, Fava 1991). Currently, this chemical substance is acknowledged as one of the most effective antimicrobial dressings during endodontic therapy.

Because of the wide use of calcium hydroxide as a routine antimicrobial intracanal medicament, the aim of this paper is to review its antimicrobial mechanisms and limitations.

Mechanisms of antimicrobial activity

Most of the endodontopathogens are unable to survive in the highly alkaline environment provided by calcium hydroxide (Heithersay 1975). Since the pH of calcium hydroxide is about 12.5, several bacterial species commonly found in infected root canals are eliminated after a short period when in direct contact with this substance (Byström et al. 1985).
Antimicrobial activity of calcium hydroxide is related to the release of hydroxyl ions in an aqueous environment. Hydroxyl ions are highly oxidant free radicals that show extreme reactivity, reacting with several biomolecules (Freeman & Crapo 1982). This reactivity is high and indiscriminate, so this free radical rarely diffuses away from sites of generation. Their lethal effects on bacterial cells are probably due to the following mechanisms:

**Damage to the bacterial cytoplasmic membrane**

The bacterial cytoplasmic membrane possesses important functions to the survival of the cell, such as (i) selective permeability and transport of solutes; (ii) electron transport and oxidative phosphorylation in aerobic species; (iii) excretion of hydrolytic exoenzymes; (iv) bearing enzymes and carrier molecules that function in the biosynthesis of DNA, cell wall polymers, and membrane lipids; and (v) bearing the receptors and other proteins of the chemotactic and other sensory transduction systems (Brooks et al. 1998).

Hydroxyl ions induce lipid peroxidation, resulting in the destruction of phospholipids, structural components of the cellular membrane. Hydroxyl ions remove hydrogen atoms from unsaturated fatty acids, generating a free lipidic radical. This free lipidic radical reacts with oxygen, resulting in the formation of a lipidic peroxide radical, which removes another hydrogen atom from a second fatty acid, generating another lipidic peroxide. Thus, peroxides themselves act as free radicals, initiating an autocatalytic chain reaction, and resulting in further loss of unsaturated fatty acids and extensive membrane damage (Halliwell 1987, Cotran et al. 1999).

**Protein denaturation**

Cellular metabolism is highly dependent on enzymatic activities. Enzymes have optimum activity and stability in a narrow range of pH, which turns around neutrality. The alkalinization provided by calcium hydroxide impedes the carbon dioxide supply to remaining bacteria in the root canal system may be maintained from the outside. In addition, bacteria located in ramifications have direct access to carbon dioxide from the periradicular tissues. There is little reason to consider that calcium hydroxide impedes the carbon dioxide supply to bacteria.

**Damage to the DNA**

Hydroxyl ions react with the bacterial DNA and induce the splitting of the strands. Genes are then lost (Imlay & Linn 1988). Consequently, DNA replication is inhibited and the cellular activity is disarranged. Free radicals may also induce lethal mutations.

Scientific evidence suggests that the three mechanisms may occur (Halliwell 1987, Imlay & Linn 1988, Cotran et al. 1999). Thus, it is difficult to establish, in a chronological sense, which is the main mechanism involved in the death of bacterial cells after exposure to a strong base.

It has been suggested that the ability of calcium hydroxide to absorb carbon dioxide may contribute to its antibacterial activity (Kontakiotis et al. 1995). However, cementum is permeable to water, ions and small molecules (Huang et al. 1992, Siqueira 1997).

Hence, carbon dioxide supply to remaining bacteria in the root canal system may be maintained from the outside. In addition, bacteria located in ramifications have direct access to carbon dioxide from the periradicular tissues. There is little reason to consider that calcium hydroxide impedes the carbon dioxide supply to bacteria.

**Root canal disinfection**

Several studies have demonstrated that calcium hydroxide exerts lethal effects on bacterial cells (Byström et al. 1985, Stuart et al. 1991, Georgopoulou et al. 1993). These effects were observed only when the substance was in direct contact with bacteria in solution. In such conditions, the concentration of hydroxyl ions is very high, reaching incompatible levels to bacterial survival. Clinically, this direct contact is not always possible.

Studies using the agar diffusion test have reported that calcium hydroxide associated with an inert substance (distilled water, saline solution or glycerine) was ineffective in inhibiting the growth of several obligate and facultative anaerobic bacteria (DiFio re et al. 1983, Siqueira & Gonçalves 1996, Abdulkader et al. 1996, Siqueira et al. 1996a, Siqueira & Uzedal 1997, Siqueira et al. 1997b). This probably was because culture media possess buffer substances in their formulations. Therefore, although calcium hydroxide could have diffused across the medium, the pH levels reached around it were not sufficient to present inhibitory activity (Siqueira & Gonçalves 1996).

Bases of alkaline metals, such as NaOH and KOH,
show high solubility and thereby may diffuse more than calcium hydroxide across the culture medium. Both bases have pronounced antibacterial activity (Siqueira et al. 1996b). On the other hand, high solubility and diffusibility increases the cytotoxic effects of these substances on host cells. Because of the high cytotoxicity of these substances, they are not indicated for use in endodontic practice.

Although hydroxyl ions possess antibacterial effects, rather high pH values are required to destroy microorganisms. Killing of bacteria by calcium hydroxide will depend on the availability of hydroxyl ions in solution, which is higher where the paste is applied. Calcium hydroxide exerts antibacterial effects in the root canal as long as they retain a very high pH. If calcium hydroxide needs to diffuse to tissues and the hydroxyl concentration is decreased as a result of the action of buffering systems (bicarbonate and phosphate), acids, proteins and carbon dioxide, its antibacterial effectiveness may be reduced or impeded (Siqueira et al. 1998, Siqueira & Uzeda 1998).

Bacteria inside dentinal tubules may constitute an important reservoir from which root canal infection or reinfection may occur during and after endodontic treatment (Oguntebi 1994). Occasionally, these remaining bacteria may cause a persistent infection that jeopardizes the outcome of endodontic therapy. Bacteria located inside dentinal tubules are protected from the effects of host defence cells and molecules, systemically administered antibiotics, and chemomechanical preparation. Therefore, treatment strategies that are directed toward the elimination of tubule infection are necessary and must include medicaments that penetrate dentinal tubules and kill bacteria.

For calcium hydroxide to act effectively as an intracanal dressing, the hydroxyl ions must be able to diffuse through dentine and pulpal tissue remnants. Studies have revealed that hydroxyl ions derived from a calcium hydroxide medication do diffuse through root dentine. Tronstad et al. (1981) reported that the pH of the monkey dentine was elevated after intracanal medication with calcium hydroxide for 4 weeks. However, the pH values were decreased in the more distant areas from the root canal. In the root canal, the pH was greater than 12.2; circumjacent dentine, in direct contact with calcium hydroxide, showed a pH varying from 8 to 11; and in the most peripheral dentine, the pH ranged from 7.4 to 9.6. Nerwich et al. (1993) investigated pH changes over 4 weeks, after application of a calcium hydroxide dressing. Apically, the pH of the inner dentine reached a plateau of approximately 9.5 after 2 weeks. In the outer dentine, although the pH began rising earlier, the maximum pH level was low, reaching just under 9 at 2 weeks. The pH of the cervical inner dentine peaked at 10.8 after 24 h and settled to a stable pH value of just above 10. The pH of the cervical outer dentine reached over 9 at 2 weeks. These results revealed that a dressing for 1 week with calcium hydroxide raised the pH of the inner dentine to approximately 9.0.

In certain conditions, such pH levels in dentine may allow the survival or growth of some bacterial strains. Bacteria vary in their pH tolerance ranges and most grow well within a range of 6–9 pH (Padan et al. 1981). Some strains of *Escherichia coli*, *Proteus vulgaris*, *Enterobacter aerogenes* and *Pseudomonas aeruginosa* can survive in pH 8 or 9 (Atlas 1997). These bacterial species have been occasionally isolated from infected root canals, usually causing secondary infections (Haapasalo et al. 1983, Tronstad 1992, Siren et al. 1997). Certain bacteria, such as some enterococci, tolerate very high pH values, varying from 9 to 11. Fungi generally also exhibit a wide pH range, growing within a range of 5–9 pH (Atlas 1997). Strains of *Prevotella intermedia*, *Fusobacterium nucleatum* and *Porphyromonas gingivalis* may show stable growth in alkaline pH values (approximately 8.0–8.3) (Marsh et al. 1993).

The pH of the medium exerts a drastic selective pressure, and only those microorganisms with adaptive mechanisms are able to proliferate. Most proteins and other biologically important molecules have a narrow pH range of optimum activity and/or stability, which turns around neutrality. Bacterial tolerance to pH changes may be because of activation of specific proton pumps, specific enzymatic systems and/or buffering devices, which help to keep the internal pH practically constant (Padan et al. 1981). In addition to these mechanisms, some bacterial products generated during growth may help bacteria to neutralize the environmental pH.

Several studies have attested the inefficacy of calcium hydroxide in eliminating bacterial cells inside dentinal tubules. Haapasalo & Orstavik (1987) reported that a calcium hydroxide paste (Calasept, Sweden, Knivsta, Sweden) failed to eliminate, even superficially, *Enterococcus faecalis* in the tubules. Safavi et al. (1990) demonstrated that *Enterococcus faecalis* remained viable in dentinal tubules after relatively extended periods of calcium hydroxide/saline solution application.
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treatment, Ørstavik & Haapasalo (1990) observed that calcium hydroxide can take up to 10 days to disinfect dentinal tubules infected by facultative bacteria. Heling et al. (1992) have found that calcium hydroxide did not show any antibacterial activity against E. faecalis inside dentinal tubules, and failed to sterilize the dentine or prevent secondary infection. Siqueira & Uzeda (1996) demonstrated that calcium hydroxide associated with saline solution was ineffective in eliminating E. faecalis and F. nucleatum cells inside dentinal tubules, even after 1 week of contact.

To be effective against bacteria located inside the dentinal tubules, the hydroxyl ions from calcium hydroxide should diffuse into dentine at sufficient concentrations. It has been reported that dentine has buffering ability because of the presence of proton donors, such as $\text{H}_2\text{PO}_4^-$, $\text{H}_2\text{CO}_3$, and $\text{HCO}_3^-$, in the hydrated layer of hydroxyapatite, which furnish additional protons to keep the pH unchanged (Wang & Hume 1988, Nerwich et al. 1993). Therefore, in order to have antibacterial effects within dentinal tubules, the ionic diffusion of calcium hydroxide should exceed the dentine buffer ability, reaching pH levels sufficient to destroy bacteria. After short-term use of calcium hydroxide, microorganisms are probably exposed to lethal levels of hydroxyl ions only at the tubule orifice.

Another factor can also help to explain the inefficacy of calcium hydroxide in disinfecting dentinal tubules. The arrangement of the bacterial cells colonizing the root canal walls can reduce the antibacterial effects of calcium hydroxide, since the cells located at the periphery of colonies can protect those located more deeply inside the tubules (Siqueira et al. 1996a, Siqueira & Uzeda 1996).

Bacteria colonizing necrotic tissue in ramifications, isthmuses and irregularities are also, probably, protected from the action of calcium hydroxide, due to pH neutralization. Therefore, a short-term dressing with calcium hydroxide appears to eliminate mainly bacterial cells in direct contact with this substance, such as bacteria located in the main root canal or in the circumvulpal dentine. These areas are also commonly affected by the chemomechanical procedures.

The ability of a medicament to dissolve and diffuse in the root canal system would seem essential for its successful action (Ørstavik 1997). A saturated aqueous suspension of calcium hydroxide possesses a high pH, which has a great cytotoxic potential. Nevertheless, this substance owes its biocompatibility to its low water solubility and diffusibility. Because of these properties, cytotoxicity is limited to the tissue area in direct contact with calcium hydroxide. On the other hand, the low solubility and diffusibility of calcium hydroxide may make it difficult to reach a rapid and significant increase in the pH to eliminate bacteria located within dentinal tubules and enclosed in anatomical variations. Likewise, the tissue buffering ability controls pH changes. Because of these factors, calcium hydroxide is a slowly working antiseptic. Prolonged exposure may allow for saturation of the dentine and tissue remnants. Theoretically, long-term use of calcium hydroxide may be necessary to obtain a bacteria-free root canal system. However, in most instances, the routine use of an intracanal medication for a long period does not seem to be an acceptable practice in modern endodontics.

The period needed for calcium hydroxide to optimally disinfect the root canal system is still unknown. Clinical studies using root canal sampling procedures, have revealed conflicting results. Čvek et al. (1976) revealed that 90% of the samples taken from root canals 3 months after medication with calcium hydroxide mixed with Ringer's solution showed no microbial growth. Byström et al. (1985) demonstrated that calcium hydroxide effectively eliminated all microorganisms when the medicament was maintained for 4 weeks. Reit & Dählen (1988) found that infection persisted in 26% of the canals after 2 weeks of dressing with calcium hydroxide. Sjögren et al. (1991) have reported that an intracanal medication with calcium hydroxide for 1 week effectively eliminated bacteria in the root canal in 100% of the cases. Ørstavik et al. (1991) observed the persistence of bacteria in 34.8% of the root canals after 1 week of dressing. Barbosa et al. (1997) reported that 12 of 45 cases (26.7%) dressed with calcium hydroxide for 1 week yielded positive cultures.

Even cases that yield negative cultures may result in failure (Sjögren 1996, Sjögren et al. 1997). This occurs because microorganisms may have been present in the root canal system and escaped detection in the samples that were taken. This can occur for several reasons, one of which is that bacteria located in isthmuses, dentinal tubules and ramifications may have been inaccessible to sampling from the main canal. In addition, smear layer and residues of calcium hydroxide pastes in the root canal walls can physically limit access to bacteria during sampling procedures. Another reason could be that, since culture has a
sensitivity to detect approximately $10^3–10^4$ cells in a sample (Zambon & Haraszthy 1995), it is possible that, at time of sampling, too few cells were present in the root canal to be recovered for this method.

Although enterococci are not normally present or are present in very low numbers in untreated cases (Byström et al. 1985, Sundqvist et al. 1998), studies have suggested that they are important agents in endodontic failure. Molander et al. (1998) examined the microbiological status of 100 root-filled teeth with periradicular lesions. Facultative anaerobes predominated amongst the isolates, corresponding to 69% of the identified strains. Enterococci were found in 32% of the investigated teeth. Under similar conditions, Möller (1966) and Sundqvist et al. (1998) isolated E. faecalis from 29% and 38% of canals that had recoverable microorganisms, respectively. It has been observed that calcium hydroxide dressing is ineffective against enterococci (Stevens & Grossman 1983, Byström et al. 1985, Haapasalo & Ørstavik 1987, Siqueira & Uzeda 1996). Therefore, the frequent isolation of enterococci questions the routine use of calcium hydroxide as an intracanal medication (Molander et al. 1998).

Bacteria may survive after intracanal medication for several reasons. First, bacterial strains present in the root canal infection may be intrinsically resistant to the medicament. Secondly, bacterial cells may be enclosed within anatomical variations inaccessible to the medicament. Thirdly, the medicament may be neutralized by tissue components and by bacterial cells or products, losing its antibacterial effects. Fourthly, medicaments may remain in the root canal system for insufficient time to reach and kill bacterial cells. Finally, bacteria may alter their pattern of gene expression after changes in the environmental conditions. This alteration may allow them to survive in unfavourable environments.

Good clinical results have been attributed to the use of calcium hydroxide as an intracanal medicament (Heithersay 1975, Tronstad 1992). Nonetheless, the antibacterial activity of calcium hydroxide is still controversial and it is not clear whether the benefits of this substance are based solely upon superior antibacterial activity (Seltzer 1988).

**Influence of the vehicle on the antimicrobial activity**

A plethora of substances have been used as vehicles for calcium hydroxide. Vehicles have different water solubility and ideally they must not change the pH of calcium hydroxide significantly.

Most of the substances used as a vehicle for calcium hydroxide do not have significant antibacterial activities. They include distilled water, saline solution and glycerine. Other substances, such as camphorated paraomonochlorophenol (CMCP) and metacresylacetate, are known to possess this property. Frank (1966) recommended mixing calcium hydroxide with CMCP in apexification procedures. Some authors criticized this by considering it unnecessary to add antimicrobial agents to calcium hydroxide, especially those that have been shown to be tissue irritating (Cvek et al. 1976, Anthony et al. 1982).

Recently, renewed interest has been generated regarding this association because of the relative inefficiency of calcium hydroxide against some microorganisms, such as E. faecalis. Although CMCP has pronounced in vitro antibacterial effects on anaerobic bacteria (Ohara et al. 1993, Siqueira et al. 1996a), studies have revealed that calcium hydroxide is superior to it against this set of microorganisms (Byström et al. 1985, Stuart et al. 1991, Georgopoulou et al. 1993). However, CMCP has been reported to be more effective in eliminating enterococci than calcium hydroxide (Stevens & Grossman 1983, Haapasalo & Ørstavik 1987, Siqueira et al. 1996a).

As discussed previously, calcium hydroxide effects are highly dependent on the availability of hydroxyl ions in solution. Culture media, tissue fluids and dentine possess buffer substances that can prevent calcium hydroxide activity by causing a pH drop. Siqueira & Uzeda (1996) verified that calcium hydroxide/saline solution paste was ineffective in eliminating E. faecalis and F. nucleatum from dentinal tubules even after 1 week of exposure. In contrast, a calcium hydroxide/CMCP/glycerine paste effectively killed bacteria in the tubules after 1 h exposure, except for E. faecalis that required 1 day of exposure. Studies using an agar diffusion test have revealed that the calcium hydroxide/CMCP paste had pronounced antibacterial activity against facultative and anaerobic bacteria, which was superior to pastes containing calcium hydroxide in inert substances (Difilore et al. 1983, Siqueira et al. 1996b, 1997b, Siqueira & Uzeda 1997).

Siqueira & Uzeda (1998) evaluated the influence of three different vehicles on the antibacterial activity of calcium hydroxide against four bacterial species commonly found in endodontic infections, using a
modification of the broth dilution method. Calcium hydroxide/CMCP/glycerine paste rapidly killed bacteria. Other calcium hydroxide pastes also killed bacteria, but required more time. These findings indicate that CMCP increased the antibacterial effectiveness of the calcium hydroxide paste.

A number of phenolic derivatives, such as CMCP, camphorated phenol, thymol and eugenol have been extensively used in dentistry for many years. Phenolic compounds possess strong antibacterial properties and halogenation intensifies their antimicrobial activities. Phenol is believed to act by disrupting lipid-containing bacterial membranes, resulting in leakage of cellular contents. At higher concentrations, these compounds act by precipitating the cytoplasmic cell proteins (O’Connor & Rubino 1991). At lower concentrations, phenolic compounds inactivate essential enzyme systems and may also cause bacterial cell wall lysis (Hugo & Russel 1998). Some properties of phenolic compounds, such as low surface tension (Naumovich 1963) and lipid solubility (O’Connor & Rubino 1991), confer a high penetrability and spreading of the medicament. Thus, the calcium hydroxide/CMCP mixture possesses a high radius of action, eliminating bacteria located in regions more distant from the vicinity where the paste was applied (Siqueira 1997).

Alencar et al. (1997) have determined the presence of MCP in calcium hydroxide/MCP paste after its use for 2, 4, 7, and 14 days as intracanal dressing in dogs. Their results showed a MCP loss of approximately 50% in the dressing after 48 h, with no further significant loss after longer periods. This finding indicates that the effects of MCP may persist in the root canal for at least 14 days.

Endodontic infections are polymicrobial and no medicament is effective against all the bacteria found in infected root canals. Combination of two medicaments may produce additive or synergistic effects. Evidence suggests that the association of calcium hydroxide with CMCP has a broader antibacterial spectrum, a higher radius of antibacterial action, and kills bacteria faster than mixtures of calcium hydroxide with inert vehicles. Therefore, CMCP cannot be considered a vehicle for calcium hydroxide, but an additional medicament.

Although CMCP has strong cytotoxic activities (Spangberg et al. 1979), studies have reported a favorable tissue response to calcium hydroxide/CMCP mixtures (Torneck et al. 1973, Holland et al. 1979). This association probably owes its biocompatibility to:

1. the small concentration of released paramono-chlorophenol (MCP). Calcium hydroxide plus CMCP yields calcium paramonochlorophenolate, which is a weak salt that progressively releases MCP and hydroxyl ions to the surrounding medium (Anthony et al. 1982). It is well known that a substance may have either beneficial or deleterious effects, depending on its concentration. The low release of MCP from the paste might not be sufficient to have cytotoxic effects.

2. denaturing effect of calcium hydroxide on connective tissue, which may prevent the tissue penetration of MCP, reducing its toxicity (Siqueira 1997).

3. the fact that the effect on periradicular tissues is probably associated with the antimicrobial effect of the paste, which allows natural healing to occur without persistent infectious irritation. If the wound area is free of bacteria when the transitory chemical irritation occurs, there is no reason to believe that tissue repair would not take place as the initial chemical irritant decreases in intensity.

Since released MCP is sufficient to exercise excellent antibacterial activity, and because MCP does not possess selective toxicity to microorganisms, it is quite acceptable that the second and/or the third hypothesis are correct.

**Physical barrier**

In addition to eliminating remaining viable bacteria unaffected by the chemomechanical preparation of the root canal, intracanal medicaments have been advocated for other reasons. They should also act as a physicochemical barrier, precluding the proliferation of residual microorganisms and preventing the reinfection of the root canal by bacteria from the oral cavity (Siqueira 1997).

Intracanal medicaments may prevent the penetration of bacteria from saliva in the root canal basically in two ways. First, medicaments possessing antibacterial properties may act as a chemical barrier against leakage by killing bacteria, thereby preventing their ingress into the root canal. The root canal system can become recontaminated when the number of bacterial cells exceeds the antibacterial activity of the medicament. In addition, saliva dilutes the medicament and may neutralize its effects, allowing the invasion of microorganisms. Secondly, medicaments that fill the entire length of the root canal act as a physical barrier...
Calcium hydroxide has a great value in endodontics, being indicated for several clinical conditions. However, it is not a panacea (Foreman & Barnes 1990). Calcium hydroxide has a limited antibacterial spectrum that does not affect all members of the endodontic microbiota. In addition, physicochemical properties of this substance may limit its effectiveness in disinfecting the entire root canal system after a short-term use. Further scientific investigation is required to elucidate its antimicrobial effectiveness and mechanisms inside the root canal system, as well as the need to associate it with other medicaments.

Conclusions

Calcium hydroxide has a great value in endodontics, being indicated for several clinical conditions. However, it is not a panacea (Foreman & Barnes 1990). Calcium hydroxide has a limited antibacterial spectrum that does not affect all members of the endodontic microbiota. In addition, physicochemical properties of this substance may limit its effectiveness in disinfecting the entire root canal system after a short-term use. Further scientific investigation is required to elucidate its antimicrobial effectiveness and mechanisms inside the root canal system, as well as the need to associate it with other medicaments.

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