The Ledermix Materials: Fact or Fiction?

Hosted by: Prof. Paul V. Abbott AO, BDSc, MDS, FRACDS(Endo), FPFA, FADI, FICD, FACD, FIADT
Endodontist

Introduced by David Redmayne Ozdent, C.E.O.
The Ledermix Materials – Fact or Fiction?

Scientifically-based Indications for Their Use in Everyday Dentistry

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The Ledermix Materials - Fact or Fiction?

Scientifically-based Indications for Their Use in Everyday Dentistry
Declaration

Prof. Abbott occasionally acts as a paid Scientific Advisor for OzDent Pty Ltd.

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Background Information

- **Ledermix Paste**
  - Developed in 1960 (by Prof. André Schroeder)
  - Commercially available since 1962
  - 59 years of research and clinical use!

- **Ledermix Cement**
  - Developed in 1962
Corticosteroids first used in Endodontics to treat acute apical periodontitis by flushing the canal with hydrocortisone – with “prompt relief of pain” (Wolfsohn 1954)

Use of a corticosteroid:antibiotic mixture was reported – “sensitivity to percussion and swelling were reduced dramatically” (Schroeder & Triadan 1961)
The Ledermix Story

- Many other clinical reports for treating *apical periodontitis*
  - Schroeder (1962, 1965); Ehrmann (1964, 1965, 1972); Olsen (1966); Baume (1968); Schneider (1968); Laws (1969); Erasquin (1972); Barker & Lockett (1971, 1972)

- And histological reports:
  - Schroeder (1962); Barker & Lockett (1971); Erasquin (1972)
Clinical and histological studies done – for pulpitis:

- Initially used hydrocortisone
- Then used triamcinolone
  - A more potent CS
- Combined with: chloramphenicol and xylocaine
  - In an ointment base
Procedure (Schroeder):

- Remove ALL caries
- Mix the CS:AB paste into a cotton pledget
- Apply to the pulp
- Close the cavity with ZO-E
- One week later - remove the pledget
- Replace with a hard setting capping cement
  ➔ e.g. Ca(OH)$_2$
- Restore the tooth

Schroeder 1981
The Ledermix Story

 Schroeder and Triadan reported outcomes for 200 teeth:

- Pain disappeared within 2-3 hours
  - Even when suppurative pulpitis

- Majority of pulps remained healthy
  - Only the suppurative cases needed further treatment (i.e. root canal treatment)
The Ledermix Story

- Initially: Triamcinolone + Chloramphenicol + Xylocaine
- In 1962 - Schroeder reported no need to include Xylocaine
- In 1962 - Ledermix was made commercially
  - **BUT** - the antibiotic component was changed to Demeclocycline
    - For commercial reasons by (Lederle Pharmaceuticals)
The Ledermix Story

- Schroeder noted direct pulp capping materials should be:
  - Dentinogenic, anti-bacterial and anti-inflammatory
- No single material is likely to have all these properties
- Therefore, he said it is “appropriate to combine materials”
- He used:
  - CS:AB - anti-inflammatory and antibacterial properties
  - Ca(OH)$_2$ - dentinogenic properties and anti-bacterial
  - ZO-E - anti-inflammatory and anti-bacterial
 Schroeder further stated that the CS has two main goals:

1. Prevent acute exacerbation of already inflamed tissues
2. Prevent the necrosis caused by Ca(OH)$_2$

And the ZO-E does not affect the Ca(OH)$_2$

Whereas $\text{Zn}_3(\text{PO}_4)_2$ is acidic and may neutralise the Ca(OH)$_2$, making it less effective
The Ledermix Story

- So ... Schroeder then mixed equal volumes of Ledermix paste with Ca(OH)$_2$ powder and applied as a pulp cap
  - After removing ALL caries
    - The first use of a 50:50 mixture !!!
- Then he placed ZO-E
  - As a hard setting base
- And restored the tooth at the same appointment
The Ledermix Story

- So ... Schroeder then mixed equal volumes of Ledermix paste with Ca(OH)$_2$ powder and applied as a pulp cap.

- **Excellent results were reported !!!**
  - Rapid pain relief
  - *Pulps had survived when reviewed*
    - *With pulp tests, radiographs, etc.*
The Ledermix Story

- Histological evidence of good healing and repair
  - No inflammation in the pulp
  - Some with tertiary dentine formation

Schroeder 1981

In Humans
The Ledermix Story

- Histological evidence of good healing and repair
  - No inflammation in the pulp
  - Some with tertiary dentine formation

Schroeder 1981
The Ledermix Story

- Then in 1962, Schroeder developed a hard setting cement
  - Same active substances as the paste
    - Triamcinolone and Demeclocycline
  - But at lower concentrations - 0.67% and 2%
  - And combined them with ZO-E and Ca(OH)$_2$

- The rationale was to:
  - Avoid the need for two appointments
  - Achieve all desired therapeutic aims with one material
  - Have a hard setting compound - ease of use
    - can restore immediately
The Ledermix Story

✓ Hence: **Ledermix Cement** was manufactured
The Ledermix Story

- BUT - the Ledermix products were controversial
- Opposition from various people - esp. in the USA
- Some of the concerns were:
  - Systemic side effects of steroids
  - Inability of steroids to stimulate calcific repair
  - Steroids lead to chronic inflammation and/or pulp necrosis
  - Development of tetracycline-resistant micro-organisms
  - Development of hypersensitivity reactions to tetracyclines
  - More specific anti-microbial agents may be available
The Ledermix Story

- Often claimed that Ledermix is "banned in the USA"
  - I still OFTEN hear this today!!!

- This is "FAKE NEWS" !!!!
  - It has NEVER been banned
The Ledermix Story

- The **TRUTH** is:
  - Lederle Pharmaceuticals have **NEVER** submitted the Ledermix products to the FDA for approval
  - This was a financial decision
    - In 1994 - Ledermix was a $500,000 per year product
    - Compared to their other drugs - worth $$Billions
    - They did not want to invest in the process for what they perceived was a small market
      - Despite me trying to persuade them!!
Some of the concerns were:

- **Systemic side effects of steroids**
- Inability of steroids to stimulate calcific repair
- Steroids lead to chronic inflammation and/or pulp necrosis
- Development of tetracycline-resistant micro-organisms
- Development of hypersensitivity reactions to tetracyclines
- More specific anti-microbial agents may be available
The Ledermix Story

? Systemic side effects of steroids

- **Abbott** - *Int Endod J 1992; 25: 189-191*
  - Showed insufficient steroid amounts used
  - Insufficient steroid released systemically to have any potential for systemic side effects
  - Compared with endogenous steroid in humans
    - Normal and under stress
# The Ledermix Story

## Table 1. Summary of corticosteroid details

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous cortisol in humans</td>
<td>20–30 mg day⁻¹</td>
</tr>
<tr>
<td>Cortisol in ‘stress situations’</td>
<td>300–400 mg day⁻¹</td>
</tr>
<tr>
<td>Cortisol:triamcinolone potency</td>
<td>1:5</td>
</tr>
</tbody>
</table>

## Table 2. Summary of calculations

<table>
<thead>
<tr>
<th></th>
<th>Ledermix cement</th>
<th>Ledermix paste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum amount of Ledermix used in</td>
<td>&lt;100</td>
<td>76.84</td>
</tr>
<tr>
<td>tooth (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum amount of triamcinolone in</td>
<td>0.37</td>
<td>0.8</td>
</tr>
<tr>
<td>tooth (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cortisol equivalent) (mg)</td>
<td>(1.85)</td>
<td>(4.0)</td>
</tr>
<tr>
<td>Triamcinolone released after 1 day</td>
<td>0.26</td>
<td>0.24</td>
</tr>
<tr>
<td>(mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cortisol equivalent) (mg)</td>
<td>(1.3)</td>
<td>(1.2)</td>
</tr>
</tbody>
</table>
The Ledermix Story

- Some of the concerns were:
  - Systemic side effects of steroids
  - Inability of steroids to stimulate calcific repair
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  - Development of tetracycline-resistant micro-organisms
  - Development of hypersensitivity reactions to tetracyclines
  - More specific anti-microbial agents may be available
The Ledermix Story

? Inability of steroids to stimulate calcific repair

- Mixed reports from histological studies
  - Schroeder 1981
The Ledermix Story

- **Typical healing response - Ledermix Cement**


  ➔ Normal pulp tissue in contact with the cement
  ➔ No inflammatory cells
  ➔ Occasionally diffuse calcifications in the pulp
  ➔ Occasionally a dentine bridge forms
The Ledermix Story

**Inability of steroids to stimulate calcific repair**

- Mixed reports
- **BUT** - the question should be:

  *Does it matter if a dentine bridge forms or not??*
The Ledermix Story

What does a dentine bridge do?

- It just makes dentists “feel good” !!
  ➔ Because we have traditionally been taught that a bridge is essential to indicate healing .... more FAKE NEWS !!!

- Indicates the pulp has been irritated and stimulated
  ➔ But this is not essential for healing

- Dentine bridge provides NO protection for the pulp in the future
  ➔ Porous, lacks usual structure
  ➔ Even normal dentine does not prevent bacterial penetration
  ➔ Once bacteria reach the bridge - it is TOO LATE !!!
The Ledermix Story

Some of the concerns were:

- Systemic side effects of steroids
- Inability of steroids to stimulate calcific repair
- Steroids lead to chronic inflammation and/or pulp necrosis
- Development of tetracycline-resistant micro-organisms
- Development of hypersensitivity reactions to tetracyclines
- More specific anti-microbial agents may be available
The Ledermix Story

? Steroids lead to chronic inflammation and/or pulp necrosis

- NOT supported by clinical and histological studies
  - Schroeder 1981
  - And many others
The Ledermix Story

- Some of the concerns were:
  - Systemic side effects of steroids
  - Inability of steroids to stimulate calcific repair
  - Steroids lead to chronic inflammation and/or pulp necrosis
  - Development of tetracycline-resistant micro-organisms
  - Development of hypersensitivity reactions to tetracyclines
  - More specific anti-microbial agents may be available
The Ledermix Story

Development of tetracycline-resistant micro-organisms

- **NO** reports in the literature after 58 years of use in many countries throughout the world

- During root canal treatment, do not rely on one medicament
  - Recommendations are to use Ca(OH)$_2$ as a subsequent dressing in all infected canals before doing the root canal filling
    - if Ledermix paste is used initially
  - Ca(OH)$_2$ has broader anti-bacterial spectrum of activity
    - will destroy any remaining bacteria
  - Hence, if resistance does occurs, Ca(OH)$_2$ will counteract it
The Ledermix Story

Some of the concerns were:

- Systemic side effects of steroids
- Inability of steroids to stimulate calcific repair
- Steroids lead to chronic inflammation and/or pulp necrosis
- Development of tetracycline-resistant micro-organisms
- Development of hypersensitivity reactions to tetracyclines
- More specific anti-microbial agents may be available
The Ledermix Story

Development of hypersensitivity reactions to tetracyclines

- Allergy to tetracycline is extremely rare
- Only two cases reported over 58 years of use
  1. Letter to Editor - *BDJ* 2013 - very little detail given
  2. Case report
     - Kaufman, Solomonov, Galieva, Abbott
     - *Int Endo J* 2014; 47: 1090-1097.
     - Confirmed tetracycline allergy via skin tests
     - Patient recovered when Ledermix removed from the tooth
The Ledermix Story

- Some of the concerns were:
  - Systemic side effects of steroids
  - Inability of steroids to stimulate calcific repair
  - Steroids lead to chronic inflammation and/or pulp necrosis
  - Development of tetracycline-resistant micro-organisms
  - Development of hypersensitivity reactions to tetracyclines
  - More specific anti-microbial agents may be available
More specific anti-microbial agents may be available

- Ehrmann (1981) stated inclusion of a tetracycline was “most unfortunate”
  - Believed a bacteriocidal agent is better than a bacteriostatic agent
    - However it is not essential to kill all bacteria
    - As long as they cannot reproduce, they will not survive
    - Other treatment strategies should also be used to make the environment within the root canal system unfavourable for bacterial survival
      - e.g. remove caries, cracks, restorations, etc.
The Ledermix Story

? More specific anti-microbial agents may be available

- Many other antibiotics have been suggested and/or tested
  - None have proven to be any better in the root canal system
- All AB’s have limited spectrum of activity
  - Root canal infections are multi-species
- Need caution:
  - Resistance more common as other AB’s are more commonly used systemically for many conditions
  - Allergy to penicillins preclude their use
More specific anti-microbial agents may be available

- There is no “perfect” antibiotic
- During root canal treatment, must not rely on one medicament
  - Recommendations are to use Ca(OH)\(_2\) as a subsequent dressing in all infected canals before doing the root canal filling
  - if Ledermix paste is used initially
  - Ca(OH)\(_2\) has broader anti-bacterial spectrum of activity
  - will destroy any remaining bacteria
  - Hence, if resistance does occurs, Ca(OH)\(_2\) will counteract it
The Ledermix Story

? More specific anti-microbial agents may be available

- Ehrmann (1981) stated inclusion of a tetracycline was “most unfortunate”

- However, subsequent studies on resorption have shown the choice of a tetracycline was actually **VERY FORTUNATE** !!
  - Due to tetracycline’s ability to inhibit clastic cells
  - Especially useful for inflammatory resorption
    -> Prevention and Interceptive treatment
The Ledermix Story

Some of the concerns were:

- Systemic side effects of steroids
- Inability of steroids to stimulate calcific repair
- Steroids lead to chronic inflammation and/or pulp necrosis
- Development of tetracycline-resistant microorganisms
- Development of hypersensitivity reactions to tetracyclines
- More specific antimicrobial agents may be available

NONE of these concerns were valid in the 1960's ... and they are still NOT valid today !!!
Ledermix Cement

Schroeder (1962)

- **C-st**: Triamcinolone - 0.67 %
- **Ab**: Demeclocycline - 2.0 %
- Calcium hydroxide - 33.4 %
- Zinc oxide - 47.2 %
- **Eugenol** - 85% of the liquid

⇒ Forms a hard-setting cement when mixed
Ledermix Cement

- Triamcinolone
  - Anti-inflammatory agent
    - In vitro - 70% is released by the end of day 1
    - Rest by the end of day 3 (Hume & Kenney - JoE 1981)
Ledermix Cement

- Triamcinolone
  - Anti-inflammatory agent
    - *In vitro* - 70% is released by the end of day 1
    - Rest by the end of day 3 (Hume & Kenney - JoE 1981)
  - Expect this to be much faster when *In Vivo*
    - i.e. *In a tooth with pulp blood flow*
    - *Due to the dynamics of diffusion and clearance*
  - *Hence: there is only a very short term application of triamcinolone*

- Calcium hydroxide - 33.4%
- Zinc oxide-eugenol - 47.2%
Ledermix Cement

- **Triamcinolone**
  - **Hence:** *there is only a very short term application of triamcinolone*
  - *There is NO evidence that it causes pulp necrosis without symptoms*
    - A long held misconception about Ledermix Cement
    - Arise from inappropriate use, lack of diagnosis, poor understanding of disease processes, poor understanding of pharmacodynamics of CS, misconceptions about CS, unrealistic expectations of the material, etc.

- **Calcium hydroxide** - 33.4%
- **Zinc oxide-eugenol** - 47.2%
Ledermix Cement

- Triamcinolone
  - Anti-inflammatory agent (1-3 days maximum effect)

- Calcium hydroxide
  - Promotes dentine repair (numerous studies)

- Zinc oxide - Eugenol
  - Anti-inflammatory and anti-bacterial

- Triamcinolone - 0.67 %
- Calcium hydroxide - 33.4 %
- Zinc oxide-eugenol - 47.2 %
Typical healing response - Ledermix Cement

Robertson 1977
Human Pulp Reactions to a Glucocorticosteroid-Antibiotic Compound

- Typical healing response with Ca(OH)$_2$

(Schroeder 1981)

- Necrosis
- Calcified tissue
- Dentine bridge
Typical healing response with Ca(OH)$_2$

(Schroeder 1981)

- Necrosis
- Calcified tissue
- Dentine bridge
- Typical healing response with Ca(OH)$_2$ (Schroeder 1981)

- Dentine “bridge” forms below the exposure site
- The necrotic layer manifests as a “hole” if the tooth is re-entered later
Predictable Management of Cracked Teeth with Reversible Pulpitis

Abbott PV, Leow N.

85 teeth - Reversible pulpitis symptoms resolved

Ledermix Cement

- Immediately ................. 71 %
- 1 day ................................ 21 %
- 2 days .............................. 6 %
- 3 days .............................. 3 %

100 %
Summary

85 teeth managed conservatively with Ledermix Cement & GIC interim restoration

- Pulp recovered ...................... 80 teeth (94.0%)
- Pulpitis continued ................ 1 tooth (1.2%)
- Pulp necrosis at 3 mths .......... 1 tooth (1.2%)
- Pulp status uncertain .......... 1 tooth (1.2%)
- Pulpitis after core ............. 2 teeth (2.4%)
Ledermix Cement - Partial Pulpotomy

Tooth 11

1 month
12 months
2 years
3 years
What materials can / should we use?

**CHOICES:**

1. Corticosteroid / Antibiotic cement
2. Calcium hydroxide
3. Bioceramic materials (e.g. MTA, Biodentine, etc)
Ledermix Cement

✓ Meets the THREE criteria required for an ideal pulp capping and pulpotomy material (Schroeder 1962, 1981)

- Anti-inflammatory
  - Triamcinolone (CS)

- Anti-bacterial
  - ZO-Eugenol
  - Demeclocycline (AB)

- Dentinogenic
  - Ca(OH)$_2$
36: Pulpless, infected root canal system with chronic apical periodontitis due to breakdown of the restoration

37: Acute irreversible pulpitis due to restoration breakdown and caries
Ledermix Paste

- Triamcinolone - 1%
- Demeclocycline - 3%

In a water soluble paste of:

- Triethanolamine NF
- Calcium chloride USP
- Zinc oxide
- Sodium sulphite (anhydrous)
- Polyethylene glycol 4,000 USP
- Distilled water
Leadmix paste - Release and diffusion through dentine

Abbott PV, Hume WR, Heithersay GS.

*Endod Dent Traumatol*
- 1988; 4: 55-62
- 1989; 5: 92-7
- 1989; 5: 98-104
- 1989; 5: 188-92
Ledermix paste – Release and Diffusion  
*Abbott et al. EDT 1988, 1989*
Initially: Very rapid release
Then: Slow, steady release
Therapeutic amounts up to ~6 weeks
No further release by 3 months

Rate of Release

Ledermix paste – Release and Diffusion

Abbott et al  EDT 1988, 1989

Therapeutic Level

6 weeks

Fully Developed Roots

Time (Log scale)
Triamcinolone (Corticosteroid)

- Measured peri-radicular concentration
  - Detected in the nanomolar range
- Sufficient for anti-inflammatory action

Ledermix paste – Release and Diffusion  
Abbott et al  
EDT 1988, 1989
Concentrations of Demeclocycline in root dentine after Ledermix paste has been applied within the root canal.
Why Use Medicaments?

- Anti-bacterial action
  - Residual bacteria in canals, tubules, fins, etc
  - Contaminants between visits
  - Periapical region
  - Periodontal tissues
- Reduce periapical inflammation
- Prevent or reduce pain
- Stimulate periapical repair
- Prevent or inhibit inflammatory resorption
Why Use Medicaments?

- **Anti-bacterial action**
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  - Periodontal tissues
- **Reduce periapical inflammation**
- **Prevent or reduce pain**
- **Stimulate periapical repair**
- **Prevent or inhibit inflammatory resorption**
The relationship of intracanal medicaments to postoperative pain in endodontics

Int Endod J 2003; 36: 868-875

School of Dental Science, Faculty of Medicine, Dentistry and Health Sciences. The University of Melbourne, 711 Elizabeth Street, Melbourne, Victoria, 3000, Australia

- 223 teeth - infected root canals with acute apical periodontitis
- Root canals instrumented “to the apices”
  - 1% NaOCl + 15% EDTAC
- Ledermix paste, Ca(OH)₂ or no dressing
- Pain scores: Pre-op and for next 4 days
Ledermix group: Significantly less post-operative pain than the Ca(OH)$_2$ group and the control group.
Ledermix group: Significantly less post-operative pain than the Ca(OH)$_2$ group and the control group

- Started with higher average pre-op. pain score
- At the 4 hours post-operative interval:
  - The greatest effect was noted
  - Pain level was well below the other groups
- Pain level remained well below the other medicaments for the next 4 days
Post-op Pain + Medicaments  Ehrmann et al - IEJ  2003

Average Pain Scores

Ca(OH)₂ No Medic Ledermix
Post-op Pain + Medicaments  Ehrmann et al - IEJ  2003

Average Pain Scores

Ledermix paste
No Medicament
Ca(OH)₂

No Medicament
Ca(OH)₂
Ledermix paste
CONCLUDED: Ledermix paste is an effective intracanal medicament for the control of post-operative pain associated with acute apical periodontitis

“The rapidity of action of the medicament with corticosteroid was striking”
Why Use Medicaments?

- Anti-bacterial action
  - Residual bacteria in canals, tubules, fins, etc
  - Contaminants between visits
  - Periapical region
  - Periodontal tissues
- Reduce periapical inflammation
- Prevent or reduce pain
- Stimulate periapical repair
- Prevent or inhibit inflammatory resorption
The effect of an antibiotic/corticosteroid paste on inflammatory root resorption in vivo

Pierce A, Lindskog S.

RESULTS ( % of root surface )

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal PDL</td>
<td>0</td>
</tr>
<tr>
<td>Inflammation in PDL</td>
<td>8.0</td>
</tr>
<tr>
<td>Surface resorption</td>
<td>0 + 89.3</td>
</tr>
<tr>
<td>Inflammatory resorption</td>
<td>89.3</td>
</tr>
<tr>
<td>Ankylosis (replacement resorption)</td>
<td>2.7</td>
</tr>
</tbody>
</table>
## RESULTS (% of root surface)

<table>
<thead>
<tr>
<th>Condition</th>
<th>No Medicm</th>
<th>Ledermix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal PDL</td>
<td>0</td>
<td>6.9</td>
</tr>
<tr>
<td>Inflammation in PDL</td>
<td>8.0</td>
<td>0</td>
</tr>
<tr>
<td>Surface resorption</td>
<td>0</td>
<td>25.1</td>
</tr>
<tr>
<td>Inflammatory resorption</td>
<td>89.3</td>
<td>0</td>
</tr>
<tr>
<td>Ankylosis (replacement resn)</td>
<td>2.7</td>
<td>68.0</td>
</tr>
</tbody>
</table>

Bench-dried for 1 hour before replanting
CS-Ab Paste & Inflammatory Resorption

Pierce & Lindskog OS:OM:OP 1987

No Medicament

Ledermix paste
Evidence for direct inhibition of dentinoclasts by a corticosteroid / antibiotic endodontic paste

Pierce A, Heithersay G, Lindskog S.

Direct inhibition of dentinoclasts by a CS-Ab paste
Pierce et al  EDT 1988; 4: 44-5

- Dentinoclasts isolated from rat teeth undergoing inflammatory root resorption

- Exposed to:
  - Demeclocycline, or
  - Ledermix paste
Direct inhibition of dentinoclasts by a CS-Ab paste
Pierce et al  EDT 1988; 4: 44-5

- **Demeclocycline**
  - Cells well-spread
  - Still attached after 24 hrs

- **Ledermix paste**
  - Cells not spreading
  - More spherical shaped
  - No dentinoclasts evident after 18 hours
Direct inhibition of dentinoclasts by a CS-Ab paste
Pierce et al  *EDT* 1988; 4: 44-5

- Results suggest that the steroid component of Ledermix paste has a direct inhibitory effect on resorbing cells
  - Consistent with the effects of steroids on osteoclasts
    - Suda *et al* 1983

- The antibiotic component also contributes to the therapeutic effect on inflammatory resorption by eliminating bacteria from the canal and from the tubules
Non-antimicrobial properties of tetracyclines

Vernillo et al - Curr Opin Perio 1994; 2: 111-8

Tetracyclines modulate host responses

- Inhibit osteoclast function
  - Synthetic tetracyclines are more potent than tetracycline

- Bind to bone and teeth
  - Slows release, prolongs action
Consistent with animal studies using TETRACYCLINES

- Sae-Lim *et al* 1998
  - Inflammatory resorption model in dogs
  - Tetracycline better than amoxicillin and control (no AB)

- Sae-Lim *et al* 1998
  - Replacement resorption model in dogs
  - Tetracycline better than amoxicillin and control (no AB)

- Cvek *et al* 1990
  - Topical doxycycline on replanted monkey teeth
  - Tetracycline reduced ankylosis, replacement resorption and inflammatory resorption
Consistent with animal studies using CORTICOSTEROIDS

- Sae-Lim et al. 1998
  - Replacement resorption model in dogs
  - Topical dexamethasone better than systemic dexamethasone and control (Viaspan)

- Chen et al. 2005
  - Replacement and Inflammatory resorption model in dogs
  - Immediate endodontic treatment
  - Triamcinolone alone better than tetracycline alone
  - Ledermix paste better overall
Effect of immediate intracanal placement of Ledermix paste on healing of replanted dog teeth after extended dry times

Bryson E, Levin L, Banchs F, Abbott P, Trope M.

Dent Traumatol 2002; 18: 316-21
Immediate Placement of Ledermix Paste –v– Ca(OH)$_2$

Bryson, Levin, Banchs, Abbott & Trope Dent Traumatol 2002

- Teeth extracted, left dry for 1 hour, replanted
- Canals cleaned and filled with:
  - Ledermix paste
  - Ca(OH)$_2$ paste
- Examined histologically after 4 months for:
  - Inflammatory & replacement resorption
  - Residual root mass
**Immediate Placement of Ledermix Paste –v– \( \text{Ca(OH)}_2 \)**

Bryson, Levin, Banchs, Abbott & Trope *Dent Traumatol* 2002

<table>
<thead>
<tr>
<th></th>
<th>No Resorption</th>
<th>Inflm + Replm Resn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledermix</strong></td>
<td>59 %</td>
<td>41 %</td>
</tr>
<tr>
<td><strong>Ca(OH)_2</strong></td>
<td>14 %</td>
<td>86 %</td>
</tr>
</tbody>
</table>

* Significant difference for all criteria
**Immediate Placement of Ledermix Paste -v- Ca(OH)$_2$**

Bryson, Levin, Banchs, Abbott & Trope *Dent Traumatol* 2002

<table>
<thead>
<tr>
<th></th>
<th>No Resorption</th>
<th>Infl$^m$ + Repl$^m$ Res$^n$</th>
<th>Residual Root Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ledermix</strong> *</td>
<td>59 %</td>
<td>41 %</td>
<td>81 %</td>
</tr>
<tr>
<td><strong>Ca(OH)$_2$</strong></td>
<td>14 %</td>
<td>86 %</td>
<td>13 %</td>
</tr>
</tbody>
</table>

* Significant difference for all criteria
“Teeth immediately treated with **Ledermix** exhibited **significantly more healing**, **less resorption** and **maintained more residual root mass** than those treated with **Ca(OH)\(_2\)**.”
Why Use Medicaments?

- Anti-bacterial action
  - Residual bacteria in canals, tubules, fins, etc
  - Contaminants between visits
  - Periapical region
  - Periodontal tissues
- Reduce periapical inflammation
- Prevent or reduce pain
- Stimulate periapical repair
- Prevent or inhibit inflammatory resorption
Limitations of Ledermix Paste

- Anti-bacterial action is limited
  - Compare AB concentrations in the dentine with the MIC$_{100}$ values for the commonly found bacteria in infected root canal systems
### MIC\textsubscript{100} values for demeclocycline and common endodontic microbes

<table>
<thead>
<tr>
<th>Organism</th>
<th>Micrograms / ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. fragilis</td>
<td>128</td>
</tr>
<tr>
<td>B. oralis</td>
<td>128</td>
</tr>
<tr>
<td>B. melaninogenicus</td>
<td>64</td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td>64</td>
</tr>
<tr>
<td>Veillonella</td>
<td>64</td>
</tr>
<tr>
<td>Eubacterium</td>
<td>64</td>
</tr>
<tr>
<td>Propionibacterium</td>
<td>32</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>32</td>
</tr>
<tr>
<td>Streptococci (aerobic)</td>
<td>32</td>
</tr>
<tr>
<td>Actinomyces</td>
<td>16</td>
</tr>
<tr>
<td>Fusobacterium necrophorum</td>
<td>16</td>
</tr>
<tr>
<td>Fusobacterium nucleatum</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Ledermix paste - Diffusion**  
Abbott et al  *EDT* 1988, 1989
Limitations of Ledermix Paste

- **Anti-bacterial action is limited**
  - Compare AB concentrations in the dentine with the MIC\(_{100}\) values
  - **Within the canal**
    - Excellent levels of AB
  - **Within dentine**
    - Adjacent to canal: Reasonable
    - Periphery: Insufficient
  - **Within peri-radicular tissues**
    - Insufficient to be predictable
Limitations of Ledermix Paste

- Anti-bacterial action is limited
- Increasing order of anti-bacterial effectiveness:
  - Ledermix < Ledermix / Ca(OH)$_2$ < Ca(OH)$_2$

Athanassiadis, Abbott, George, Walsh

Endodontic Medicaments
Endodontic Medicaments

Abbott PV.

Australian Dental Journal

Literature Review → 1990; 35: 438-48

Guidelines for Clinical Use → 1990; 35: 491-6
Endodontic Medicaments

Choices:

- Corticosteroid / antibiotic - CS / AB
  - e.g. Ledermix paste

- Calcium hydroxide - Ca(OH)$_2$
  - e.g. Calasept Plus paste, Calmix

- 50:50 mixture - CS / AB + Ca(OH)$_2$
  - e.g. Ledermix + Calasept Plus pastes
Endodontic Medicaments

Major Functions and Choices:

- **Anti-inflammatory**
  - Ledermix paste
    - e.g. Irreversible Pulpitis
    - Acute Ap. Periodontitis

- **Anti-bacterial**
  - Ledermix paste
  - Calcium hydroxide - Ca(OH)$_2$
    - e.g. RCF + infected RCS
    - Pulpless, infected RCS

- **Stimulate hard tissue repair**
  - Calcium hydroxide - Ca(OH)$_2$
    - e.g. Apexification
50:50 mix of Ledermix / Ca(OH)$_2$

- Originally used by Schroeder - 1962, 1972, 1981
- Advocated by Heithersay - 1984, 1986
- Promoted by Abbott - 1990, 1999
50:50 mix of Ledermix / Ca(OH)$_2$

- Several research papers:
  - Bhaskar et al - 1969
  - Abbott et al - *Endod Dent Trauma* 1989
  - Taylor et al - *Endod Dent Trauma* 1990
  - Cai, Abbott, Castro Salgado - *Materials* 2018
  - Cai, Abbott, Castro Salgado - *Aust Endo J* 2018
50:50 mix of Ledermix / Ca(OH)$_2$

- Slower release of Ledermix paste components
  - Dressing lasts longer than Ledermix paste used alone
    - Maintains canal sterility for longer

- No change in activity of components

- Increased anti-bacterial spectrum compared to Ledermix paste used alone

- Only a small reduction in pH levels reached in dentine

- Lower tissue toxicity
  - Compared with Ca(OH)$_2$
50:50 mix of Ledermix / Ca(OH)$_2$

- **50:50 mix of CS / AB & Ca(OH)$_2$**
  - Saline-based Ca(OH)$_2$ - e.g. Calasept Plus
    - Pre-mix on a glass slab
    - Then apply the mixture with a file or spiral filler
  
  - Methyl cellulose based / PEG Ca(OH)$_2$ - e.g. Pulpdent, Calmix
    - Place the CS / AB in the canal first (with file or spiral filler)
    - Then place the Ca(OH)$_2$ in canal - i.e. mix in the canal (with file or spiral filler)
My Typical Treatment Approach

1st Appointment
- Consult & Diagnose
- Investigate
- Negotiate Canals
- Medicate canals
- Interim Restoration

2nd Appointment
- Working Lengths
- Prepare Canals
- Re-medicate canals

3rd Appointment
- Root Canal Filling
- Refer back to Dentist

Medicaments

Irreversible Pulpitis or Elective RCT -
1. Ledermix Paste
2. Ledermix + Ca(OH)₂

Infected Canals and Apical Periodontitis -
1. Ledermix + Ca(OH)₂
2. Ca(OH)₂
Summary

- The Ledermix materials have been used extremely successfully for almost 60 years.
- Significant scientific research supports their use:
  - Clinical, radiographic, histological, humans, animals, etc.
- Major function: Anti-inflammatory
- Second function: Anti-resorption
- Third function: Anti-bacterial
- There are many mis-conceptions / perceptions:
  - It’s time for the “anti” people to move on !!!
The Ledermix Story

- Some of the concerns were:
  - Systemic side effects of steroids
  - Inability of steroids to stimulate calcific repair
  - Steroids lead to chronic inflammation and/or pulp necrosis
  - Development of tetracycline-resistant microorganisms
  - Development of hypersensitivity reactions to tetracyclines
  - More specific antimicrobial agents may be available

None of these concerns were valid in the 1960's and they are still NOT valid today!!
The Ledermix Materials - Fact or Fiction?

Scientifically-based Indications for Their Use in Everyday Dentistry