In vitro STUDIES OF THE PHARMACODYNAMICS OF THE ACTIVE COMPONENTS OF LEDERMIX PASTE, A CORTICOSTEROID-ANTIBIOTIC ROOT CANAL DRESSING MATERIAL

VOLUME II

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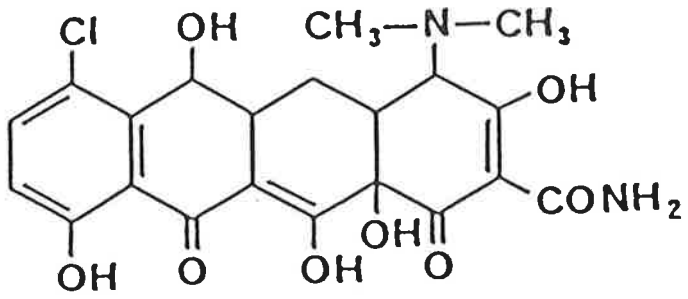
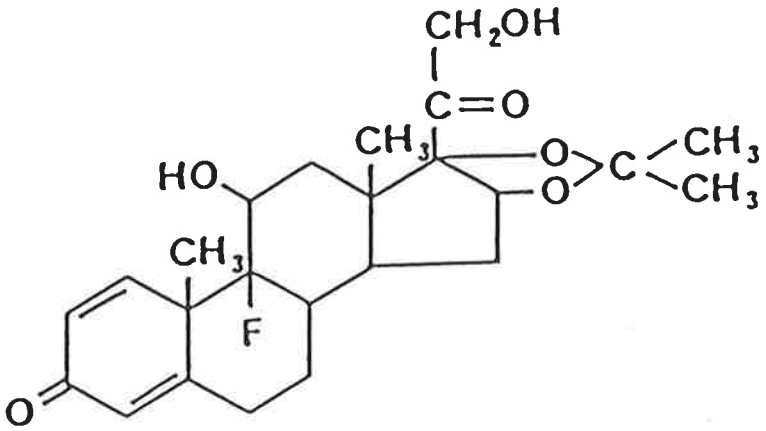
FIG.1-1: The chemical structure of triamcinolone.



9-alpha-fluoro-11-beta, 21 dihydroxy-16 alpha,
17-alpha-isopropyldenedioxy-1,4-pregnaliene-3,20 dione
Mol. Wt. 394.5

FIG.1-2: The chemical structure of demeclocycline.



7-chloro-6-demethylchlortetracycline

Mol. Wt. 464.9

TABLE 2-1 A summary of commonly reported endodontic microbes

GROUP A - ANAEROBIC BACTERIA (Obligate, non-sporulating)

i) Gram-negative rods: Bacteroides - B.oralis, B.melaninogenicus, B.fragilis, B. asaccharolyticus.

ii) Gram-negative cocci: Veilloneella, Neisseria (anaerobic).

iii) Gram-positive rods: Eubacterium - E.alactolyticum. Lactobacillus (anaerobic). Corynebacterium (anaerobic). Proprionibacterium.

iv) Gram-positive cocci: Peptostreptococcus - P.anaerobius. Peptococcus.

v) Gram stain variable: Actinomyces - A.bovus, A.israeli.

GROUP B - FACULTIVELY ANAEROBIC BACTERIA

i) Gram-negative cocci: Neisseria.

ii) Gram-positive rods: Lactobacillus (aerobic). Diptheroids - Proprionibacterium acnes.

iii) Gram-positive cocci: Streptococcus - Str.viridans, Enterococcus, Beta haemolytic strep.

GROUP C - AEROBIC BACTERIA

i) Gram-negative cocci: Neisseria (aerobic).

ii) Gram-positive rods: Corynebacterium (aerobic).

iii) Gram-positive cocci: Streptococcus - Str.salivarius, Alpha haemolytic strep., Gamma haemolytic strep.

	Penicillin V.	Ampicillin	Amoxycillin	Carbenicillin	Cephalothin	Cefamandole	Cefazaflur	Chloramphenicol	Clindamycin	Erythromycin	Tetracycline	Doxycycline	Metronidazole
Bacteroides fragilis	>256	>256	>256	>512	>512	>512	>256	32.0	8.0	64.0	128	32.0	16.0
Bacteroides melaninogenicus	32.0	4.0	8.0	8.0	32.0	8.0	64.0	4.0	0.5	1.0	64.0	64.0	4.0
Bacteroides oralis	>256	>256	128	>512	256	256	>256	128	>256	>256	128	128	>256
Fusobacterium nucleatum	4.0	32.0	2.0	8.0	1.0	0.5	0.5	2.0	0.5	64.0	0.5	0.5	4.0
Fusobacterium necrophorum	>256	>256	>256	>512	0.5	0.5	>256	2.0	0.5	32.0	16.0	8.0	1.0
Peptococcus	0.5	1.0	2.0	4.0	8.0	64.0	1.0	8.0	>256	>256	64.0	32.0	128
Peptostreptococcus	32.0	16.0	16.0	128	8.0	32.0	8.0	8.0	1.0	2.0	64.0	16.0	>256
Veillonella	8.0	>256	8.0	128	4.0	16.0	32.0	4.0	0.5	16.0	64.0	16.0	4.0
Eubacterium	8.0	2.0	0.5	32.0	32.0	32.0	64.0	4.0	2.0	0.5	64.0	16.0	>256
Proprionibacterium	2.0	0.5	1.0	32.0	1.0	0.5	64.0	8.0	0.5	1.0	32.0	32.0	>256
Actinomyces	0.5	-	0.5	0.5	-	-	0.5	8.0	0.5	-	16.0	4.0	>256
Lactobacillus	2.0	32.0	2.0	16.0	0.5	4.0	64.0	16.0	64.0	>256	32.0	16.0	>256
Streptococci (aerobic)	16.0	0.5	16.0	128	0.5	0.5	>256	8.0	8.0	0.5	32.0	8.0	>256

Table 2-2: MIC_{100} values of commonly reported endodontic bacteria for some antibiotic agents.

MIC's expressed as micrograms/millilitre.

(from Sutter and Finegold, 1976).

Table 2-3: Percent diffusional surface areas of differently-treated dentine surfaces (from Pashley et al, 1978a).

DENTINE SURFACE	TRITIATED WATER (per cent)	131 I-ALBUMIN (per cent)
Highly-polished	1.72	0.74
Bur-roughened	1.86	0.68
Acid-etched	7.89	6.3
Oxalate-treated	2.24	1.44

FIG. 4-1: Plastic root canal model in vial.

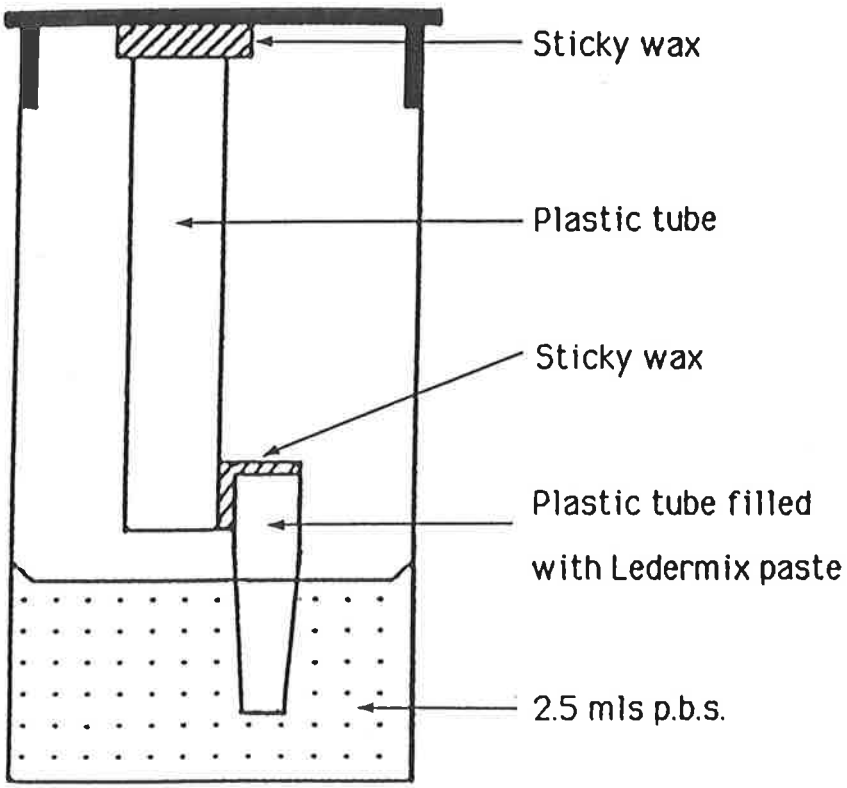


FIG. 4-2: Prepared tooth with apical foramen sealed.

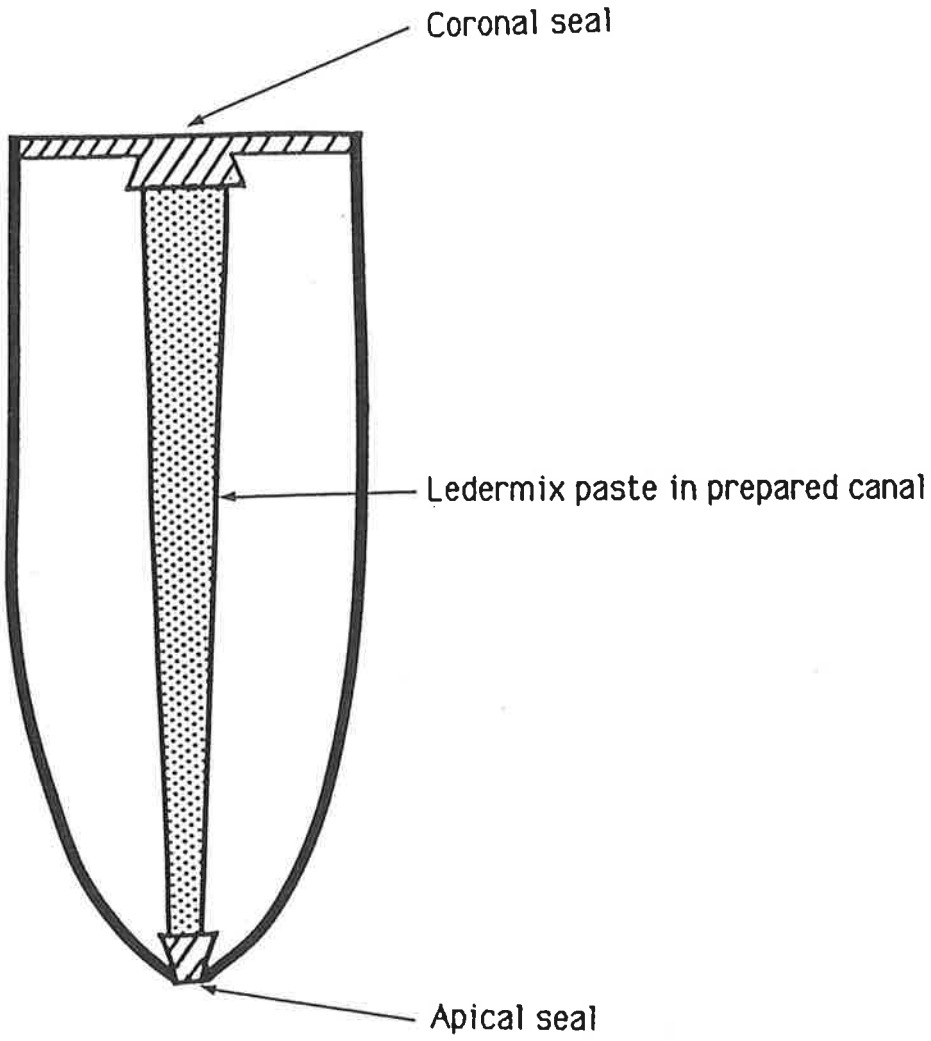


FIG. 4-3: Prepared tooth in vial.

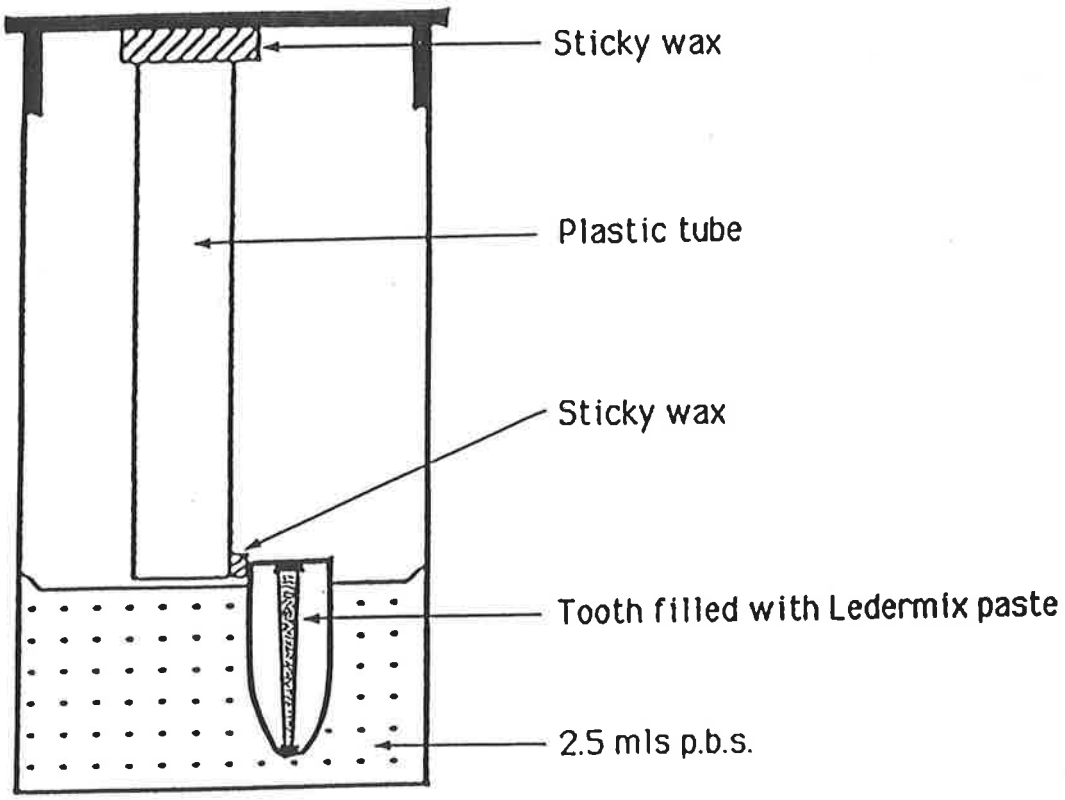


FIG. 4-4: Prepared tooth with apical foramen unsealed.

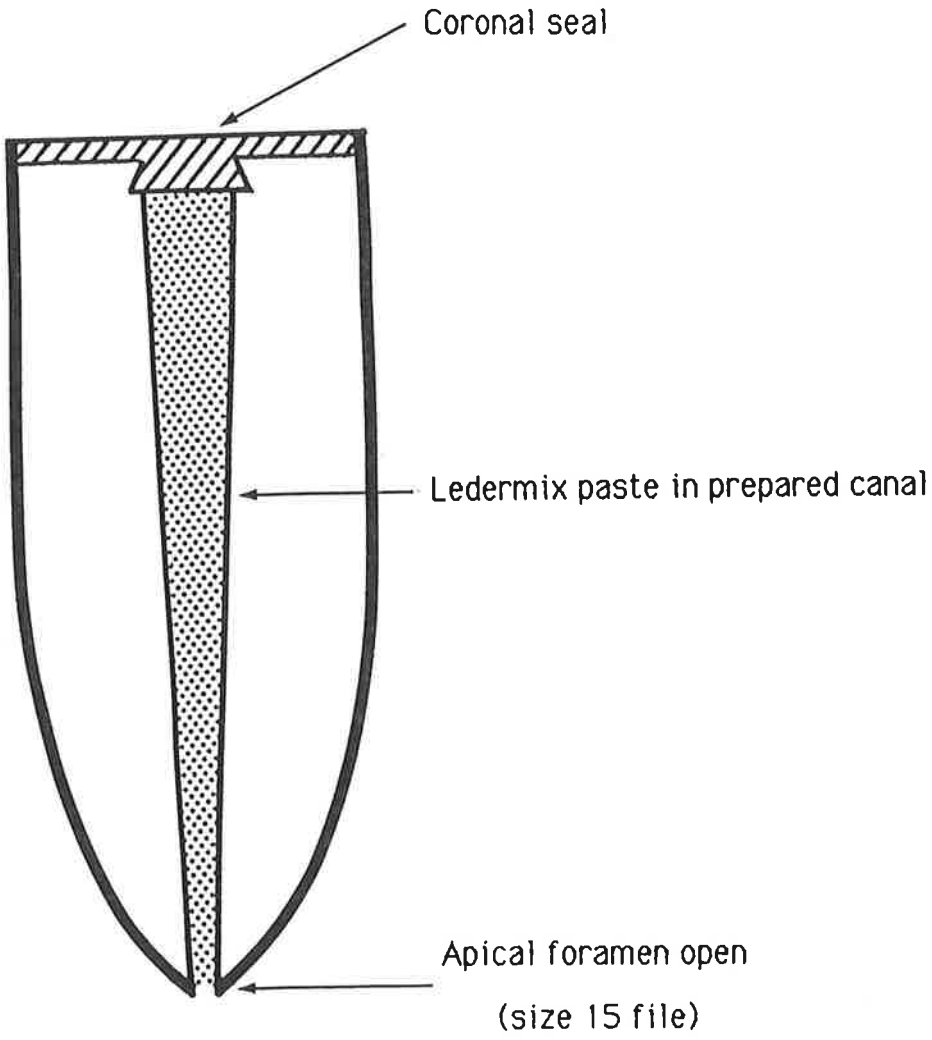
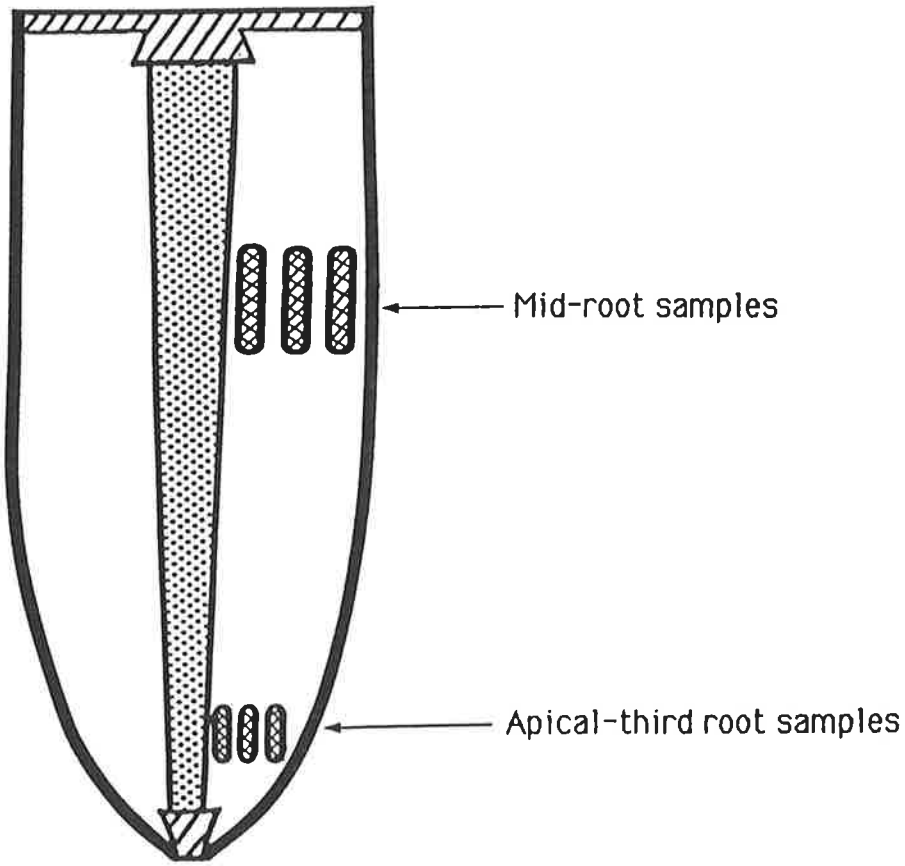


FIG. 4-5: Areas of the root from which dentine samples were obtained.



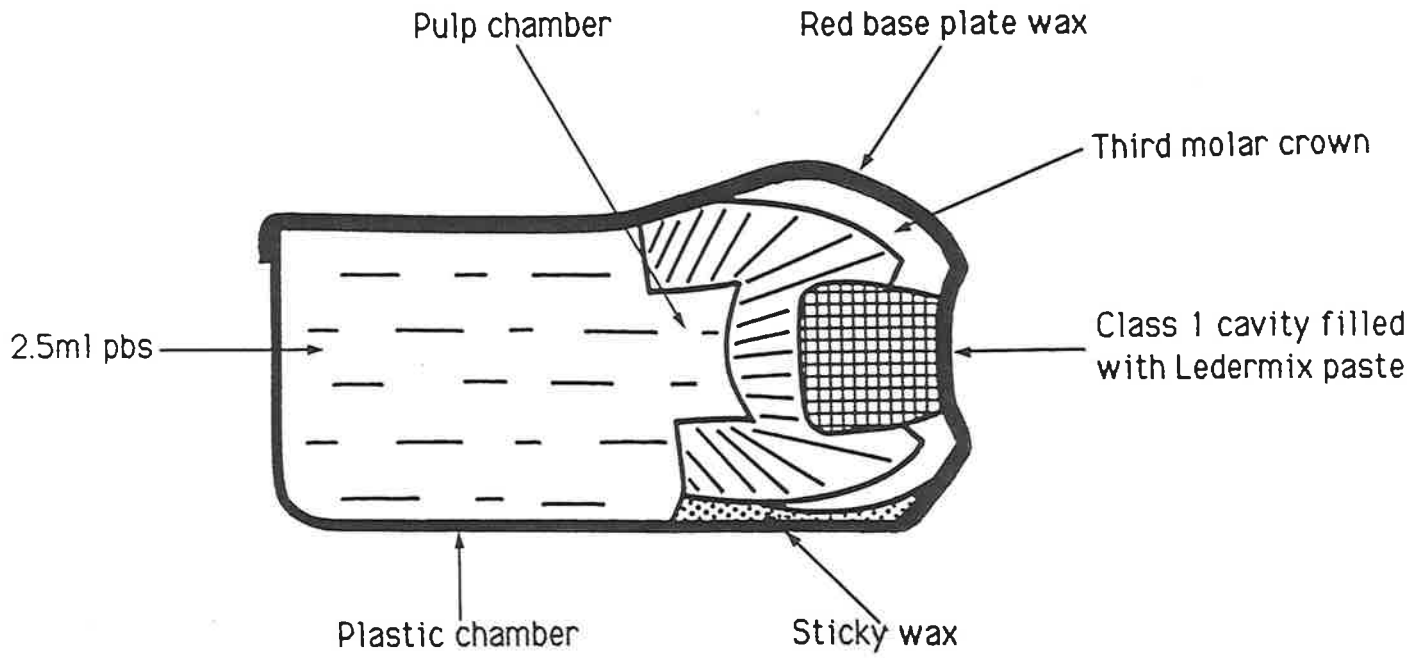


FIG. 4-6: Tooth crown waxed into a hemi-cylindrical chamber.

FIG. 4-7: Areas from which coronal dentine samples were obtained.

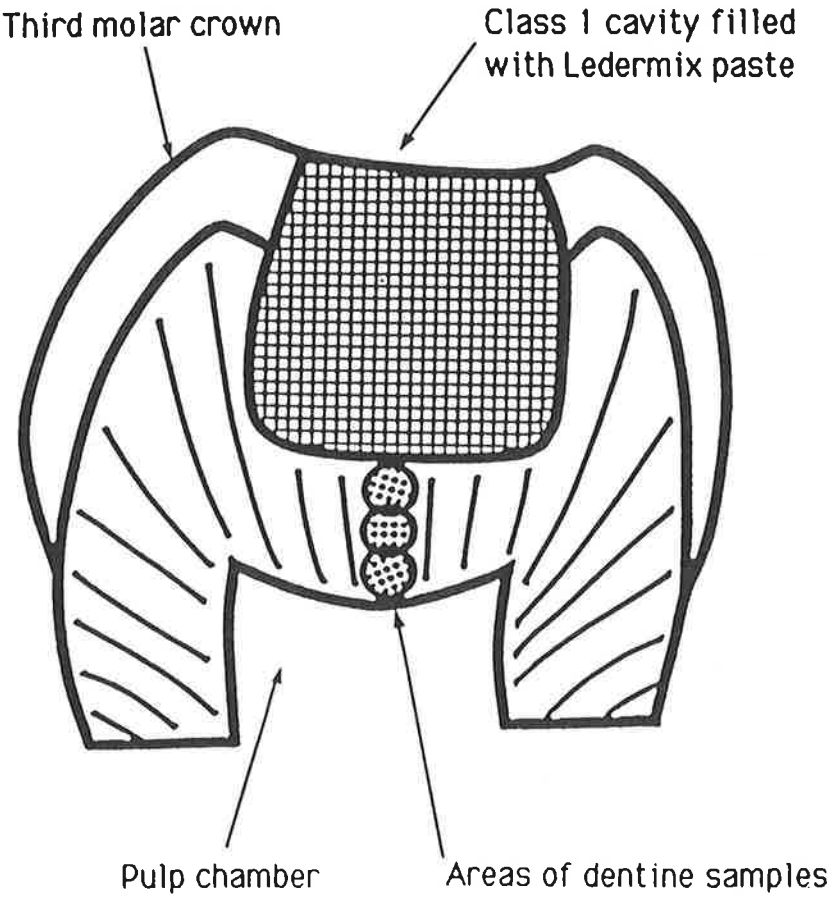


FIG. 5-1: Graph of optical density (OD) versus wavelength for a standard sample of demeclocycline (10^{-4}M).

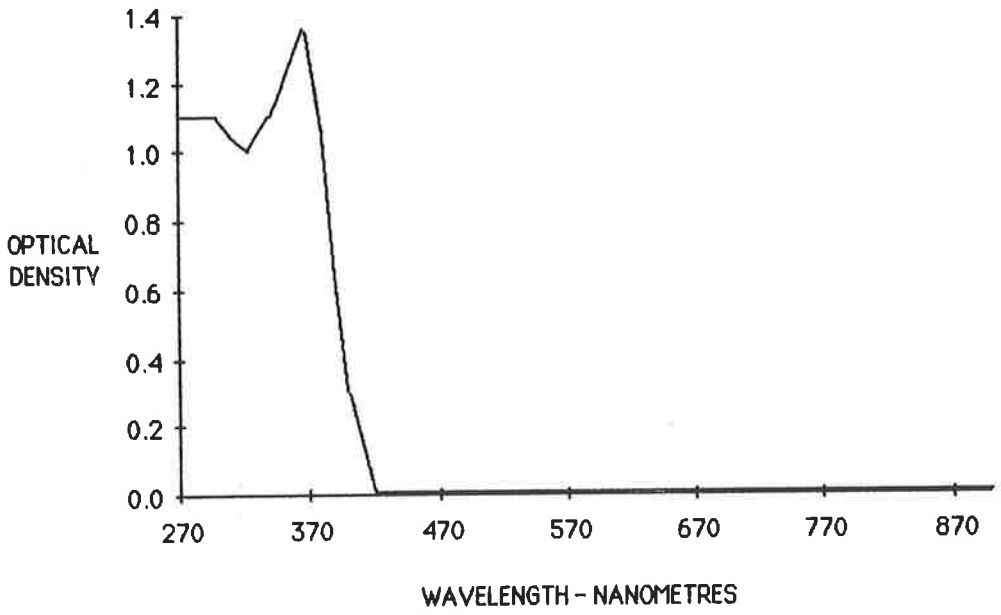


Table 5-1: Relationship between optical density (OD) and demeclocycline concentration.

Sam. No.	CONCENTRATION DEMECLOCYCLINE	LOG [Dem.]	MEAN OPTICAL DENSITY	LOG (O.D.)
1	0.0000001	-7	0.002	-2.7
2	0.0000003	-6.52	0.004	-2.4
3	0.000001	-6	0.014	-1.85
4	0.000003	-5.52	0.041	-1.38
5	0.00001	-5	0.144	-0.84
6	0.00003	-4.52	0.416	-0.38
7	0.0001	-4	1.39	0.14

LOG [Dem.] versus LOG (O.D.)

Correl. coeff.	0.9999
Gradient	1.00522
Intercept y-axis	4.169

FIG. 5-2: Graph of the relationship between optical density (OD) and the concentration of demeclocycline.

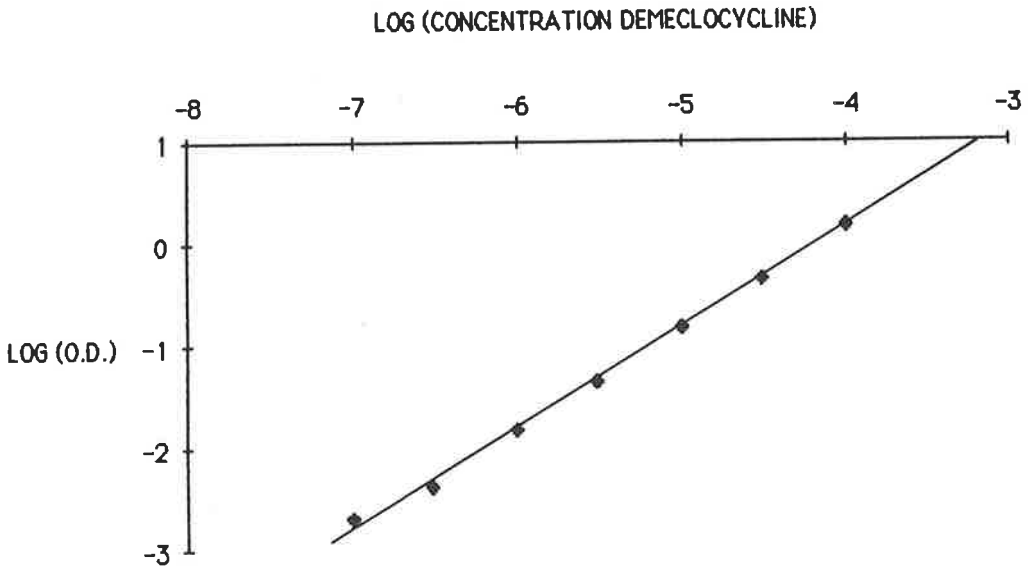


Table 5-2: Relationship between counts per minute (CPM) and the total number of nanomoles of triamcinolone plus tritiated triamcinolone.

BATCH No. 1

Sam. No.	WEIGHT LABELLED LEDERMIX PASTE	WEIGHT 3H-TRIAM.	NANOMOLES TOTAL TRIAM.	COUNTS PER MINUTE (÷1000)
1	0.41 mg	0.00414 mg	10.49	12.954
2	2.0 mg	0.0202 mg	51.2	51.028
3	3.4 mg	0.0343 mg	86.95	93.661
4	6.5 mg	0.0656 mg	166.29	157.404
5	7.22 mg	0.0729 mg	184.79	177.113
6	10.79 mg	0.109 mg	276.3	268.28

NANOMOLES OF TOTAL TRIAM. versus CPM (÷1000)

Correl. coeff.	0.999
Gradient	0.9481
Intercept y-axis	4.1213

FIG. 5-3: Graph of the relationship between the counts per minute (CPM) and the concentration of triamcinolone.

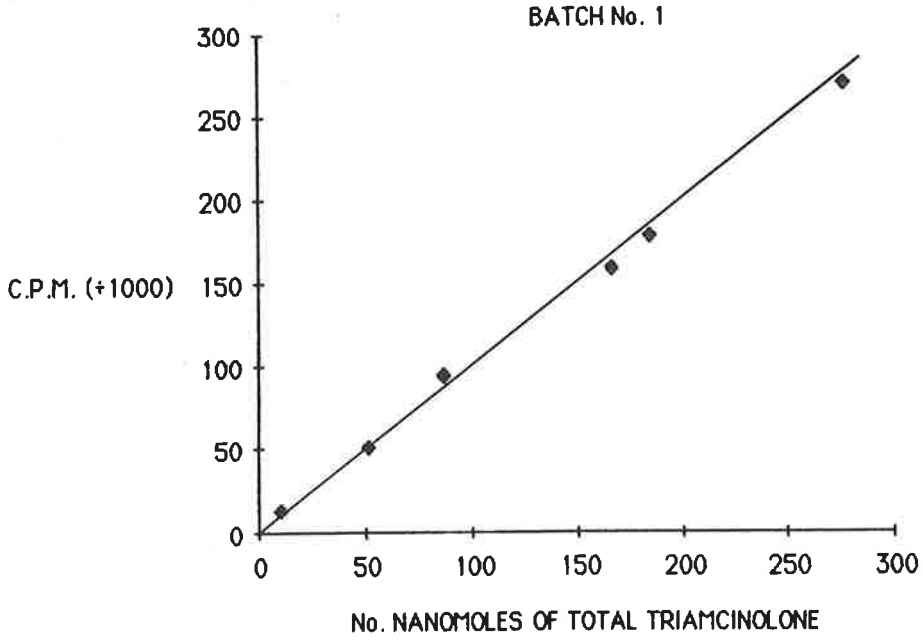


Table 5-3: Relationship between counts per minute (CPM) and the total number of nanomoles of triamcinolone plus tritiated triamcinolone.

BATCH No. 2

Sam. No.	WEIGHT LABELLED LEDERMIX PASTE	WEIGHT 3H-TRIAM.	NANOMOLES TOTAL TRIAM.	COUNTS PER MINUTE (÷1000)
1	0.25 mg	0.0025 mg	6.34	10.332
2	0.484 mg	0.0049 mg	12.42	15.53385
3	0.84 mg	0.0085 mg	21.55	29.36571
4	1.054 mg	0.0106 mg	26.87	29.94286
5	1.246 mg	0.0126 mg	31.94	32.01
6	1.912 mg	0.0193 mg	48.92	47.36

NANOMOLES OF TOTAL TRIAM. versus CPM (÷1000)

Correl. coeff.	0.983
Gradient	0.8542
Intercept y-axis	6.3455

FIG. 5-4: Graph of the relationship between the counts per minute (CPM) and the concentration of triamcinolone.

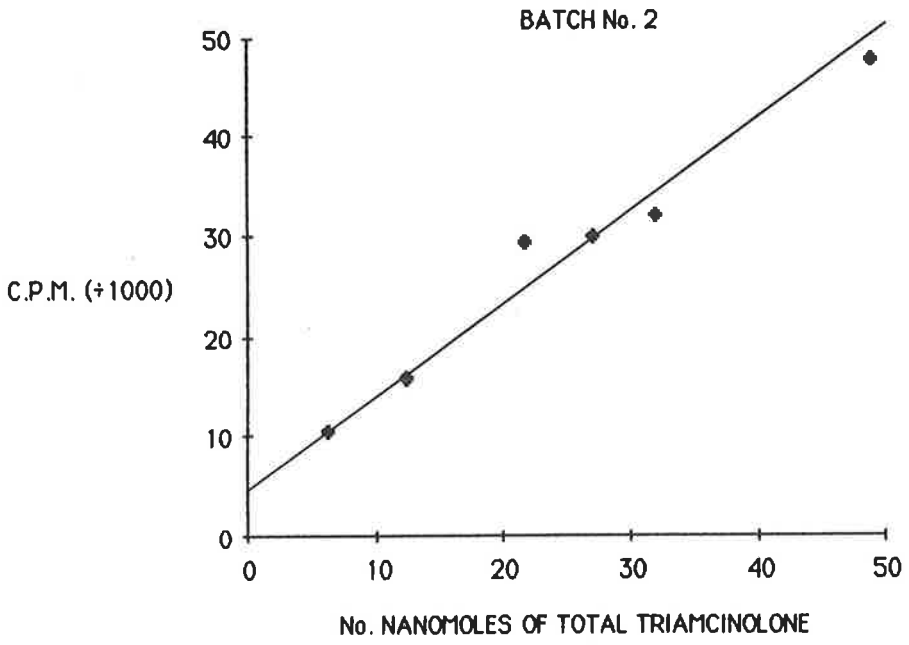


Table 5-4: Relationship between counts per minute (CPM) and the number of nanomoles of tritiated tetracycline.

Sam. No.	WEIGHT LABELLED LEDERMIX PASTE	NANOMOLES TETRACYCLINE	COUNTS PER MINUTE (÷1000)
1	0.017 mg	0.0012	6.19394
2	0.0436 mg	0.0032	11.46778
3	0.0801 mg	0.0058	18.69818
4	0.1321 mg	0.0095	30.9857
5	0.1702 mg	0.0123	40.436
6	0.2042 mg	0.0147	42.828

NANOMOLES OF TETRACYCLINE versus CPM (÷1000)

Correl. coeff.	0.9949
Gradient	2879.74
Intercept y-axis	2.688

FIG. 5-5: Graph of the relationship between the counts per minute (CPM) and the concentration of tetracycline.

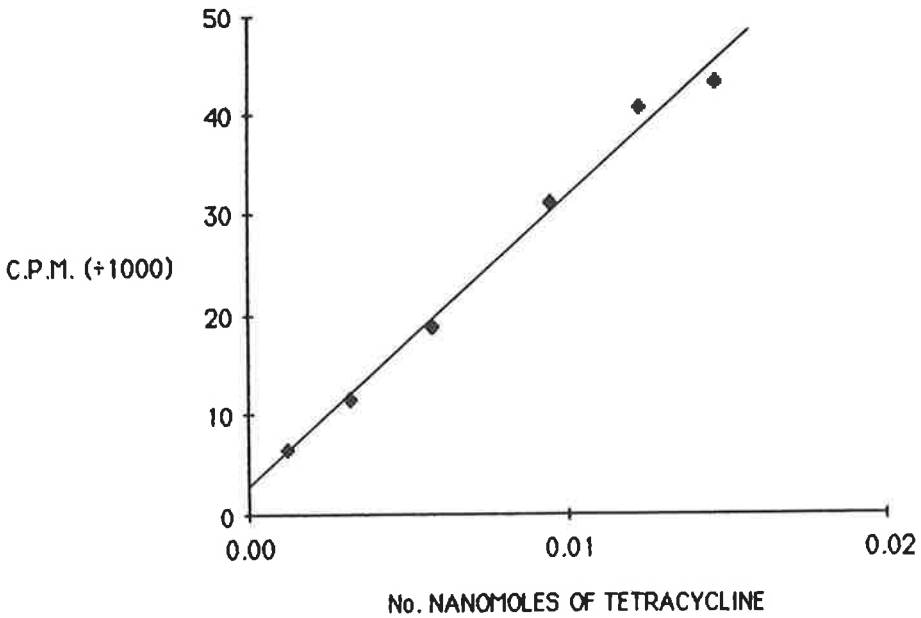


Table 5-5: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste in plastic canal models at 22°C and 37°C.

Sam. No.	END TIME	22deg. C.	37 deg. C.	SIGNIFICANCE
1	0.3 min	0.74	60.26	S.
2	1.0 min	0.11	14.12	S.
3	4.0 mins	0.15	5.13	S.
4	14 mins	0.11	2.1	S.
5	44 mins	0.03	0.52	S.
6	2.5 hrs	0.02	0.12	S.
7	8 hrs	0.004	0.02	S.
8	1 day	0.02	0.05	S.
9	3 days	0.008	0.02	S.
10	10 days	0.006	0.01	S.
11	33 days	0.001	0.003	S.
12	14 weeks	0.0001	0.0008	S.
	Surf. area of tip	0.61sq.mm.	0.61sq.mm.	N.S.
	No. nanomoles	8,846	8,846	N.S.

FIG. 5-6: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models at different temperatures.

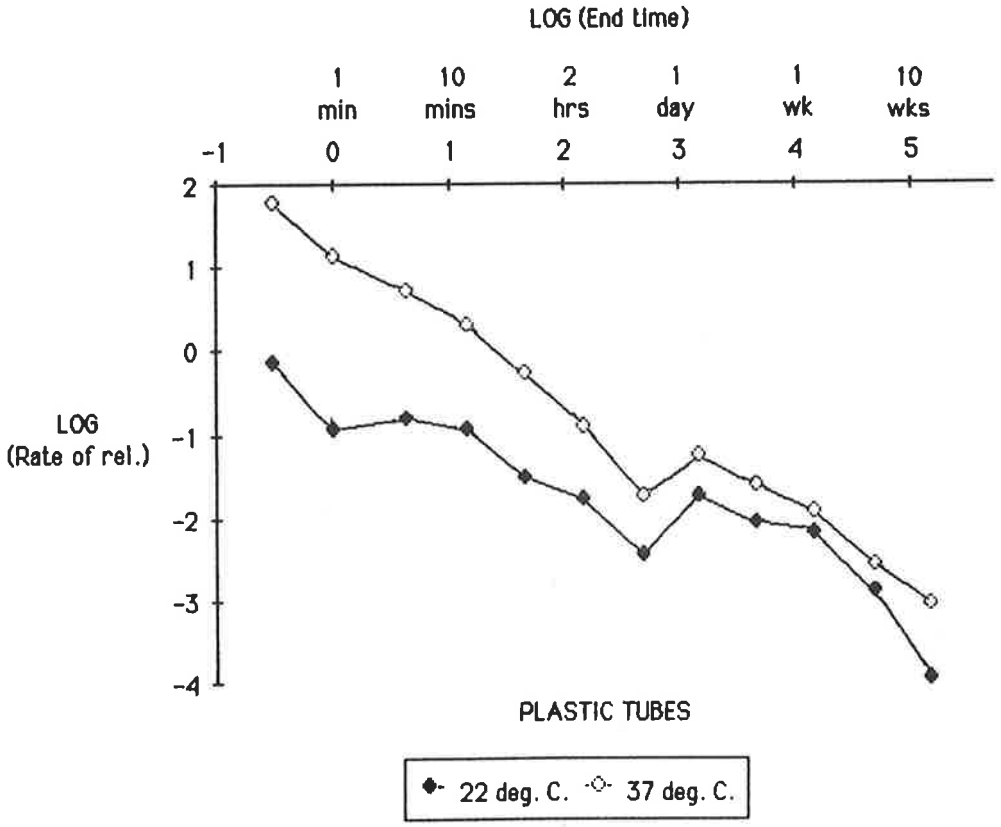


Table 5-6: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from 0.026 mls of Ledermix paste in plastic canal models with different tip diameters.

Sam. No.	END TIME	Diam. 0.88mm	Diam. 1.4mm	Diam. 2.0mm
1	0.3 min	14.79	19.5	151.36
2	1.0 min	7.24	14.45	89.12
3	4.0 mins	2.14	6.46	23.44
4	14 mins	0.5	1.74	7.58
5	44 mins	0.14	0.48	2.24
6	2.5 hrs	0.05	0.028	0.41
7	8 hrs	0.01	0.015	0.11
8	1 day	0.007	0.009	0.04
9	3 days	0.03	0.025	0.02
10	10 days	0.002	0.001	0.01
11	33 days	0.0003	0.002	0.005
12	14 weeks	0.0007	0.0008	0.001
	Surf. area of tip	0.61sq.mm.	1.54sq.mm.	3.14sq.mm.

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.88 - 1.4	0.88 - 2.0	1.4 - 2.0
1	0.3 min	N.S.	S.	S.
2	1.0 min	S.	S.	S.
3	4.0 mins	S.	S.	S.
4	14 mins	S.	S.	S.
5	44 mins	S.	S.	S.
6	2.5 hrs	S.	S.	S.
7	8 hrs	N.S.	S.	S.
8	1 day	S.	S.	S.
9	3 days	N.S.	N.S.	N.S.
10	10 days	N.S.	S.	S.
11	33 days	S.	S.	S.
12	14 weeks	N.S.	S.	N.S.

FIG. 5-7: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models with different tip diameters and a constant paste volume of 0.026 mls.

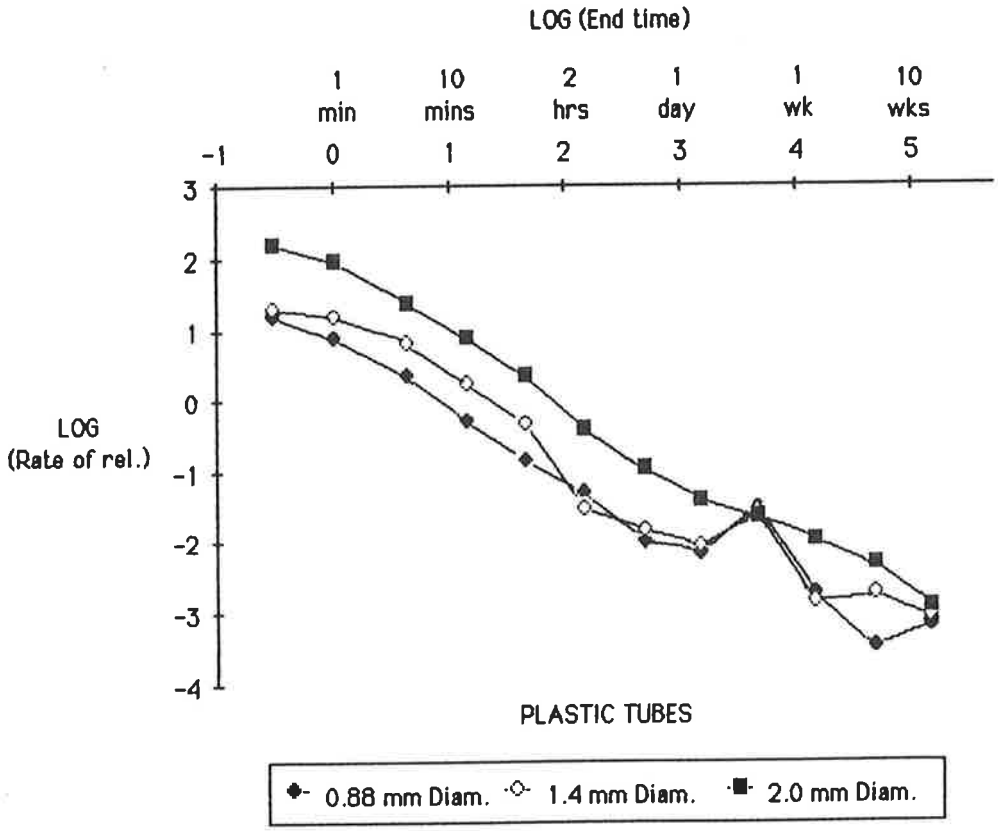


Table 5-7: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from 0.055 mls of Ledermix paste in plastic canal models with different tip diameters.

Sam. No.	END TIME	Diam. 0.88mm	Diam. 1.4mm	Diam. 2.0mm
1	0.3 min	9.33	35.48	34.67
2	1.0 min	6.03	18.62	53.7
3	4.0 mins	0.98	4.68	20.89
4	14 mins	0.29	1.58	9.33
5	44 mins	0.12	0.5	1.51
6	2.5 hrs	0.03	0.03	0.2
7	8 hrs	0.01	0.02	0.03
8	1 day	0.006	0.01	0.03
9	3 days	0.017	0.01	0.03
10	10 days	0.009	0.007	0.004
11	33 days	0.002	0.001	0.002
12	14 weeks	0.0002	0.0006	0.0006
	Surf. area of tip	0.61sq.mm.	1.54sq.mm.	3.14sq.mm.

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.88 - 1.4	0.88 - 2.0	1.4 - 2.0
1	0.3 min	N.S.	S.	N.S.
2	1.0 min	S.	S.	S.
3	4.0 mins	S.	S.	S.
4	14 mins	S.	S.	S.
5	44 mins	S.	S.	S.
6	2.5 hrs	N.S.	S.	S.
7	8 hrs	S.	N.S.	N.S.
8	1 day	N.S.	S.	S.
9	3 days	N.S.	S.	N.S.
10	10 days	N.S.	S.	N.S.
11	33 days	N.S.	N.S.	N.S.
12	14 weeks	S.	S.	N.S.

FIG. 5-8: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models with different tip diameters and a constant paste volume of 0.055 mls.

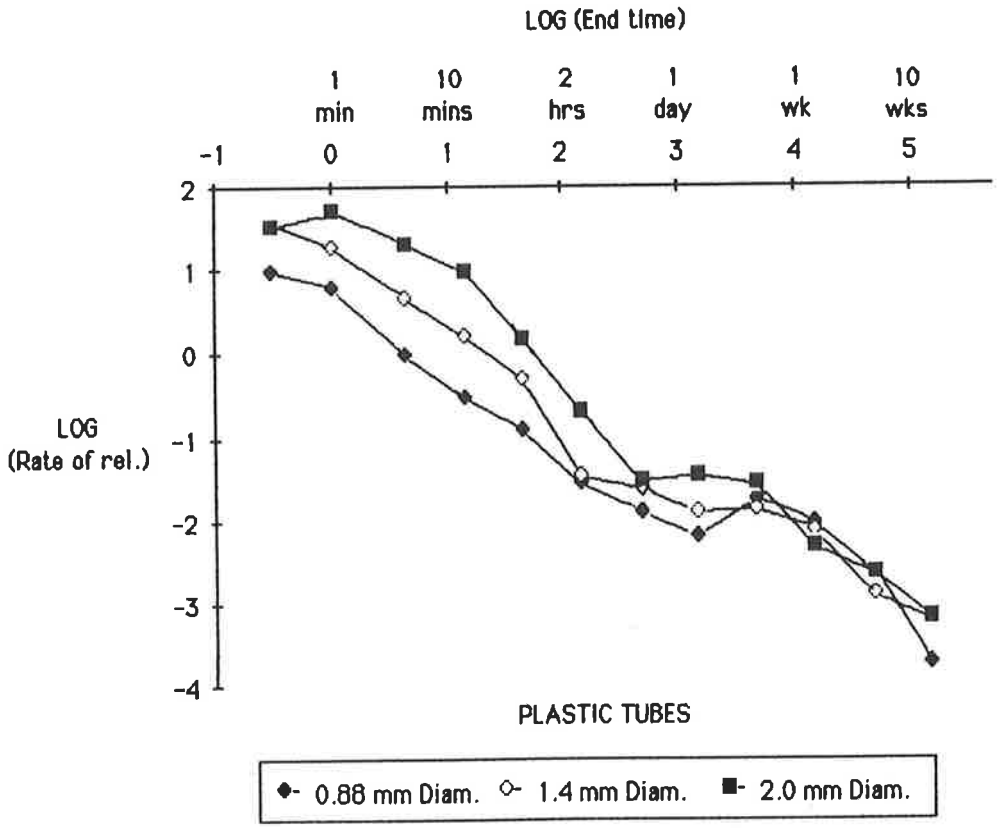


Table 5-8: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from 0.085 mls of Ledermix paste in plastic canal models with different tip diameters.

Sam. No.	END TIME	Diam. 0.88mm	Diam. 1.4mm	Diam. 2.0mm
1	0.3 min	38.9	28.2	47.86
2	1.0 min	9.77	26.3	95.5
3	4.0 mins	3.63	6.03	43.65
4	14 mins	1.15	3.55	9.55
5	44 mins	0.32	0.6	1.32
6	2.5 hrs	0.07	0.08	0.31
7	8 hrs	0.01	0.03	0.08
8	1 day	0.007	0.01	0.05
9	3 days	0.04	0.01	0.02
10	10 days	0.01	0.01	0.007
11	33 days	0.002	0.002	0.003
12	14 weeks	0.0008	0.0002	0.001
	Surf. area of tip	0.61sq.mm.	1.54sq.mm.	3.14sq.mm.

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.88 - 1.4	0.88 - 2.0	1.4 - 2.0
1	0.3 min	N.S.	N.S.	N.S.
2	1.0 min	N.S.	S.	S.
3	4.0 mins	N.S.	S.	S.
4	14 mins	N.S.	S.	N.S.
5	44 mins	N.S.	S.	N.S.
6	2.5 hrs	N.S.	S.	S.
7	8 hrs	N.S.	S.	S.
8	1 day	N.S.	S.	S.
9	3 days	N.S.	S.	N.S.
10	10 days	N.S.	S.	S.
11	33 days	N.S.	N.S.	N.S.
12	14 weeks	S.	N.S.	S.

FIG. 5-9: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models with different tip diameters and a constant paste volume of 0.085 mls.

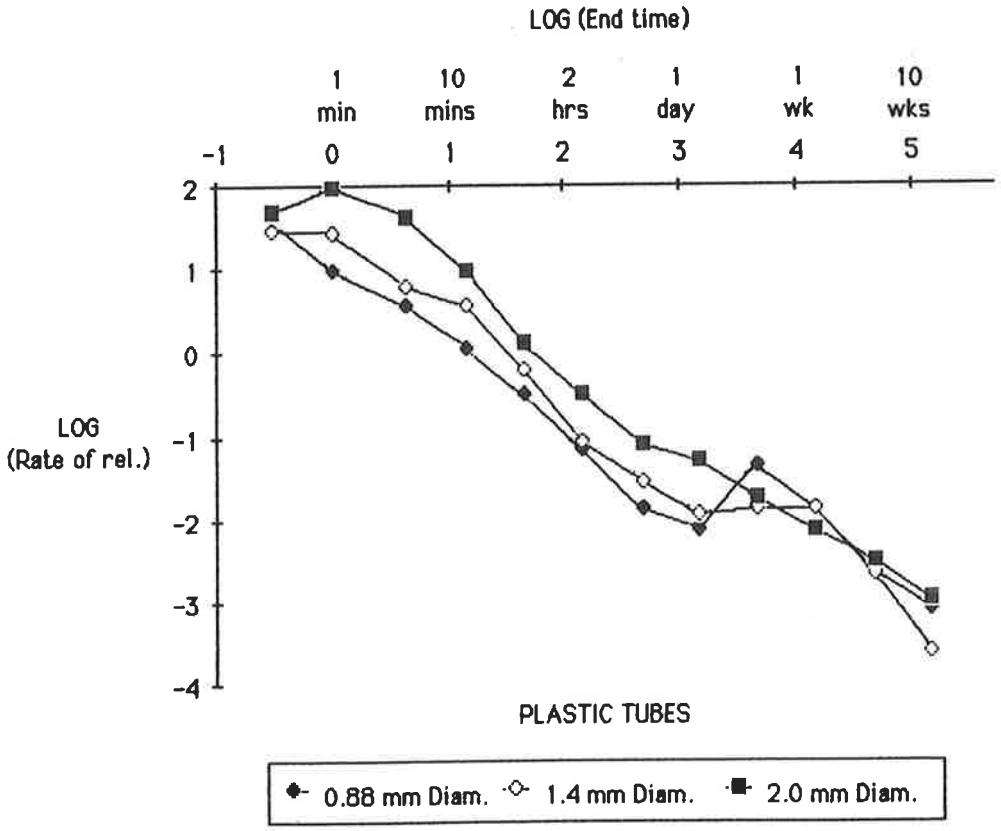


Table 5-9: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from different volumes of Ledermix paste in plastic canal models with a tip diameter of 0.88 mm.

Sam. No.	END TIME	Vol. 0.026mls	Vol. 0.055mls	Vol. 0.085mls
1	0.3 min	14.79	9.33	38.9
2	1.0 min	7.24	6.03	9.77
3	4.0 mins	2.14	0.98	3.63
4	14 mins	0.5	0.29	1.15
5	44 mins	0.14	0.12	0.32
6	2.5 hrs	0.05	0.03	0.07
7	8 hrs	0.01	0.01	0.01
8	1 day	0.007	0.006	0.007
9	3 days	0.03	0.017	0.04
10	10 days	0.002	0.009	0.01
11	33 days	0.0003	0.002	0.002
12	14 weeks	0.0007	0.0002	0.0008
	No. nanomoles	2,838	4,889	8,846

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.026 - 0.054	0.026 - 0.085	0.054 - 0.085
1	0.3 min	N.S.	S.	S.
2	1.0 min	N.S.	N.S.	N.S.
3	4.0 mins	N.S.	N.S.	S.
4	14 mins	N.S.	N.S.	S.
5	44 mins	N.S.	N.S.	N.S.
6	2.5 hrs	N.S.	N.S.	N.S.
7	8 hrs	N.S.	N.S.	N.S.
8	1 day	N.S.	N.S.	N.S.
9	3 days	N.S.	N.S.	S.
10	10 days	S.	S.	N.S.
11	33 days	S.	S.	N.S.
12	14 weeks	S.	N.S.	S.

FIG. 5-10: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models with different paste volumes and a constant tip diameter of 0.88 mm.

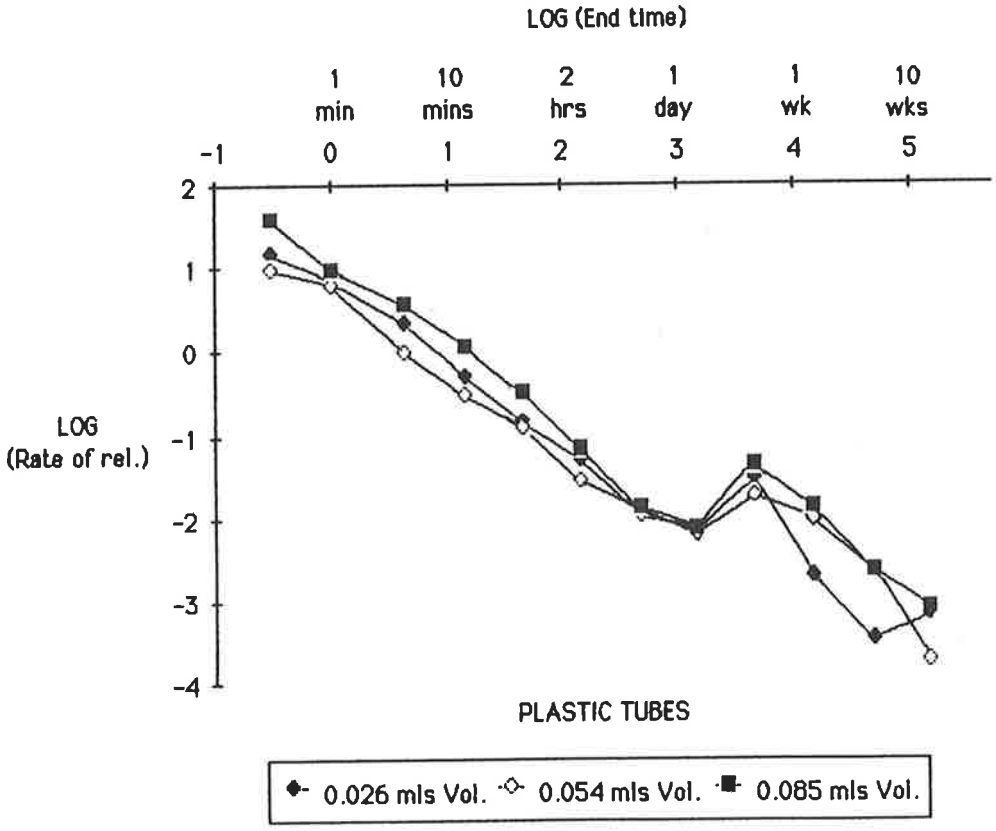


Table 5-10: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from different volumes of Ledermix paste in plastic canal models with a tip diameter of 1.4 mm.

Sam. No.	END TIME	Vol. 0.026mls	Vol. 0.055mls	Vol. 0.085mls
1	0.3 min	19.5	35.48	28.2
2	1.0 min	14.45	18.62	26.3
3	4.0 mins	6.46	4.68	6.03
4	14 mins	1.74	1.58	3.55
5	44 mins	0.48	0.5	0.6
6	2.5 hrs	0.03	0.03	0.08
7	8 hrs	0.02	0.02	0.03
8	1 day	0.009	0.01	0.01
9	3 days	0.025	0.01	0.01
10	10 days	0.001	0.007	0.01
11	33 days	0.002	0.001	0.002
12	14 weeks	0.0008	0.0006	0.0002
	No. nanomoles	2,838	4,889	8,846

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.026 - 0.054	0.026 - 0.085	0.054 - 0.085
1	0.3 min	N.S.	N.S.	N.S.
2	1.0 min	N.S.	N.S.	N.S.
3	4.0 mins	N.S.	N.S.	N.S.
4	14 mins	N.S.	N.S.	N.S.
5	44 mins	N.S.	N.S.	N.S.
6	2.5 hrs	N.S.	N.S.	N.S.
7	8 hrs	N.S.	S.	N.S.
8	1 day	N.S.	N.S.	N.S.
9	3 days	N.S.	N.S.	N.S.
10	10 days	S.	S.	N.S.
11	33 days	N.S.	N.S.	N.S.
12	14 weeks	N.S.	S.	S.

FIG. 5-11: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models with different paste volumes and a constant tip diameter of 1.4 mm.

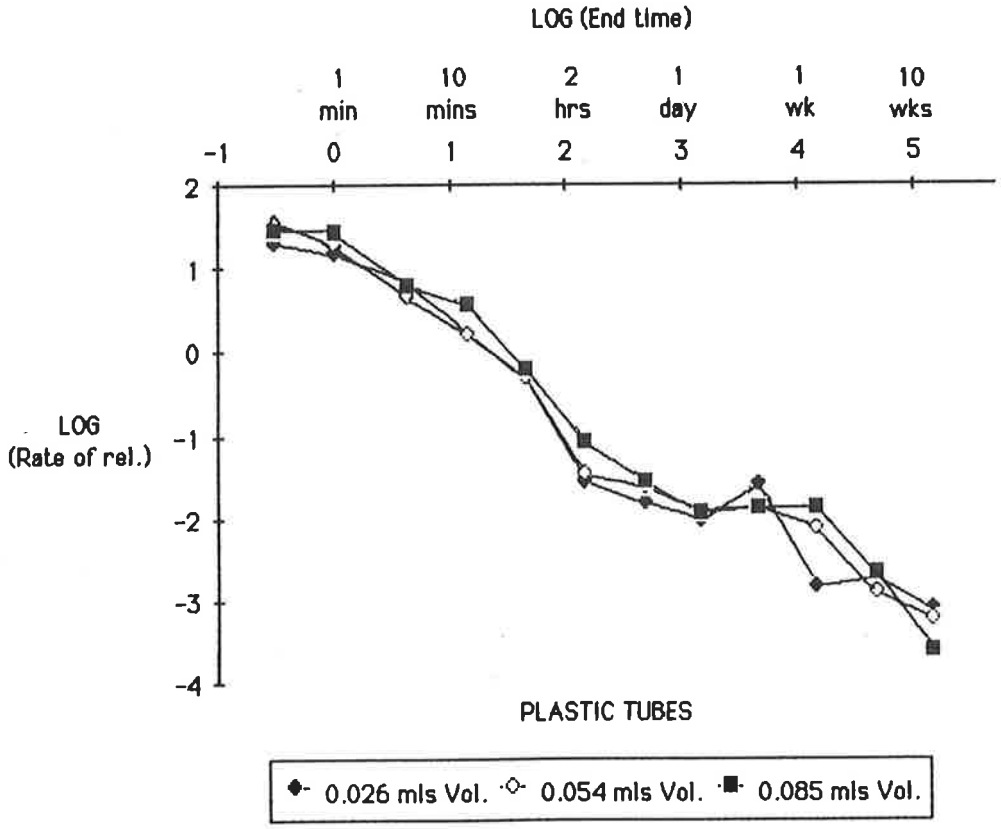


Table 5-11: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from different volumes of Ledermix paste in plastic canal models with a tip diameter of 2.0 mm.

Sam. No.	END TIME	Vol. 0.026mls	Vol. 0.055mls	Vol. 0.085mls
1	0.3 min	151.36	34.67	47.86
2	1.0 min	89.12	53.7	95.5
3	4.0 mins	23.44	20.89	43.65
4	14 mins	7.58	9.33	9.55
5	44 mins	2.24	1.51	1.32
6	2.5 hrs	0.41	0.2	0.31
7	8 hrs	0.11	0.03	0.08
8	1 day	0.04	0.03	0.05
9	3 days	0.02	0.03	0.02
10	10 days	0.01	0.004	0.007
11	33 days	0.005	0.002	0.003
12	14 weeks	0.001	0.0006	0.001
	No. nanomoles	2,838	4,889	8,846

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.026 - 0.054	0.026 - 0.085	0.054 - 0.085
1	0.3 min	S.	N.S.	N.S.
2	1.0 min	N.S.	N.S.	N.S.
3	4.0 mins	N.S.	S.	N.S.
4	14 mins	N.S.	N.S.	N.S.
5	44 mins	N.S.	N.S.	N.S.
6	2.5 hrs	N.S.	N.S.	N.S.
7	8 hrs	S.	N.S.	S.
8	1 day	N.S.	N.S.	S.
9	3 days	N.S.	N.S.	S.
10	10 days	S.	S.	N.S.
11	33 days	S.	N.S.	N.S.
12	14 weeks	N.S.	N.S.	N.S.

FIG. 5-12: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in plastic canal models with different paste volumes and a constant tip diameter of 2.0 mm.

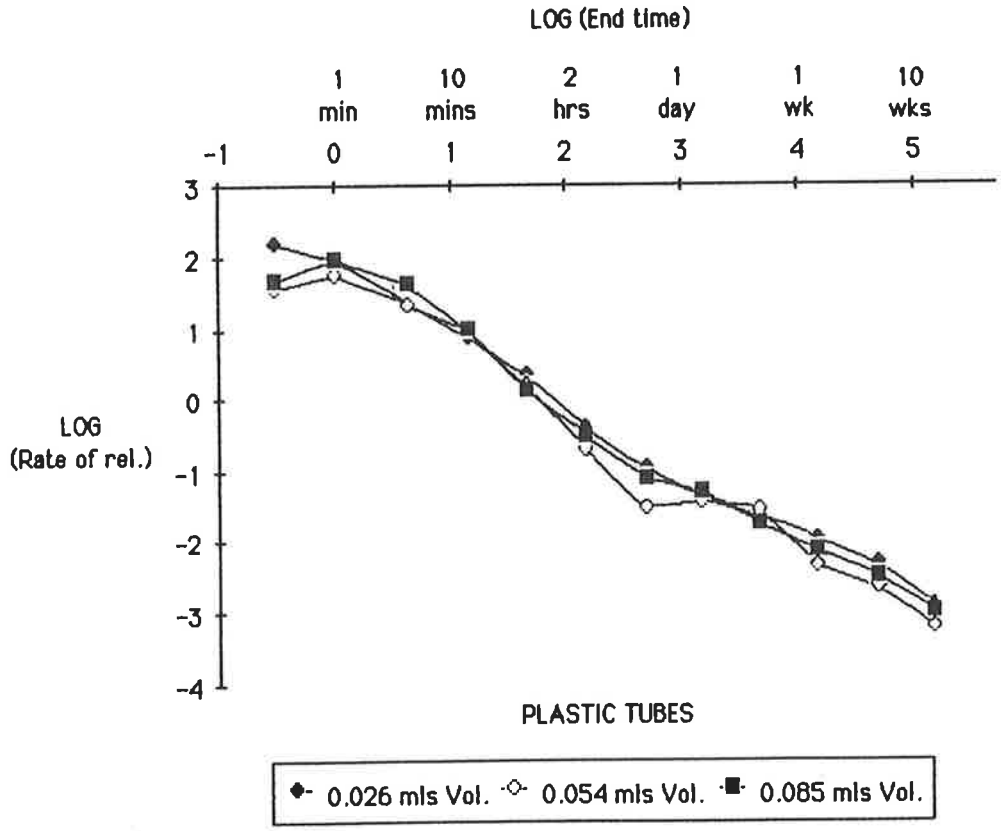


Table 5-12: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from 0.026 mls of Ledermix paste in plastic canal models with different tip diameters.

Sam. No.	END TIME	Diam. 0.88mm	Diam. 1.4mm	Diam. 2.0mm
1	0.3 min	2.4	5.37	63.1
2	1.0 min	0.72	3.98	25.12
3	4.0 mins	0.87	1.58	6.92
4	14 mins	0.26	0.58	2.45
5	44 mins	0.11	0.24	1.2
6	2.5 hrs	0.04	0.09	0.46
7	8 hrs	0.01	0.05	0.26
8	1 day	0.01	0.03	0.08
9	3 days	0.02	0.03	0.03
10	10 days	0.008	0.002	0.009
11	33 days	0.0004	0.002	0.003
12	14 weeks	0.0005	0.002	0.0004
	Surf. area of tip	0.61sq.mm.	1.54sq.mm.	3.14sq.mm.

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.88 - 1.4	0.88 - 2.0	1.4 - 2.0
1	0.3 min	N.S.	S.	S.
2	1.0 min	S.	S.	S.
3	4.0 mins	S.	S.	S.
4	14 mins	S.	S.	S.
5	44 mins	S.	S.	S.
6	2.5 hrs	S.	S.	S.
7	8 hrs	S.	S.	S.
8	1 day	S.	S.	S.
9	3 days	N.S.	N.S.	N.S.
10	10 days	S.	N.S.	S.
11	33 days	S.	S.	N.S.
12	14 weeks	S.	N.S.	S.

FIG. 5-13: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in plastic canal models with different tip diameters and a constant paste volume of 0.026 mls.

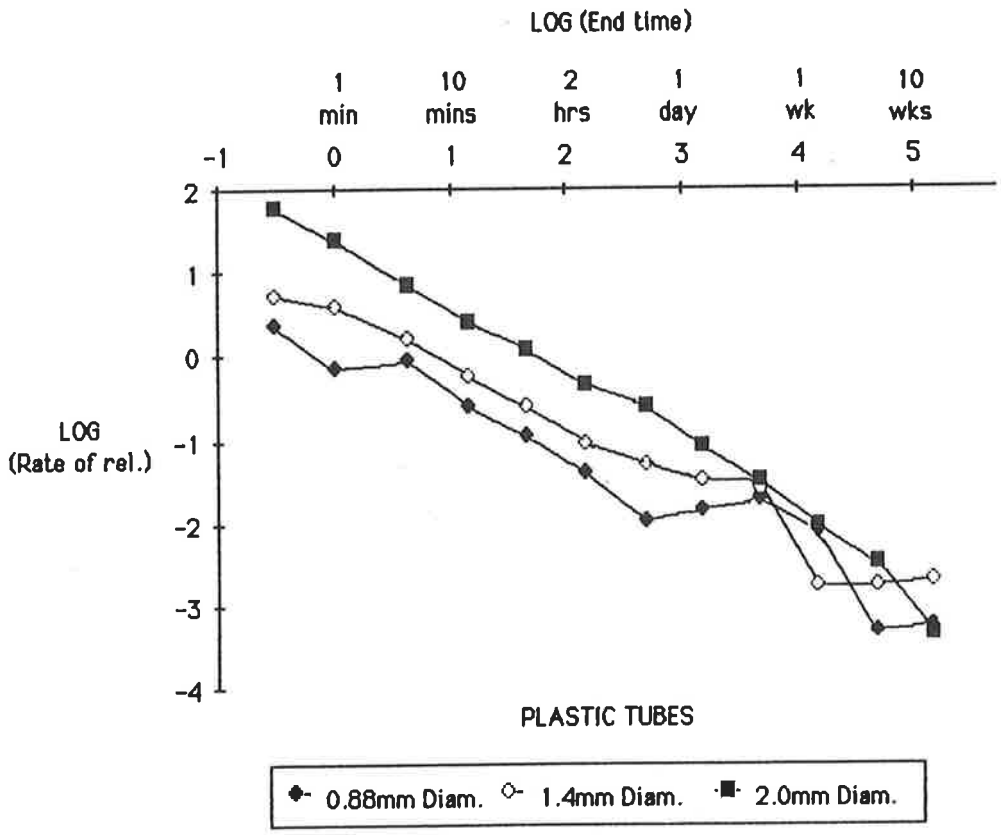


Table 5-13: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from 0.055 mls of Ledermix paste in plastic canal models with different tip diameters.

Sam. No.	END TIME	Diam. 0.88mm	Diam. 1.4mm	Diam. 2.0mm
1	0.3 min	3.24	11.48	2.63
2	1.0 min	1.35	4.68	3.02
3	4.0 mins	0.23	1.38	3.47
4	14 mins	0.19	0.5	1.41
5	44 mins	0.08	0.23	0.58
6	2.5 hrs	0.05	0.09	0.3
7	8 hrs	0.02	0.06	0.14
8	1 day	0.02	0.03	0.07
9	3 days	0.04	0.03	0.03
10	10 days	0.02	0.01	0.01
11	33 days	0.003	0.002	0.002
12	14 weeks	0.0004	0.002	0.003
	Surf. area of tip	0.61sq.mm.	1.54sq.mm.	3.14sq.mm.

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.88 - 1.4	0.88 - 2.0	1.4 - 2.0
1	0.3 min	N.S.	S.	N.S.
2	1.0 min	N.S.	N.S.	N.S.
3	4.0 mins	S.	S.	S.
4	14 mins	S.	S.	S.
5	44 mins	S.	S.	S.
6	2.5 hrs	S.	S.	S.
7	8 hrs	S.	S.	S.
8	1 day	S.	S.	S.
9	3 days	S.	S.	N.S.
10	10 days	S.	S.	N.S.
11	33 days	S.	S.	N.S.
12	14 weeks	S.	S.	N.S.

FIG. 5-14: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in plastic canal models with different tip diameters and a constant paste volume of 0.055 mls.

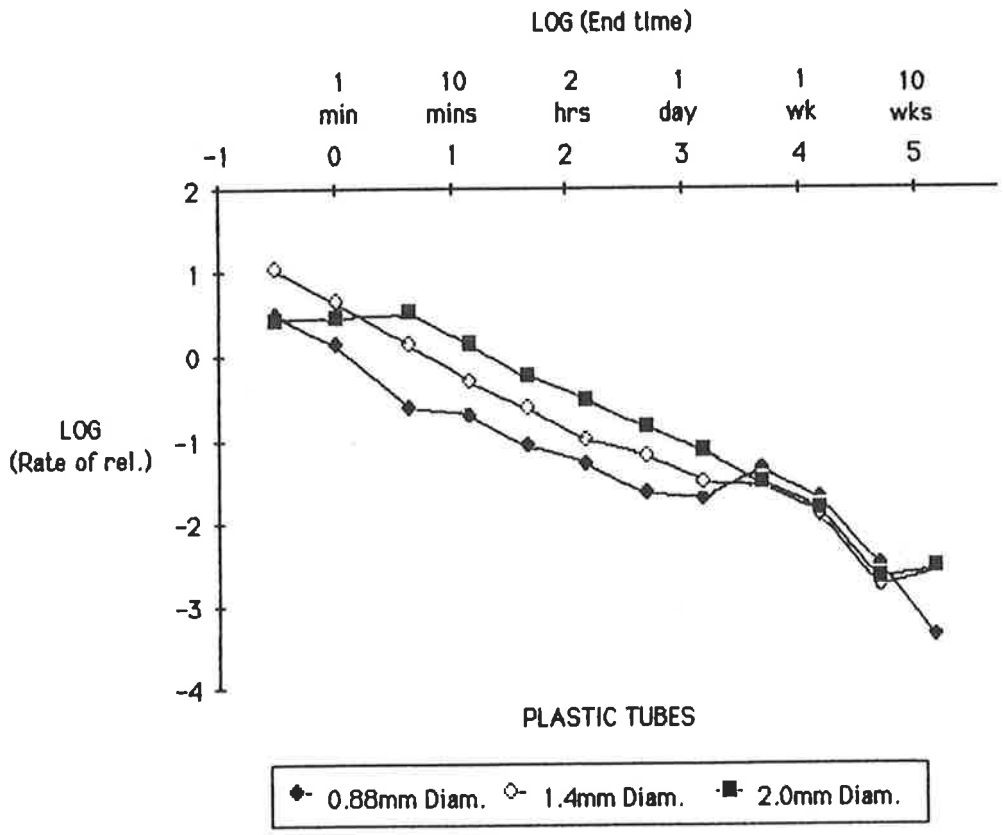


Table 5-14: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from 0.085 mls of Ledermix paste in plastic canal models with different tip diameters.

Sam. No.	END TIME	Diam. 0.88mm	Diam. 1.4mm	Diam. 2.0mm
1	0.3 min	5.75	8.71	15.49
2	1.0 min	0.63	6.92	28.18
3	4.0 mins	0.43	1.7	11.22
4	14 mins	0.29	1.05	3.31
5	44 mins	0.09	0.29	0.91
6	2.5 hrs	0.04	0.12	0.47
7	8 hrs	0.01	0.07	0.23
8	1 day	0.01	0.04	0.13
9	3 days	0.01	0.04	0.07
10	10 days	0.03	0.03	0.02
11	33 days	0.008	0.003	0.008
12	14 weeks	0.001	0.0003	0.004
	Surf. area of tip	0.61sq.mm.	1.54sq.mm.	3.14sq.mm.

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.88 - 1.4	0.88 - 2.0	1.4 - 2.0
1	0.3 min	N.S.	N.S.	N.S.
2	1.0 min	S.	S.	S.
3	4.0 mins	S.	S.	S.
4	14 mins	S.	S.	S.
5	44 mins	S.	S.	S.
6	2.5 hrs	S.	S.	S.
7	8 hrs	S.	S.	S.
8	1 day	S.	S.	S.
9	3 days	S.	S.	S.
10	10 days	N.S.	S.	S.
11	33 days	S.	N.S.	S.
12	14 weeks	S.	S.	S.

FIG. 5-15: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in plastic canal models with different tip diameters and a constant paste volume of 0.085 mls.

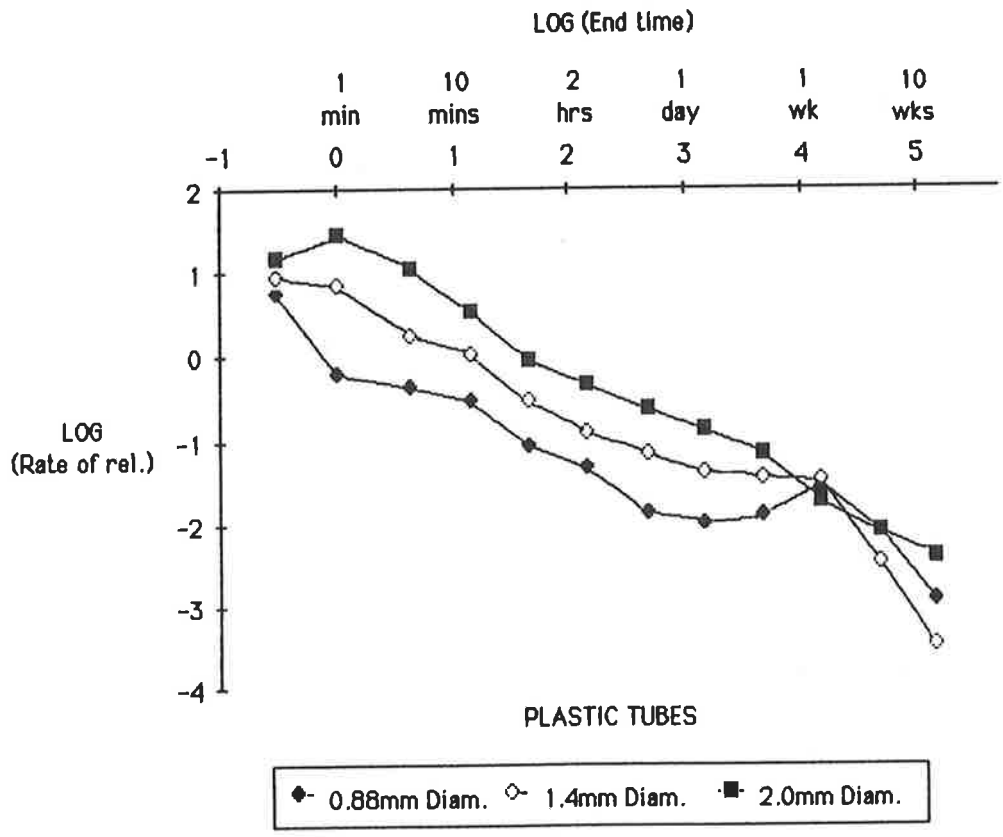


Table 5-15: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from different volumes of Ledermix paste in plastic canal models with a tip diameter of 0.88 mm.

Sam. No.	END TIME	Vol. 0.026mls	Vol. 0.055mls	Vol. 0.085mls
1	0.3 min	2.4	3.24	5.75
2	1.0 min	0.72	1.35	0.63
3	4.0 mins	0.87	0.23	0.43
4	14 mins	0.26	0.19	0.29
5	44 mins	0.11	0.08	0.09
6	2.5 hrs	0.04	0.05	0.04
7	8 hrs	0.01	0.02	0.01
8	1 day	0.01	0.02	0.01
9	3 days	0.02	0.04	0.01
10	10 days	0.008	0.02	0.03
11	33 days	0.0004	0.003	0.008
12	14 weeks	0.0005	0.0004	0.001
	No. nanomoles	1,052	1,813	3,280

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.026 - 0.054	0.026 - 0.085	0.054 - 0.085
1	0.3 min	N.S.	N.S.	N.S.
2	1.0 min	N.S.	N.S.	N.S.
3	4.0 mins	S.	S.	N.S.
4	14 mins	N.S.	N.S.	N.S.
5	44 mins	N.S.	N.S.	N.S.
6	2.5 hrs	N.S.	N.S.	N.S.
7	8 hrs	S.	N.S.	N.S.
8	1 day	N.S.	N.S.	S.
9	3 days	S.	N.S.	S.
10	10 days	S.	S.	S.
11	33 days	S.	S.	S.
12	14 weeks	N.S.	N.S.	S.

FIG. 5-16: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in plastic canal models with different paste volumes and a constant tip diameter of 0.88 mm.

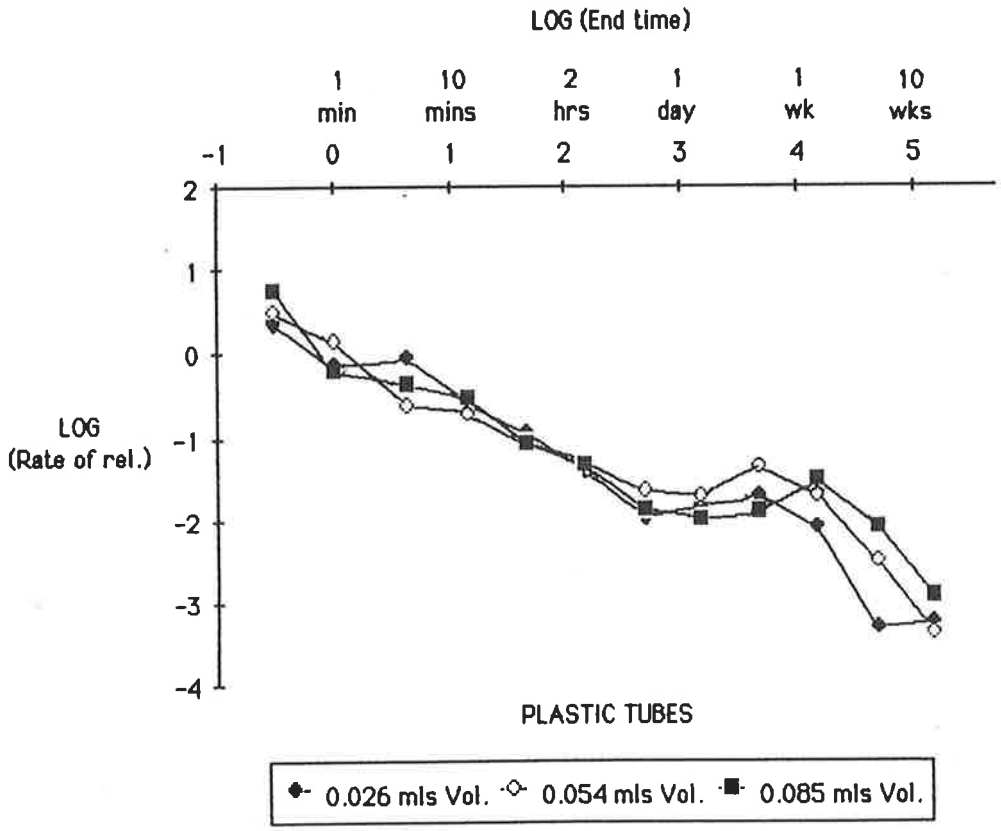


Table 5-16: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from different volumes of Ledermix paste in plastic canal models with a tip diameter of 1.4 mm.

Sam. No.	END TIME	Vol. 0.026mls	Vol. 0.055mls	Vol. 0.085mls
1	0.3 min	5.37	11.48	8.71
2	1.0 min	3.98	4.68	6.92
3	4.0 mins	1.58	1.38	1.7
4	14 mins	0.58	0.5	1.05
5	44 mins	0.24	0.23	0.29
6	2.5 hrs	0.09	0.09	0.12
7	8 hrs	0.05	0.06	0.07
8	1 day	0.03	0.03	0.04
9	3 days	0.03	0.03	0.04
10	10 days	0.002	0.01	0.03
11	33 days	0.002	0.002	0.003
12	14 weeks	0.002	0.002	0.0003
	No. nanomoles	1,052	1,813	3,280

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.026 - 0.054	0.026 - 0.085	0.054 - 0.085
1	0.3 min	N.S.	N.S.	N.S.
2	1.0 min	N.S.	N.S.	N.S.
3	4.0 mins	N.S.	N.S.	N.S.
4	14 mins	N.S.	N.S.	N.S.
5	44 mins	N.S.	N.S.	N.S.
6	2.5 hrs	N.S.	N.S.	N.S.
7	8 hrs	N.S.	N.S.	N.S.
8	1 day	N.S.	N.S.	N.S.
9	3 days	N.S.	N.S.	N.S.
10	10 days	S.	S.	S.
11	33 days	N.S.	N.S.	S.
12	14 weeks	N.S.	S.	S.

FIG. 5-17: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in plastic canal models with different paste volumes and a constant tip diameter of 1.4 mm.

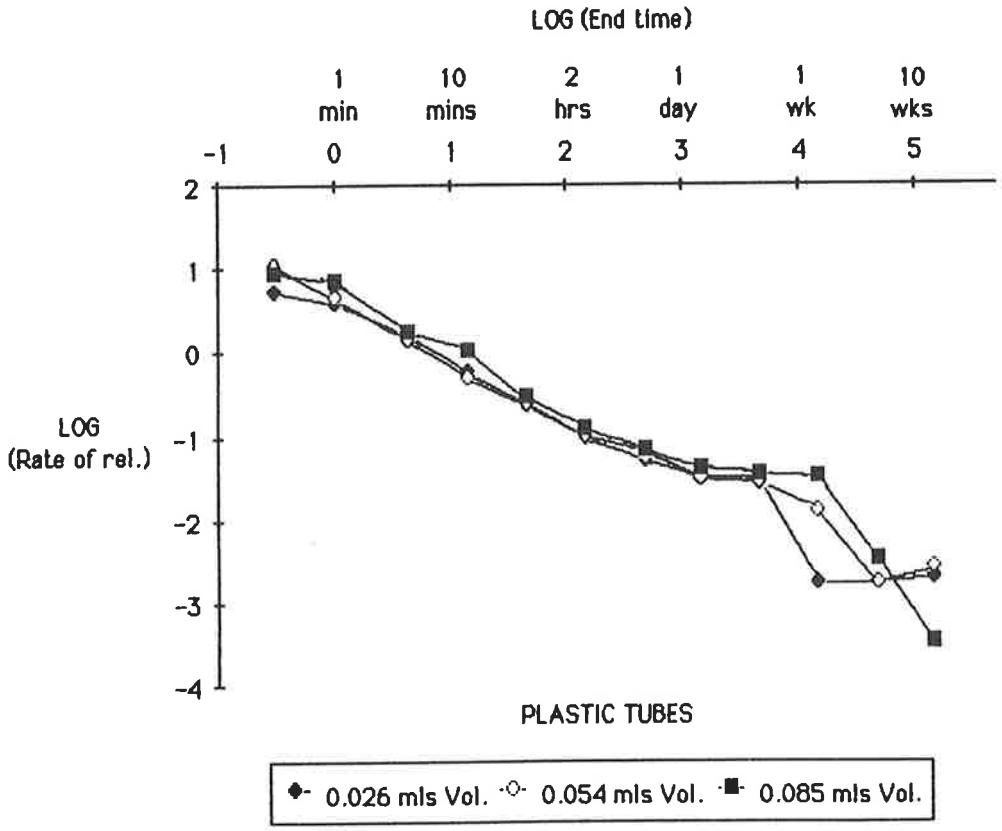


Table 5-17: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from different volumes of Ledermix paste in plastic canal models with a tip diameter of 2.0 mm.

Sam. No.	END TIME	Vol. 0.026mls	Vol. 0.055mls	Vol. 0.085mls
1	0.3 min	63.1	2.63	15.49
2	1.0 min	25.12	3.02	28.18
3	4.0 mins	6.92	3.47	11.22
4	14 mins	2.45	1.41	3.31
5	44 mins	1.2	0.58	0.91
6	2.5 hrs	0.46	0.3	0.47
7	8 hrs	0.26	0.14	0.23
8	1 day	0.08	0.07	0.13
9	3 days	0.03	0.03	0.07
10	10 days	0.009	0.01	0.02
11	33 days	0.003	0.002	0.008
12	14 weeks	0.0004	0.002	0.004
	No. nanomoles	1,052	1,813	3,280

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	0.026 - 0.054	0.026 - 0.085	0.054 - 0.085
1	0.3 min	S.	N.S.	S.
2	1.0 min	S.	N.S.	S.
3	4.0 mins	S.	N.S.	S.
4	14 mins	N.S.	N.S.	N.S.
5	44 mins	S.	N.S.	S.
6	2.5 hrs	S.	N.S.	S.
7	8 hrs	S.	N.S.	S.
8	1 day	N.S.	S.	S.
9	3 days	N.S.	S.	S.
10	10 days	S.	S.	N.S.
11	33 days	S.	S.	S.
12	14 weeks	S.	S.	N.S.

FIG. 5-18: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in plastic canal models with different paste volumes and a constant tip diameter of 2.0 mm.

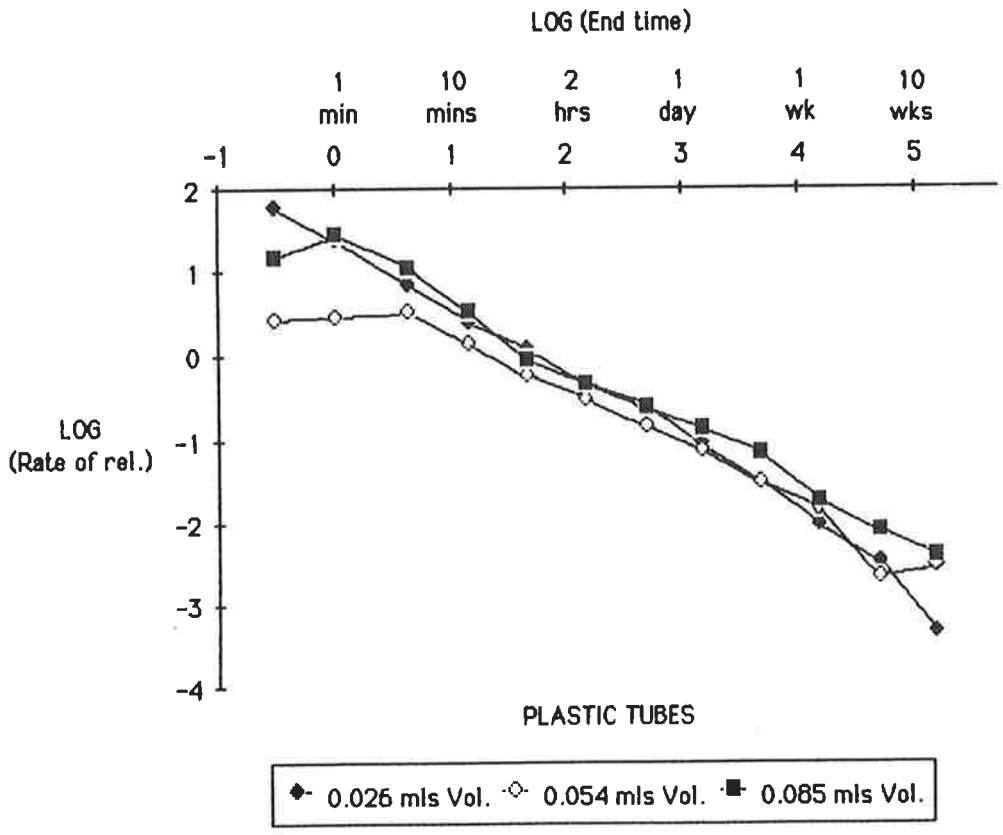


Table 5-18: The relationship of time and the mean per cent cumulative release of demeclocycline and triamcinolone from Ledermix paste in plastic canal models.

Sam. No.	END TIME	DEMECLOCYCLINE	TRIAMCINOLONE
1	0.3 min	0.23	0.14
2	1.0 min	0.8	0.46
3	4.0 mins	1.4	0.83
4	14 mins	2.2	1.32
5	44 mins	2.62	1.8
6	2.5 hrs	2.84	2.52
7	8 hrs	2.99	3.58
8	1 day	3.29	5.6
9	3 days	4.92	11.08
10	10 days	6.14	18.53
11	33 days	7.3	22.95
12	14 weeks	8.2	32.3

Table 5-19: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste in extracted human teeth of different ages.

Sam. No.	END TIME	30 y.o. M.	50 y.o. M.	39 y.o. F.
1	1 hour	0.102	0.355	0.302
2	3 hours	0.026	0.126	0.126
3	8 hours	0.013	0.044	0.046
4	1 day	0.009	0.007	0.009
5	3 days	0.008	0.006	0.006
6	10 days	0.003	0.003	0.003
7	31 days	0.001	0.001	0.001
8	14 weeks	0.0004	0.0003	0.0003
	Mean Lat. Area (sq. mm.)	44.06	40.25	34.9
	Mean nanomoles	665.5	633.6	487.8

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	30 y.o. M.- 50 y.o. M	30 y.o. M.- 39 y.o. F.	50 y.o. M.- 39 y.o. F.
1	1 hour	S.	S.	N.S.
2	3 hours	S.	S.	N.S.
3	8 hours	S.	S.	N.S.
4	1 day	N.S.	N.S.	N.S.
5	3 days	N.S.	N.S.	N.S.
6	10 days	N.S.	N.S.	N.S.
7	31 days	N.S.	N.S.	N.S.
8	14 weeks	N.S.	N.S.	N.S.

FIG. 5-19: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in extracted human teeth of different ages.

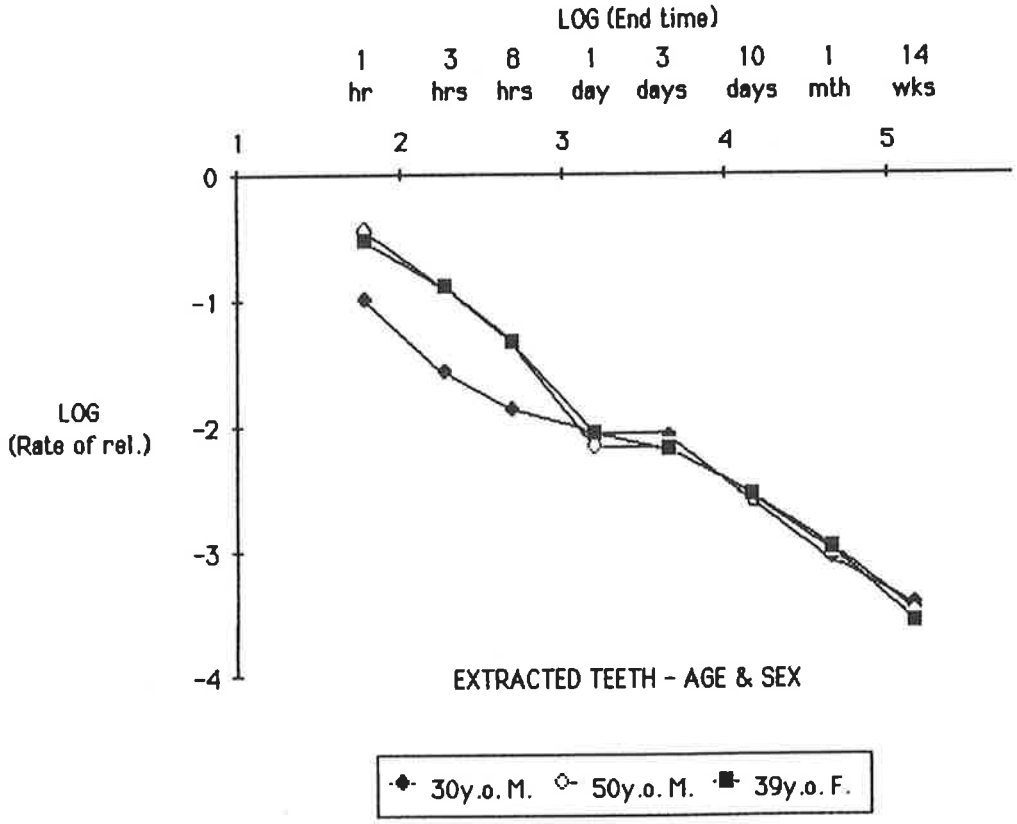


Table 5-20: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from Ledermix paste in extracted human teeth of different ages.

Sam. No.	END TIME	30 y.o. M.	50 y.o. M.	39 y.o. F.
1	1 hour	0.01	0.012	0.011
2	3 hours	0.01	0.014	0.026
3	8 hours	0.015	0.023	0.025
4	1 day	0.009	0.007	0.009
5	3 days	0.003	0.004	0.003
6	10 days	0.001	0.002	0.001
7	31 days	0.0009	0.0008	0.0007
8	14 weeks	0.0006	0.0005	0.0004
	Mean Lat. Area (sq. mm.)	44.06	40.25	34.9
	Mean nanomoles	177.7	234.9	180.7

SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS

Sam. No.	END TIME	30 y.o. M.- 50 y.o. M	30 y.o. M.- 39 y.o. F.	50 y.o. M.- 39 y.o. F.
1	1 hour	N.S.	N.S.	N.S.
2	3 hours	N.S.	S.	N.S.
3	8 hours	N.S.	N.S.	N.S.
4	1 day	N.S.	N.S.	N.S.
5	3 days	N.S.	N.S.	N.S.
6	10 days	N.S.	N.S.	N.S.
7	31 days	N.S.	N.S.	N.S.
8	14 weeks	N.S.	N.S.	N.S.

FIG. 5-20: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in extracted human teeth of different ages.

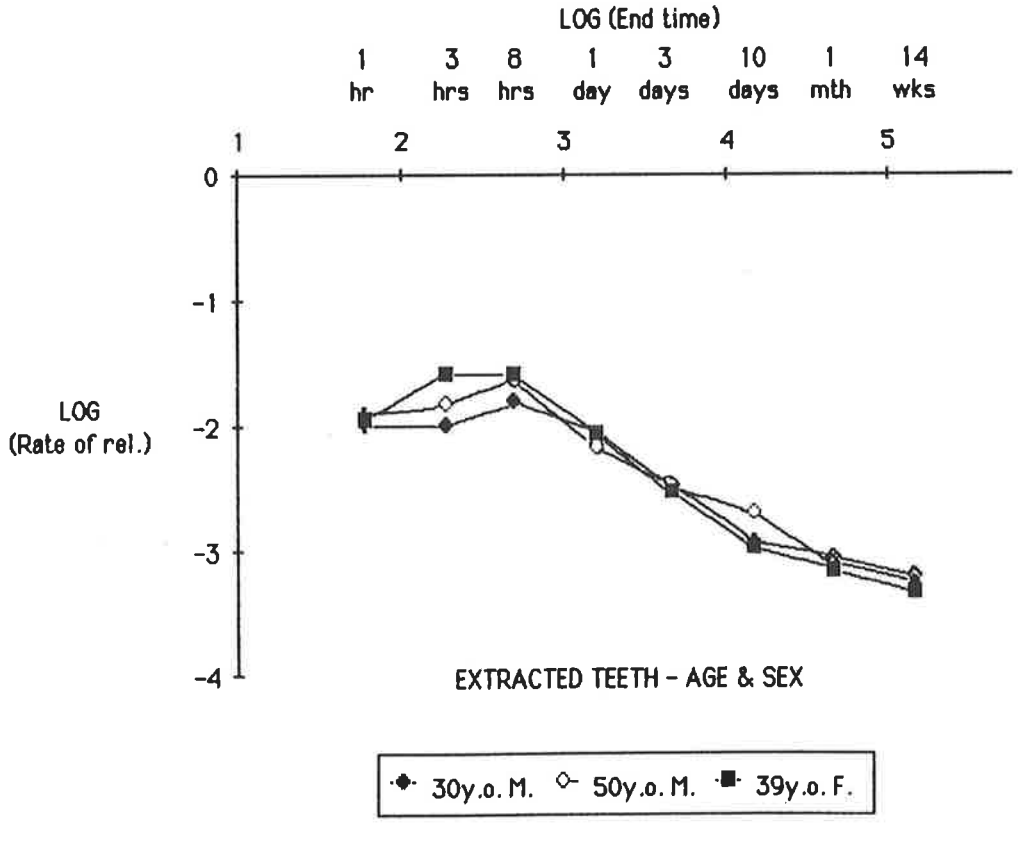


Table 5-21: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste in extracted human teeth with different internal lateral surface areas of the canal walls.

		MEAN LATERAL SURFACE AREA (sq. mm.)		
Sam. No.	END TIME	26.3	45.6	63.4
1	1 hour	0.19	0.219	0.263
2	3 hours	0.051	0.063	0.089
3	8 hours	0.022	0.028	0.033
4	1 day	0.006	0.007	0.007
5	3 days	0.007	0.007	0.01
6	10 days	0.002	0.003	0.003
7	31 days	0.0009	0.001	0.001
8	14 weeks	0.0003	0.0003	0.0004
	Mean nanomoles	370.88	712.64	955.27

		SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS		
Sam. No.	END TIME	26.3sq.mm.- 45.6sq.mm.	26.3sq.mm.- 63.4sq.mm.	45.6sq.mm.- 63.4sq.mm.
1	1 hour	N.S.	N.S.	N.S.
2	3 hours	N.S.	N.S.	N.S.
3	8 hours	N.S.	N.S.	N.S.
4	1 day	N.S.	N.S.	N.S.
5	3 days	N.S.	N.S.	N.S.
6	10 days	N.S.	N.S.	N.S.
7	31 days	N.S.	N.S.	N.S.
8	14 weeks	N.S.	S.	N.S.

FIG. 5-21: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in extracted human teeth with canals of different internal lateral surface areas.

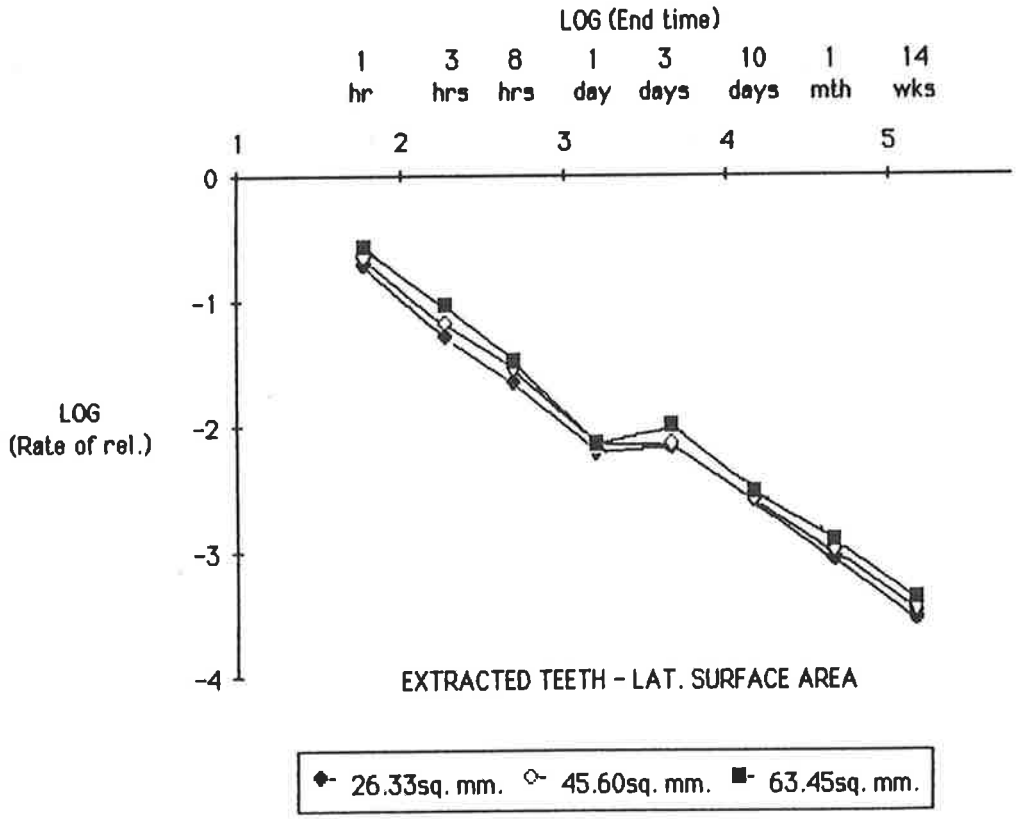


Table 5-22: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from Ledermix paste in extracted human teeth with different internal lateral surface areas of the canal walls.

		MEAN LATERAL SURFACE AREA (sq. mm.)		
Sam. No.	END TIME	26.3	45.6	63.4
1	1 hour	0.012	0.011	0.013
2	3 hours	0.011	0.015	0.015
3	8 hours	0.013	0.018	0.022
4	1 day	0.006	0.006	0.013
5	3 days	0.002	0.004	0.007
6	10 days	0.001	0.001	0.002
7	31 days	0.0005	0.0009	0.001
8	14 weeks	0.0003	0.0006	0.0009
	Mean nanomoles	120.02	235.03	255.15

		SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS		
Sam. No.	END TIME	26.3sq.mm.- 45.6sq.mm.	26.3sq.mm.- 63.4sq.mm.	45.6sq.mm.- 63.4sq.mm.
1	1 hour	N.S.	N.S.	N.S.
2	3 hours	N.S.	N.S.	N.S.
3	8 hours	N.S.	S.	N.S.
4	1 day	N.S.	S.	N.S.
5	3 days	S.	S.	S.
6	10 days	N.S.	N.S.	N.S.
7	31 days	S.	S.	N.S.
8	14 weeks	S.	S.	N.S.

FIG. 5-22: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in extracted human teeth with canals of different internal lateral surface areas.

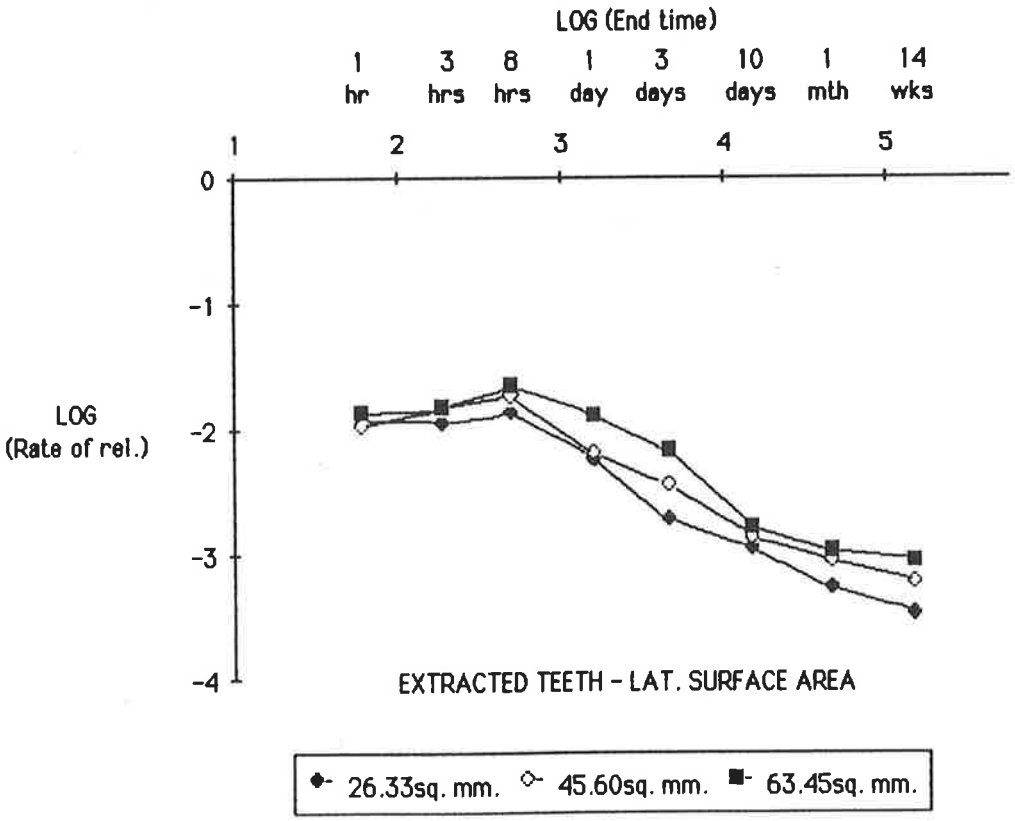


Table 5-23: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste in extracted human teeth with either the apical foramina sealed or unsealed.

Sam. No.	END TIME	APEX OPEN	APEX SEALED	SIGNIFICANCE
1	1 hour	0.49	0.436	N.S.
2	3 hours	0.204	0.19	N.S.
3	8 hours	0.028	0.025	N.S.
4	1 day	0.021	0.019	N.S.
5	3 days	0.009	0.008	N.S.
6	10 days	0.003	0.003	N.S.
7	31 days	0.002	0.001	N.S.
8	14 weeks	0.0003	0.0003	N.S.
	Mean Lat. Area (sq. mm.)	42.22	40.16	N.S.
	Mean nanomoles	389.6	418.9	N.S.

FIG. 5-23: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in extracted human teeth with the apical foramina either sealed or unsealed.

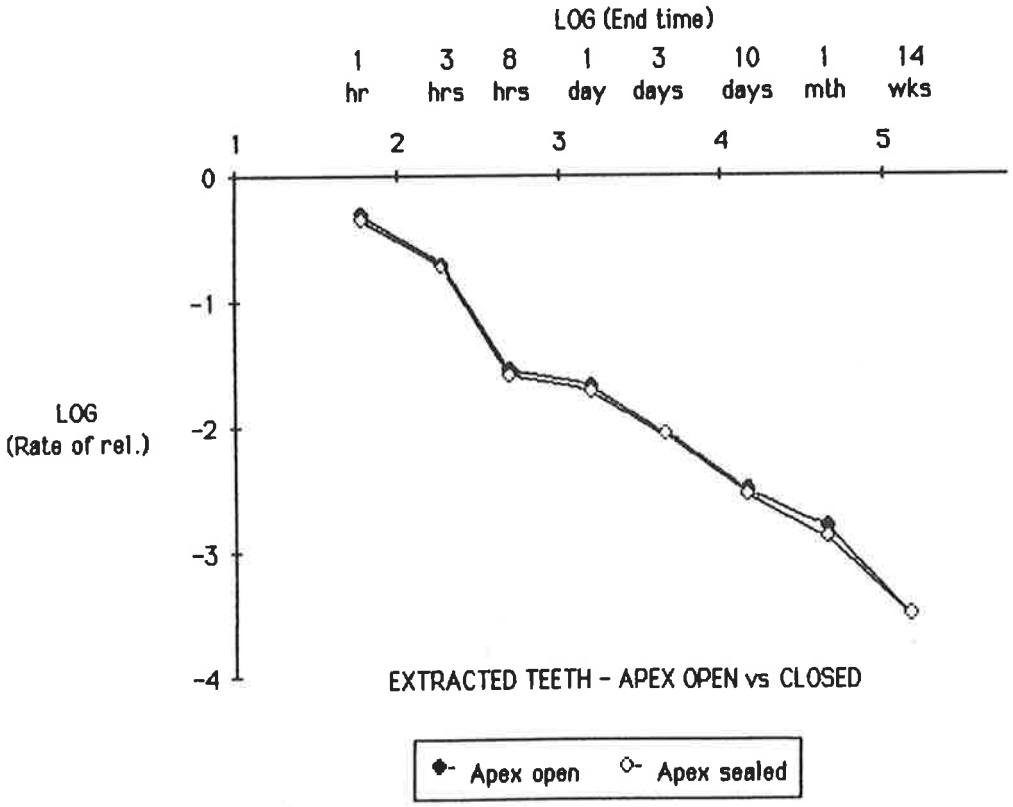


Table 5-24: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from Ledermix paste in extracted human teeth with either the apical foramina sealed or unsealed.

Sam. No.	END TIME	APEX OPEN	APEX SEALED	SIGNIFICANCE
1	1 hour	0.1	0.034	S.
2	3 hours	0.049	0.018	S.
3	8 hours	0.021	0.014	N.S.
4	1 day	0.009	0.007	N.S.
5	3 days	0.003	0.002	N.S.
6	10 days	0.001	0.001	N.S.
7	31 days	0.0009	0.0006	N.S.
8	14 weeks	0.0006	0.0005	N.S.
	Mean Lat. Area (sq. mm.)	42.22	40.16	N.S.
	Mean nanomoles	160.3	163.6	N.S.

FIG. 5-24: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in extracted human teeth with the apical foramina either sealed or unsealed.

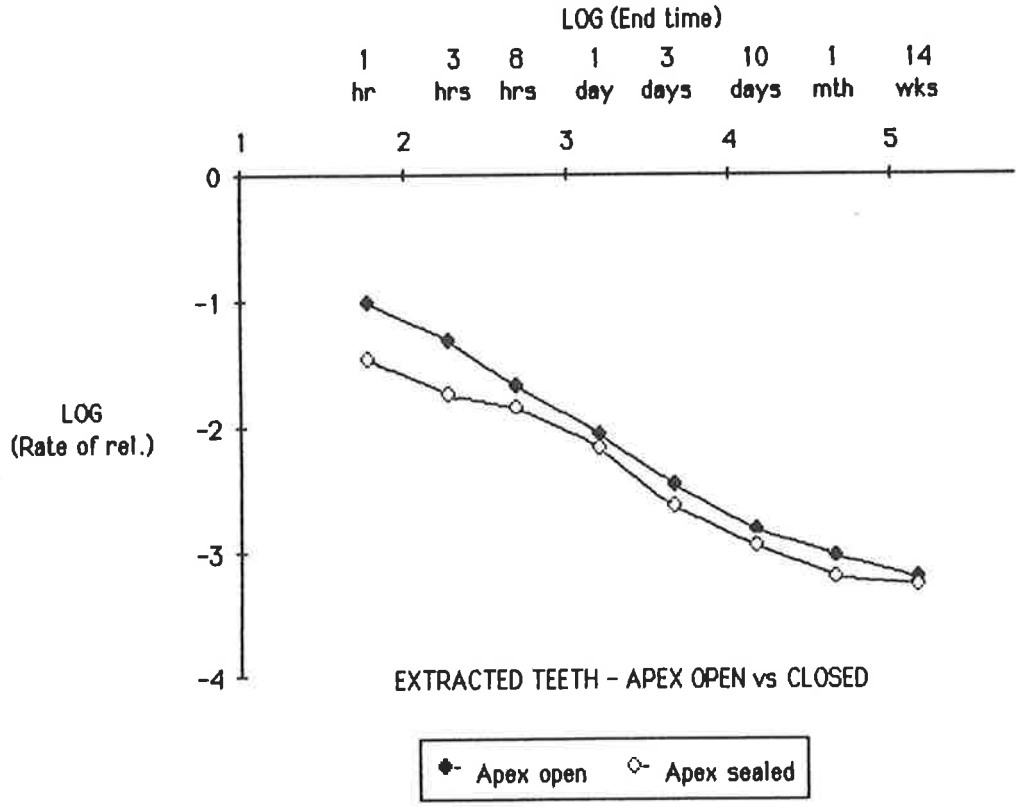


Table 5-25: Comparison between the mean per cent cumulative release of demeclocycline from Ledermix paste in extracted human teeth with either the apical foramina sealed or unsealed.

Sam. No.	END TIME	APEX OPEN	APEX SEALED	SIGNIFICANCE
1	1 hour	8.4	7.6	N.S.
2	3 hours	15.3	14.2	N.S.
3	8 hours	21.6	20.1	N.S.
4	1 day	28.9	27.1	N.S.
5	3 days	35.9	33.9	N.S.
6	10 days	45.1	42.8	N.S.
7	31 days	58.3	53.9	N.S.
8	14 weeks	66.2	59.7	N.S.
	Mean Lat. Area (sq. mm.)	42.22	40.16	N.S.
	Mean nanomoles	389.6	418.9	N.S.

FIG. 5-25: Graph of the relationship between time and the mean per cent cumulative release of demeclocycline from Ledermix paste in extracted human teeth with the apical foramina either sealed or unsealed.

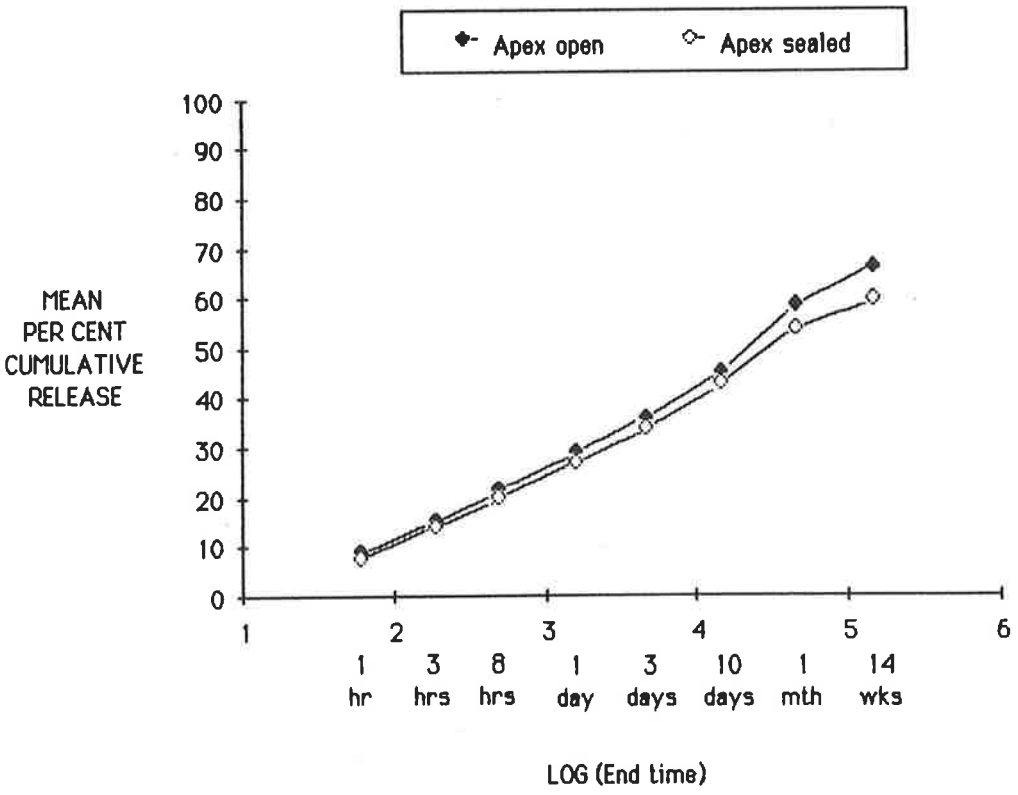


Table 5-26: Comparison between the mean per cent cumulative release of triamcinolone from Ledermix paste in extracted human teeth with either the apical foramina sealed or unsealed.

Sam. No.	END TIME	APEX OPEN	APEX SEALED	SIGNIFICANCE
1	1 hour	4.4	2.1	S.
2	3 hours	9.1	3.9	S.
3	8 hours	21.2	12.1	S.
4	1 day	29.2	18.3	S.
5	3 days	36.6	24.4	S.
6	10 days	47.4	32.4	S.
7	31 days	67.2	50.1	S.
8	14 weeks	98.3	78.8	S.
	Mean Lat. Area (sq. mm.)	42.22	40.16	N.S.
	Mean nanomoles	160.3	163.6	N.S.

FIG. 5-26: Graph of the relationship between time and the mean per cent cumulative release of triamcinolone from Ledermix paste in extracted human teeth with the apical foramina either sealed or unsealed.

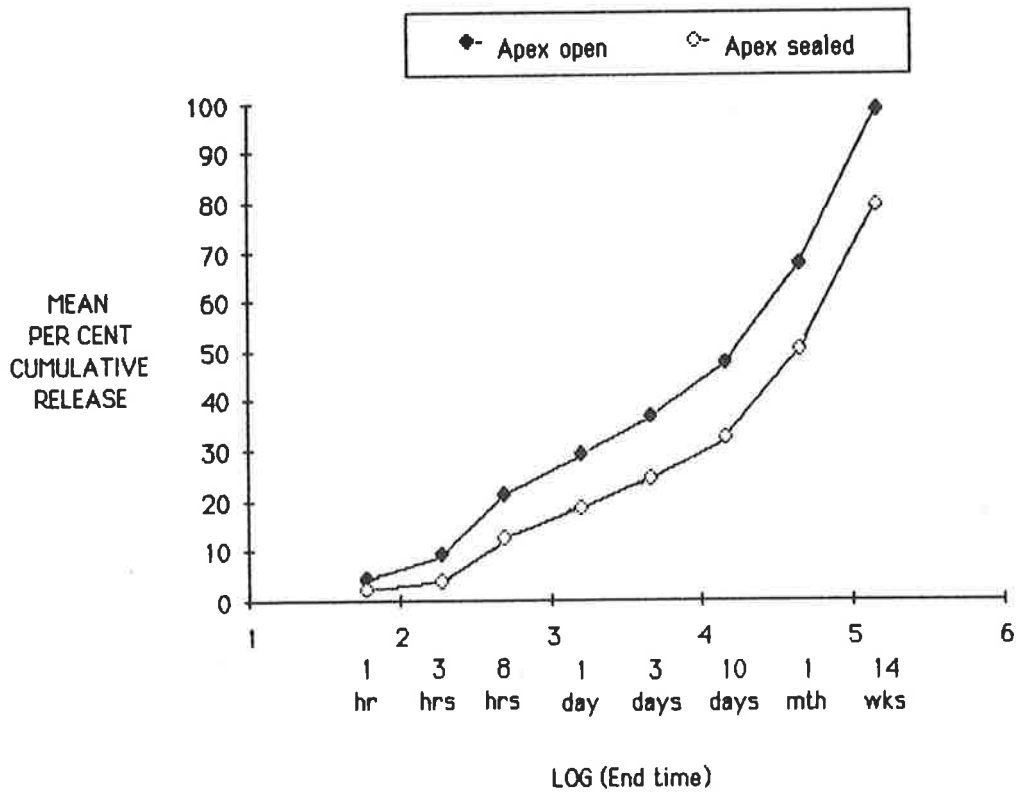


Table 5-27: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste in extracted human teeth using different irrigating solutions during the root canal preparation procedures.

Sam. No.	END TIME	E.D.T.A.C.	SAVLON	SIGNIFICANCE
1	1 hour	0.676	0.347	S.
2	3 hours	0.347	0.224	S.
3	8 hours	0.115	0.059	S.
4	1 day	0.024	0.018	S.
5	3 days	0.01	0.006	S.
6	10 days	0.004	0.002	S.
7	31 days	0.001	0.0007	S.
8	14 weeks	0.0003	0.0002	N.S.
	Mean Lat. Area (sq. mm.)	40.16	48.73	N.S.
	Mean nanomoles	418.9	694.8	S.

FIG. 5-27: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in extracted human teeth using different irrigating solutions during the root canal preparation procedures.

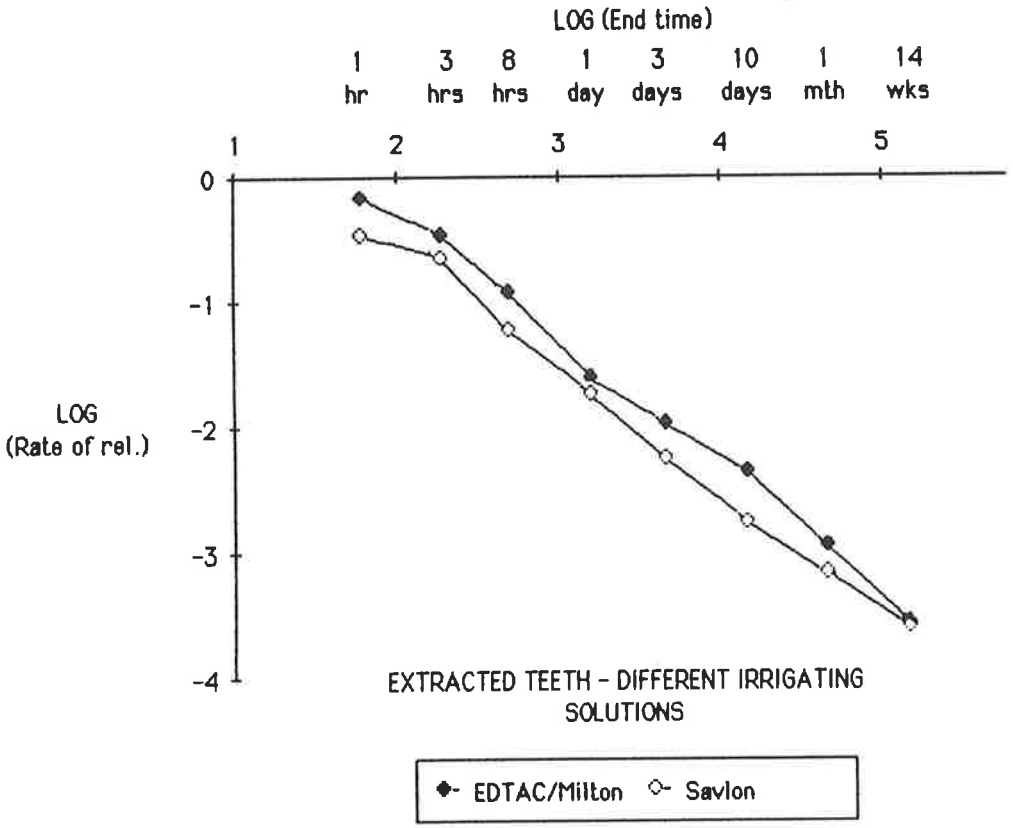


Table 5-28: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from Ledermix paste in extracted human teeth using different irrigating solutions during the root canal preparation procedures.

Sam. No.	END TIME	E.D.T.A.C.	SAVLON	SIGNIFICANCE
1	1 hour	0.151	0.02	S.
2	3 hours	0.102	0.031	S.
3	8 hours	0.043	0.03	S.
4	1 day	0.017	0.013	S.
5	3 days	0.005	0.003	S.
6	10 days	0.003	0.001	S.
7	31 days	0.0008	0.0007	N.S.
8	14 weeks	0.0004	0.0004	N.S.
	Mean Lat. Area (sq. mm.)	40.16	48.73	N.S.
	Mean nanomoles	163.6	257.7	S.

FIG. 5-28: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in extracted human teeth using different irrigating solutions during the root canal preparation procedures.

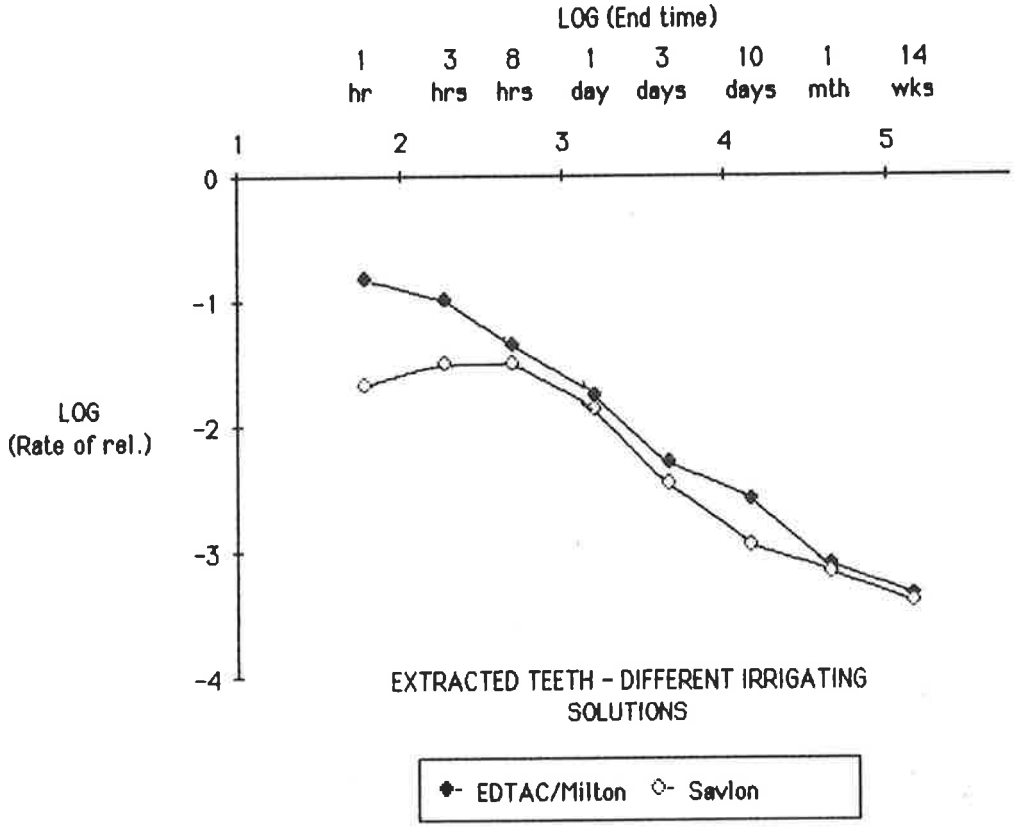


Table 5-29: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste in extracted human teeth with the cementum layer either removed or left intact.

Sam. No.	END TIME	NO CEMENTUM	+ CEMENTUM	SIGNIFICANCE
1	1 hour	0.513	0.102	S.
2	3 hours	0.155	0.026	S.
3	8 hours	0.112	0.013	S.
4	1 day	0.032	0.009	S.
5	3 days	0.014	0.008	S.
6	10 days	0.008	0.002	S.
7	31 days	0.003	0.0008	S.
8	14 weeks	0.0007	0.0004	S.
	Mean Lat. Area (sq. mm.)	39.87	44.06	N.S.
	Mean nanomoles	704	665.5	N.S.

FIG. 5-29: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste in extracted human teeth with the cementum layer either removed or left intact.

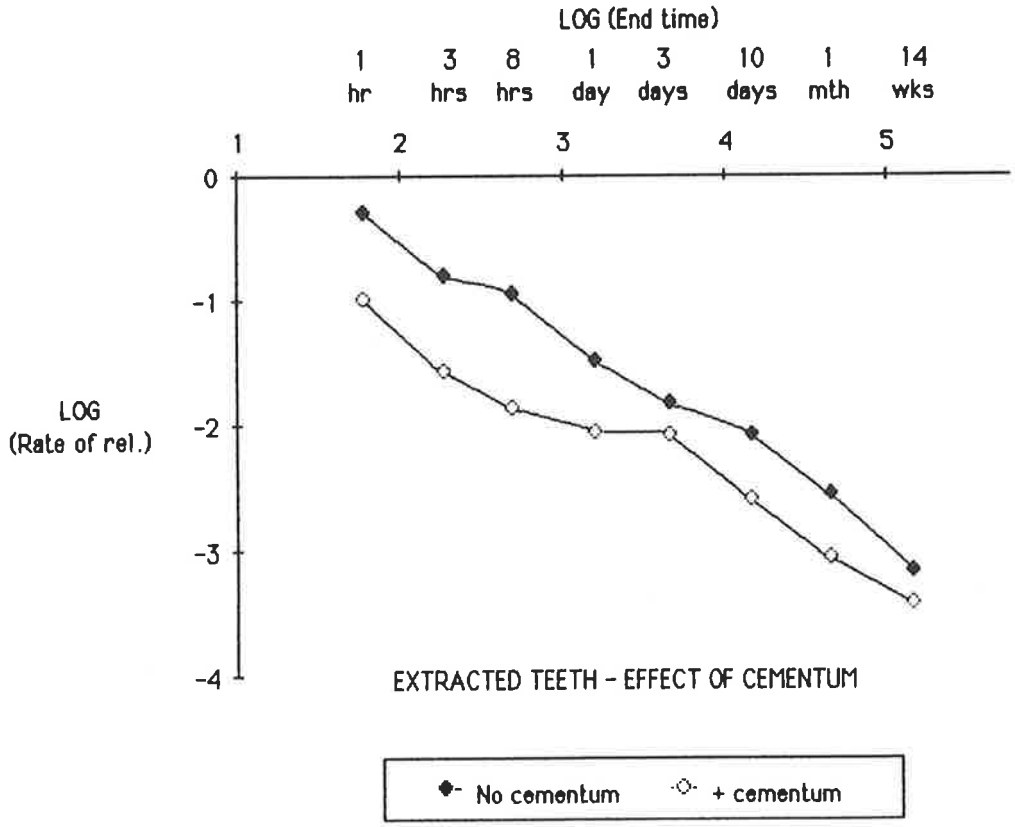


Table 5-30: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from Ledermix paste in extracted human teeth with the cementum layer either removed or left intact.

Sam. No.	END TIME	NO CEMENTUM	+ CEMENTUM	SIGNIFICANCE
1	1 hour	0.126	0.01	S.
2	3 hours	0.107	0.01	S.
3	8 hours	0.048	0.015	S.
4	1 day	0.018	0.009	S.
5	3 days	0.009	0.003	S.
6	10 days	0.005	0.001	S.
7	31 days	0.002	0.0009	S.
8	14 weeks	0.0002	0.0006	S.
	Mean Lat. Area (sq. mm.)	39.87	44.06	N.S.
	Mean nanomoles	260.9	177.7	N.S.

FIG. 5-30: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste in extracted human teeth with the cementum layer either removed or left intact.

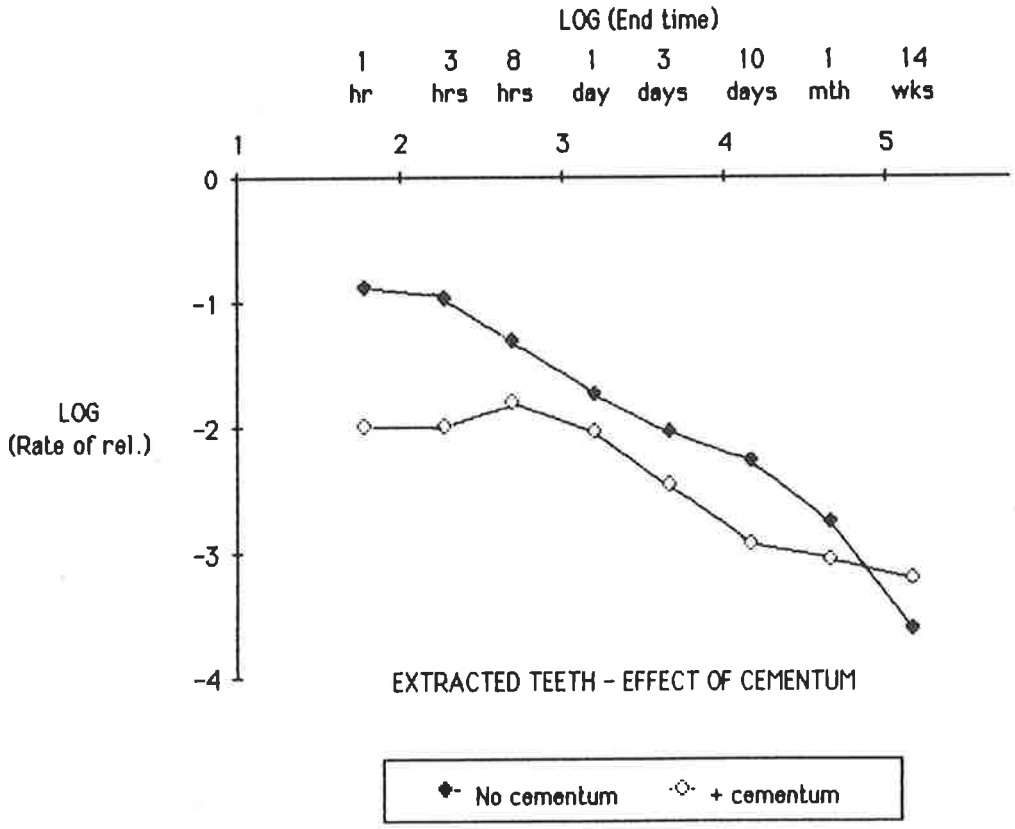


Table 5-31: Comparison between the mean rates of release (nanomoles/minute) of demeclocycline from Ledermix paste alone and when combined with Pulpdent paste in extracted human teeth.

Sam. No.	END TIME	LED. + PD.	LED. ONLY	SIGNIFICANCE
1	1 hour	0.23	0.49	S.
2	3 hours	0.12	0.204	S.
3	8 hours	0.055	0.028	S.
4	1 day	0.017	0.021	S.
5	3 days	0.007	0.009	S.
6	10 days	0.002	0.003	S.
7	31 days	0.0008	0.002	S.
8	14 weeks	0.0006	0.0003	S.
	Mean Lat. Area (sq. mm.)	41.7	42.22	N.S.
	Mean nanomoles	399.2	389.6	N.S.

FIG. 5-31: Graph of the relationship between time and the mean rates of release of demeclocycline from Ledermix paste alone or in combination with Pulpdent paste in extracted human teeth.

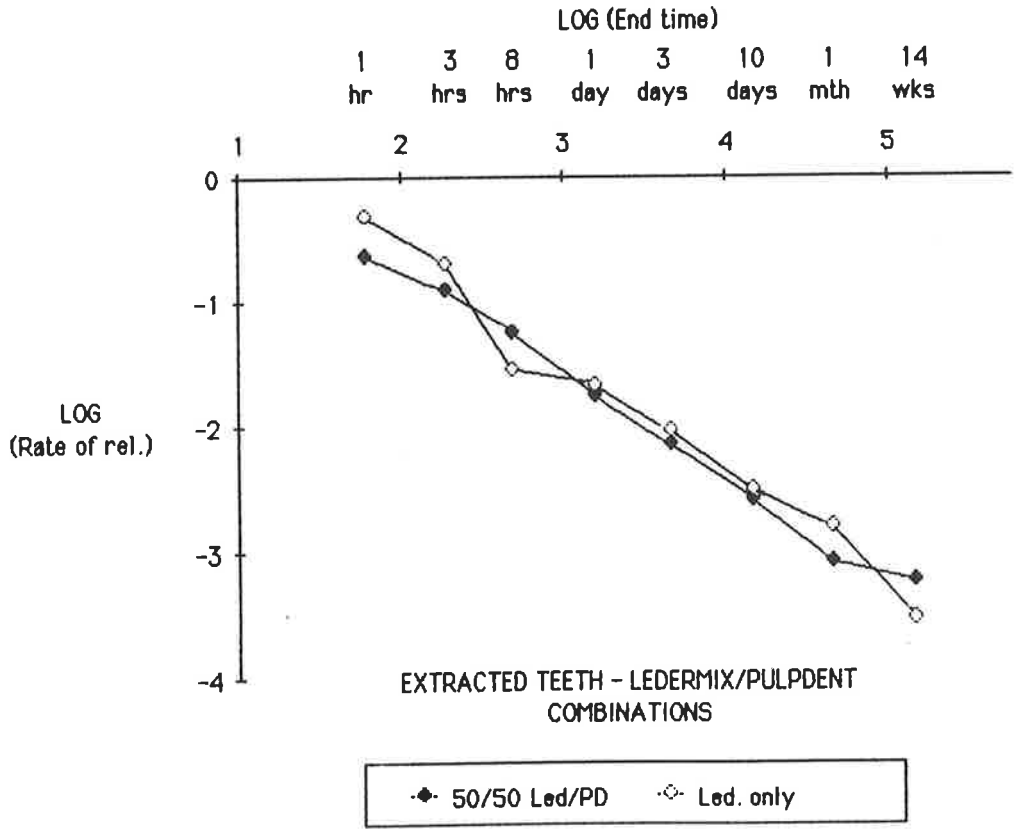


Table 5-32: Comparison between the mean rates of release (nanomoles/minute) of triamcinolone from Ledermix paste alone and when combined with Pulpdent paste in extracted human teeth.

Sam. No.	END TIME	LED. + PD.	LED. ONLY	SIGNIFICANCE
1	1 hour	0.033	0.095	S.
2	3 hours	0.02	0.049	S.
3	8 hours	0.019	0.021	N.S.
4	1 day	0.01	0.009	N.S.
5	3 days	0.005	0.003	N.S.
6	10 days	0.002	0.001	N.S.
7	31 days	0.0008	0.0009	N.S.
8	14 weeks	0.0003	0.0006	S.
	Mean Lat. Area (sq. mm.)	41.7	42.22	N.S.
	Mean nanomoles	152.1	160.3	N.S.

FIG. 5-32: Graph of the relationship between time and the mean rates of release of triamcinolone from Ledermix paste alone or in combination with Pulpdent paste in extracted human teeth.

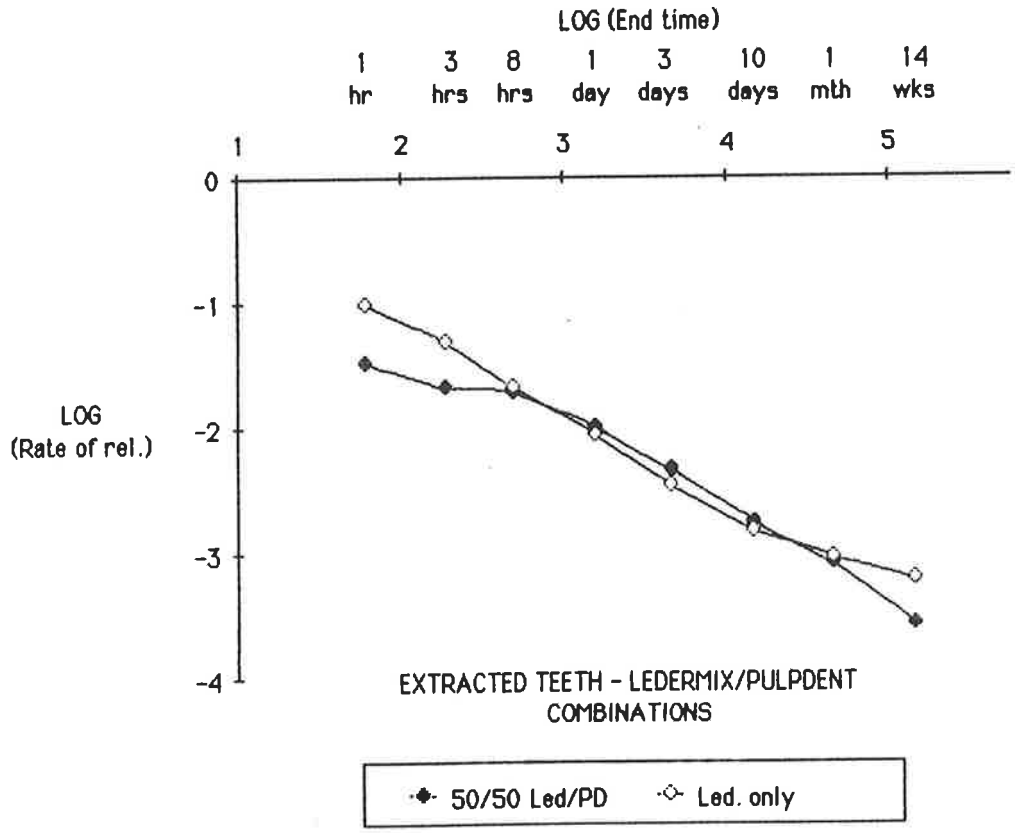


Table 5-33: Comparison between the mean per cent cumulative release of demeclocycline from Ledermix paste alone and when combined with Pulpdent paste in extracted human teeth.

Sam. No.	END TIME	LED. + PD	LED. ONLY	SIGNIFICANCE
1	1 hour	3.5	8.4	S.
2	3 hours	7.4	15.3	S.
3	8 hours	12.1	21.6	S.
4	1 day	16.7	28.9	S.
5	3 days	22.4	35.9	S.
6	10 days	29.3	45.1	S.
7	31 days	36.1	58.3	S.
8	14 weeks	43.5	66.2	S.
	Mean Lat. Area (sq. mm.)	41.7	42.22	N.S.
	Mean nanomoles	399.2	389.6	N.S.

FIG. 5-33: Graph of the relationship between time and the mean per cent cumulative release of demeclocycline from Ledermix paste alone and in combination with Pulpdent paste in extracted human teeth.

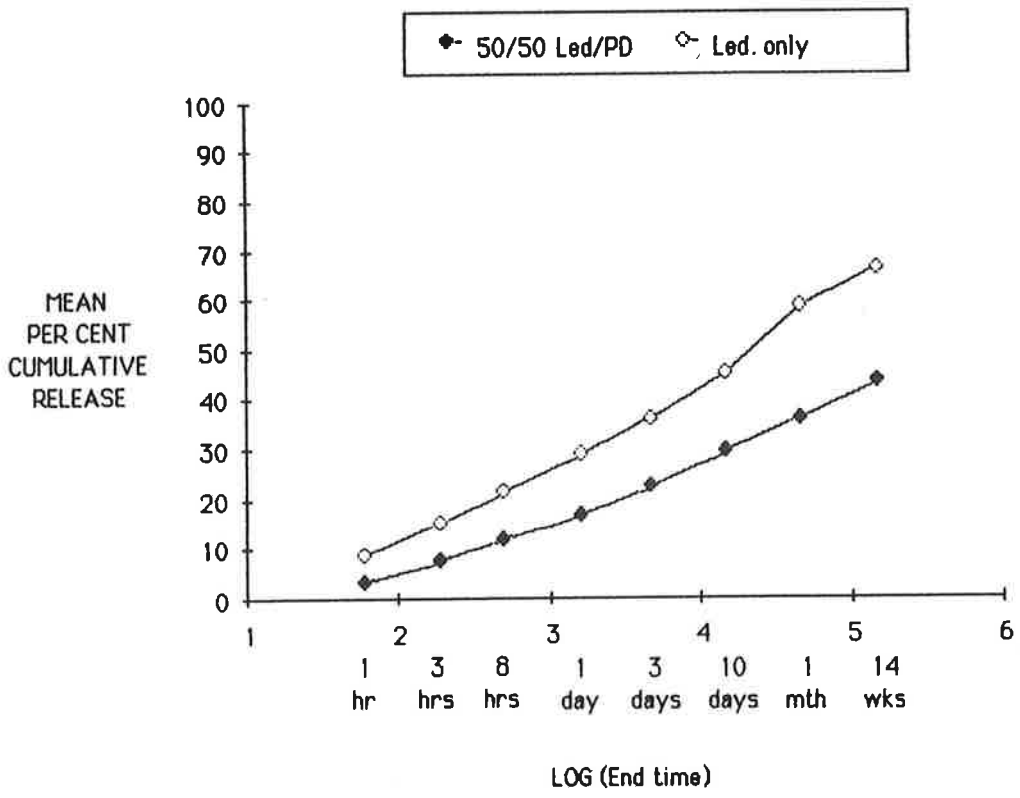


Table 5-34: Comparison between the mean per cent cumulative release of triamcinolone from Ledermix paste alone and when combined with Pulpdent paste in extracted human teeth.

Sam. No.	END TIME	LED. + PD.	LED. ONLY	SIGNIFICANCE
1	1 hour	1.5	4.4	S.
2	3 hours	3.7	9.1	S.
3	8 hours	7.6	21.2	S.
4	1 day	15.6	29.2	S.
5	3 days	25.4	36.6	S.
6	10 days	33.2	47.4	S.
7	31 days	46.7	67.2	S.
8	14 weeks	73.6	98.3	S.
	Mean Lat. Area (sq. mm.)	41.7	42.22	N.S.
	Mean nanomoles	152.1	160.3	N.S.

FIG. 5-34: Graph of the relationship between time and the mean per cent cumulative release of triamcinolone from Ledermix paste alone and in combination with Pulpdent paste in extracted human teeth.

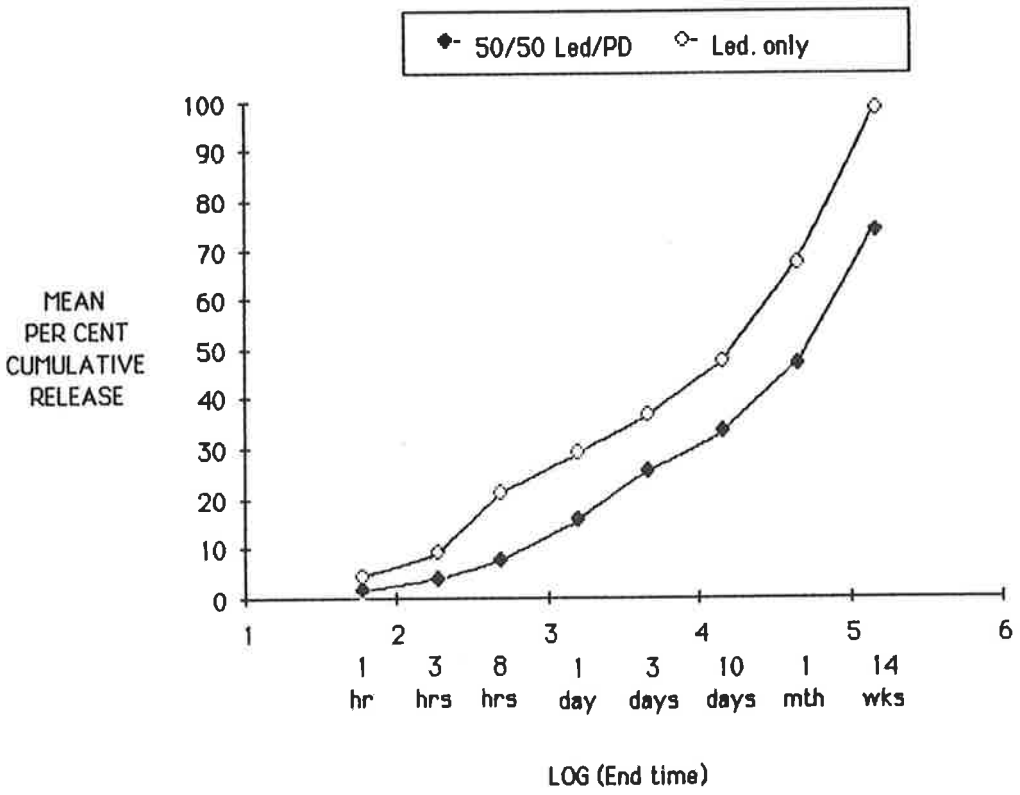


Table 5-35: Concentration (micrograms/millilitre) of demeclocycline within the root dentine after 1 week.

MID-ROOT LEVEL

Mean distance from root canal (mm)	Mean concentration (micrograms/millilitre)
1.5 - 2.5	1.7
0.6 - 1.5	2.1
0 - 0.6	21.1

APICAL THIRD LEVEL

Mean distance from root canal (mm)	Mean concentration (micrograms/millilitre)
1.2 - 1.9	1.4
0.6 - 1.2	3.3
0 - 0.6	21.1

FIG. 5-35: Diagram showing the concentration of demeclocycline within the root dentine at the mid-root and apical third root levels after 1 week.

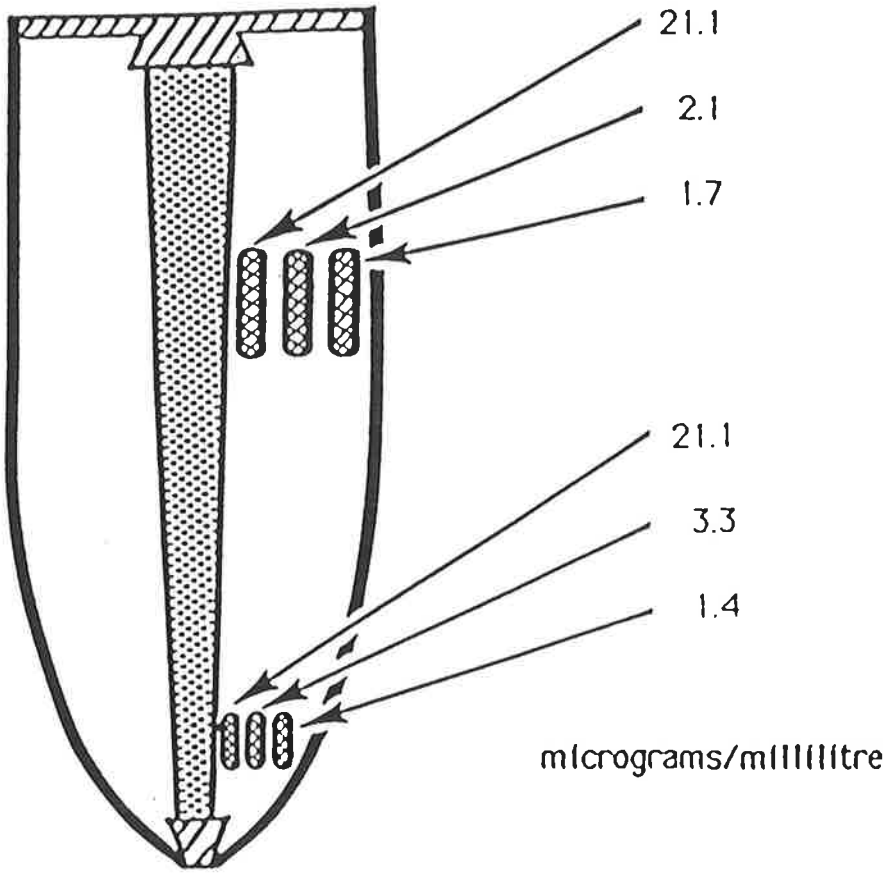


Table 5-36: Concentration (micrograms/millilitre) of triamcinolone within the root dentine after 1 week.

MID ROOT LEVEL

Mean distance from root canal (mm)	Mean concentration (micrograms/millilitre)
1.0 - 1.6	0.14
0.5 - 1.0	0.15
0 - 0.5	1.2

APICAL THIRD LEVEL

Mean distance from root canal (mm)	Mean concentration (micrograms/millilitre)
0.8 - 1.2	0.16
0.3 - 0.8	0.16
0 - 0.3	0.47

FIG. 5-36: Diagram showing the concentration of triamcinolone within the root dentine at the mid-root and apical third root levels after 1 week.

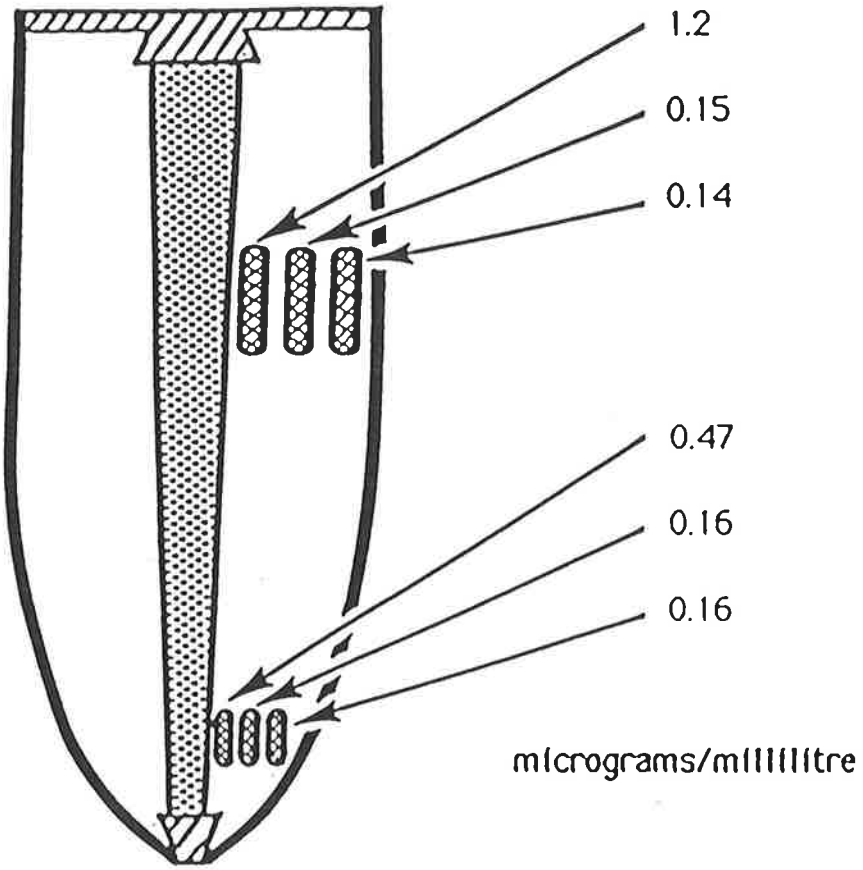


Table 5-37: The mean rates of release (nanomoles/minute) through coronal dentine of demeclocycline and triamcinolone from Ledermix paste.

Sam. No.	END TIME	DEMECLOCYCLINE	TRIAMCINOLONE
1	1 hour	0.045	0.019
2	2 hours	0.047	0.059
3	4 hours	0.03	0.06
4	8 hours	0.018	0.066
5	1 day	0.01	0.023
6	2 days	0.007	0.01
7	4 days	0.004	0.004
8	8 days	0.002	0.004
	Mean thickness of dentine (mm)	1.89	1.75

FIG. 5-37: Graph of the relationship between time and the rates of release of demeclocycline and triamcinolone from Ledermix paste through the coronal dentine.

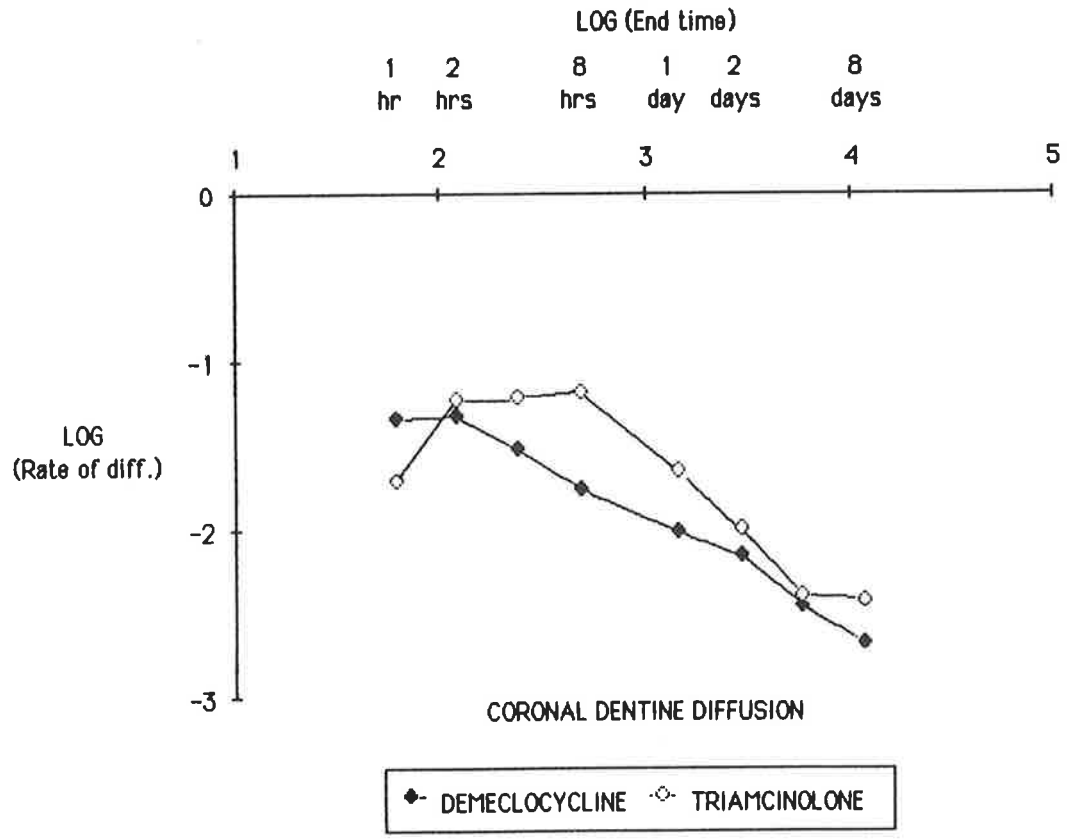


Table 5-38: Concentration (micrograms/millilitre) of demeclocycline within the coronal dentine after 2 days and 8 days.

	MEAN CONCENTRATION (micrograms/millilitre)	
Mean distance from pulp chamber (mm)	2 DAYS	8 DAYS
1.0 - 1.8	10.7	6.2
0.5 - 1.0	10	1.4
0 - 0.5	0.4	0.3

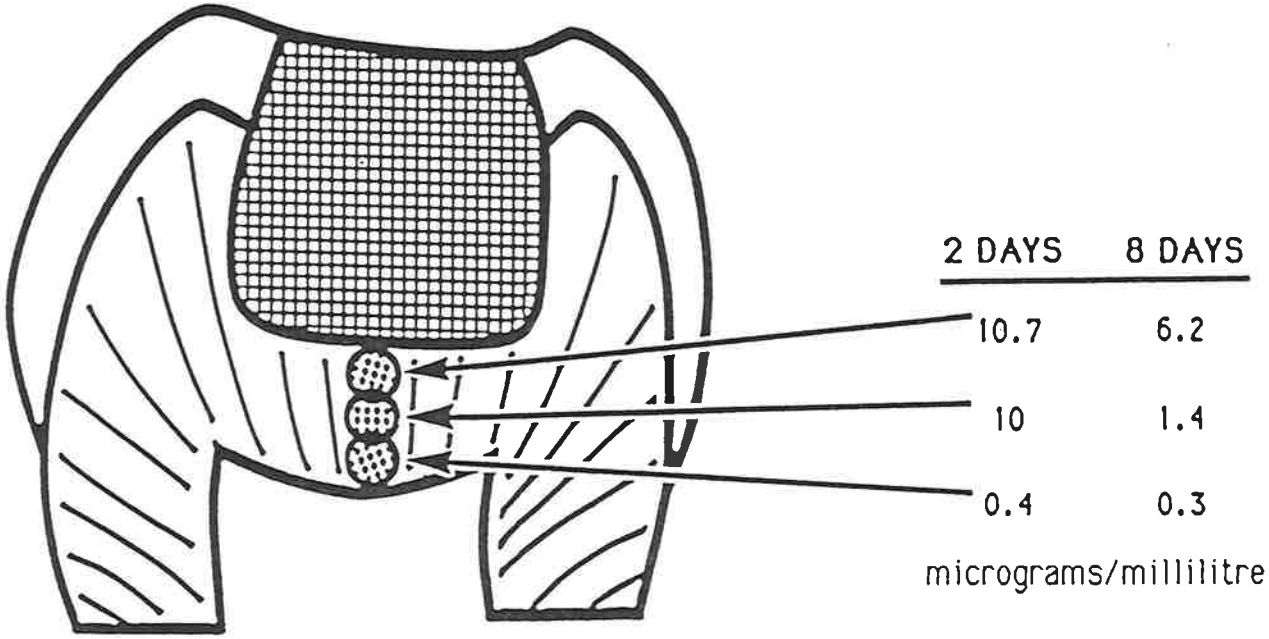


FIG. 5-38: Diagram showing the concentration of demeclocycline within the coronal dentine at three different levels after 2 days and 8 days.

Table 5-39: Concentration (micrograms/millilitre) of triamcinolone within the coronal dentine after 2 days and 8 days.

Mean distance from pulp chamber (mm)	MEAN CONCENTRATION (micrograms/millilitre) 2 DAYS	8 DAYS
1.0 - 1.8	1.8	0.9
0.5 - 1.0	0.6	0.3
0 - 0.5	0.13	0.13

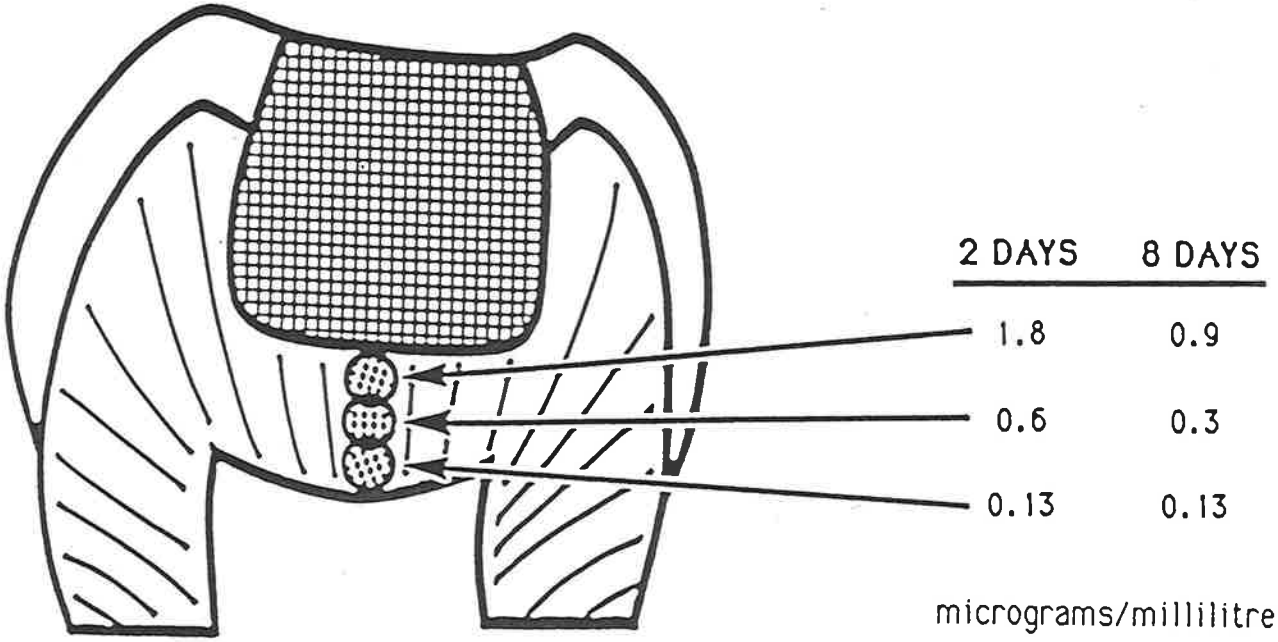


FIG. 5-39: Diagram showing the concentration of triamcinolone within the coronal dentine at three different levels after 2 days and 8 days.

APPENDIX 1

ABBREVIATIONS

Å	Ångström
$Ca(OH)_2$	Calcium Hydroxide
C.P.M.	Counts per minute
Diam.	Diameter
E.D.T.A.	15% solution of the disodium salt of ethylene-diaminetetra-acetic acid (according to von der Fehr and Nygaard-Östby,1963.)
E.D.T.A.C.	15% solution of the disodium salt of ethylene-diaminetetra-acetic acid with cetrimide (according to von der Fehr and Nygaard-Östby, 1963).
HCl	Hydrochloride
hr(s)	hour(s)
LED	Ledermix paste
Log_{10}	Logarithm to the base 10
Log	Logarithm to the base 10
M	Molar concentration e.g. 10^{-4} Molar
Milton's	1 per cent solution of sodium hypochlorite
min(s)	minute(s)
ml(s)	millilitre(s)
mm	millimetres
NaOCl	sodium hypochlorite

NM	Nanometres
NS	Not significant at the 0.05 level of significance using the student t-test.
OD	Optical Density
PD	Pulpdent paste (calcium hydroxide/methyl cellulose)
rel.	release
S	Significant at the 0.05 level of significance using the student t-test
sq. mm.	square millimetre
TMJ	Temporo-mandibular joint
Vol.	Volume
wk(s)	week(s)
^{3}H-triamcinolone	tritiated triamcinolone
^{3}H-tetracycline	tritiated tetracycline
50:50	a mix of equal volumes of Ledermix paste and Pulpdent paste.

APPENDIX 2

EXPERIMENTAL MATERIALS, FORMULAE AND SOURCES

SOLUTIONS:

Phosphate-buffered saline (pbs)

0.2M Na_2HPO_4

0.2M NaH_2PO_4

0.15M NaCl

pH 7.4 (all purchased from ANAX Australia)

Scintillation cocktail

500 ml Triton X -100 (Ajax Chemicals, Sydney, NSW)

7.5 g 2,5 diphenyloxazole (Ajax Chemicals, Sydney, NSW)

250 mg 1,4 -di[2-(5-phenyloxazolyl)] benzine

(Koch-Light Laboratories, Colnbrook, England)

in 1 litre of Toluene (Ajax Chemicals, Sydney, NSW)

E.D.T.A.C. solution

143 g Ethylenediamine tetra-acetic acid

0.84 g Cetyltrimethylammonium bromide

1000 cc Distilled water

NaOH - added until pH reaches 7.4

(Courtesy of Adelaide Dental Hospital)

Milton's Solution

Available chlorine 1% as sodium hypochlorite (NaOCl), and sodium chloride 16.5%.

(Milton Pharmaceutical Company, Villawood, NSW)

Savlon

1 per cent aqueous solution

Contains: 0.03 percent chlorhexidine gluconate

0.3 per cent cetrimide.

(I.C.I. Australia Ltd.)

MATERIALS:

Barbed broach - Nervnadeln CC-cord, Vereinigte Dentalwerke, KG, Munchen, Germany.

Burs - High speed - Tungsten carbide Jet 330, Tapered fissure 169L.

- Low speed - Round No.6, Round No.1/2.

- all burs courtesy of Adelaide Dental Hospital.

Cuvettes - Laboratory Supplies, Adelaide, S.A.

Demeclocycline HCl - Sigma Chemical Company, St. Louis, USA.

Distilled/deionised water - Dept. of Dentistry, Univ. of Adelaide.

Glass vials - with plastic lid - Laboratory Supplies, Adelaide, S.A., Cat.#18/03.

Hedstrom files - Micro Mega Brand - courtesy of Adelaide Dental Hosp.

Ledermix paste - Lederle Pharmaceuticals, Wolfratshausen.

Neos spiral root filler - courtesy of Adelaide Dental Hospital.

Paper points - Produits Dentaires S.A., Vevey, Suisse.

Plastic pipette tips - ANAX Australia, Cat.#960.

Pulpdent - Pulpdent Corporation of America, Brooklyn, Mass; USA.

Tritiated-tetracycline - New England Nuclear, Boston, Mass; USA.

Tritiated-triamcinolone acetonide - Amersham International, Buckinghamshire, England.

Visar Fil - DenMat Corporation, Santa Maria, California, 93456.

Waxes - Sticky wax - ASH, Amalgamated Dental Trade Distributors, London, England.

- Red Base Plate wax - Investo Manufacturing Company, Camellia, NSW.

EQUIPMENT:

Balance - Mettler Instrument Corporation, Princeton, N.J., USA. Model H54AR.

Calipers - Dixon, USA.

Incubator - Laboro, Selbys Scientific Instruments, Adelaide, S.A.

Liquid Scintillation Spectrometer - Packard Tri-Carb, Model 2405.

Liquid Scintillation Spectrometer - Beckman, Fullerton, California, USA. Model LS2800.

Micrometer - C.H. Baker, London. Model 17166.

Spectrophotometer - Lambda 5 UV/VIS. Perkin-Elmer Corporation, Instrument Division, Norwalk, CT, USA.

APPENDIX 3

PHARMACOLOGICAL ASPECTS OF CORTICOSTEROIDS AND TETRACYCLINES

A.3.1 CORTICOSTEROIDS - GENERAL

The two adrenal glands are part of the endocrine system and each consists of an outer layer, or cortex, and an inner layer, or medulla. The cortex is the site of corticosteroid production, whilst the medulla releases catecholamines. Steroid hormones are also produced by the gonads and they are not markedly different from those of the adrenal cortex in structure - their similar chemistry may be related to the fact that both these endocrine systems have related embryologic origin.

The steroid hormones of the adrenal cortex fall into three general classes:

a) The Glucocorticoids: e.g. hydrocortisone. These regulate the fat, protein and carbohydrate metabolism, inhibit inflammatory and allergic processes and retard the growth of connective tissue (these steroids also have some regulatory effect on sodium and potassium plasma levels).

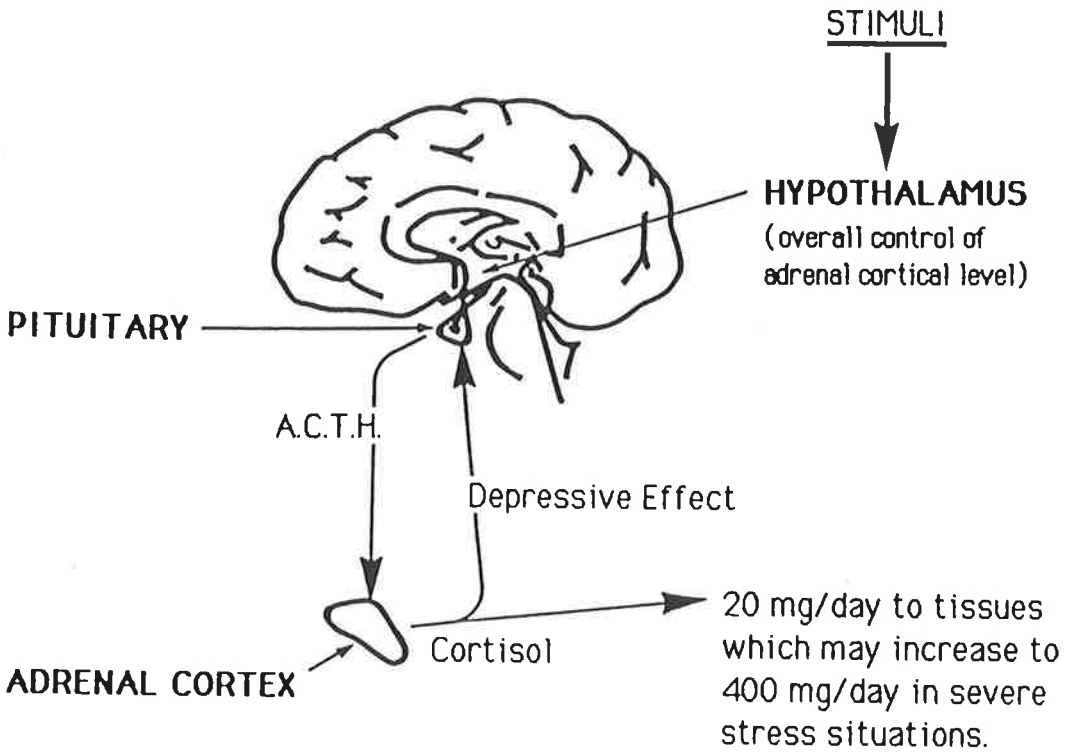
b) The Mineralocorticoids: e.g. aldosterone. These regulate the metabolism of potassium, sodium and chlorine, and the water balance. They promote inflammatory processes and the growth of mesenchymal tissue.

c) The Sex Hormones: These hormones have androgenic or oestrogenic activity and primarily affect secondary sex characteristics in their specific target organs.

Therapeutic interest is focused on the Glucocorticoids and their synthetic derivatives. Therefore the following discussion will be limited to this group only.

The secretion of Glucocorticoids is determined by the release of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. The release of ACTH is controlled by the hypothalamus which is governed by a corticosteroid negative feedback mechanism (see Fig. A.3-1). An increased blood level of cortisol decreases the production of ACTH, and, on the other hand, if the plasma cortisol level falls, then the anterior pituitary is stimulated to increase its output of ACTH. The daily secretion of cortisol in the adult is between 20-30 mg. This level may rise to the equivalent of 300-400 mg daily in "stress" situations (Walton and Thompson, 1975).

FIG. A.3-1: Normal adrenal cortical cycle
(from Parnell 1964, Walton and Thompson 1975).



A.3.2 CHEMISTRY OF CORTICOSTEROIDS

All steroid hormones have a cyclopenthanoperhydrophenanthrene ring as their nucleus (see Fig.1-1). The variation and complexity of the different steroids is derived from the large number of ways different organic radicals can be attached to the basic skeleton and this results in a profound effect on the physiological properties and behaviour of the compounds (Cope, 1972).

About fifty steroids have been isolated but only a few have physiologic activity (Haynes and Larner, 1975).

Hydrocortisone (cortisol) is the main free circulating corticosteroid in plasma. Its normal level is about 12 mg/dl. A number of derivatives of hydrocortisone have been synthesised and many of these are more potent than hydrocortisone. The greater potency may arise from:

1) a greater affinity of the steroid for the receptor protein,

2) a greater ability of the steroid-receptor complex to act at the nuclear level, or

3) less rapid degeneration in the body.

(Harper et al, 1977).

Triamcinolone acetonide is a derivative of the synthetic corticosteroid prednisolone. It is approximately five times more potent than hydrocortisone on a dose-weight basis and has virtually no mineralocorticoid effects. Triamcinolone also has the longest plasma half-life of the commonly used corticosteroid preparations (see Table A.3-1)[Fauci et al, 1976].

Table A.3-1: A comparison of common corticosteroid preparations (from Fauci et al, 1976).

COMPOUND	EQUIVALENT POTENCY (mg)	Na- RETAINING POTENCY	PLASMA 1/2-LIFE (mins)
Cortisone	25	2+	30
Cortisol	20	2+	90
Prednisone	5	1+	60
Prednisolone	5	1+	200
Methylprednisolone	4	0	180
Triamcinolone	4	0	300
Dexamethasone	0.75	0	200

A.3.3 MECHANISMS OF ACTION OF CORTICOSTEROIDS AND LOCAL EFFECTS IN DENTAL USE

The most important effect of corticosteroids in relation to their use in dentistry is the control of inflammation. The macroscopic signs of inflammation are heat, redness, swelling and tenderness.

At the microscopic level the inflammatory reaction occurs with the following effects: oedema, fibrin deposition, capillary dilatation, phagocytic migration and phagocytic activity and later, capillary proliferation, fibroblast proliferation, collagen depostion and then cicatrization (scar tissue formation)[Stanley, 1984]. The permeability of mast cell walls increases and they release histamine and heparin. The permeability of capillaries also increases to allow the cellular diapedesis and transudation of plasma (Cope, 1964).

Several theories have been suggested to explain the mechanism of action of corticosteroids against inflammation. These will be discussed briefly below.

Most of the physiologic effects and action involves permeation of the cell membrane at the level of the nucleus in R.N.A. and protein synthesis (Baxter et al, 1972). It involves binding to specific intra-cellular receptor proteins with molecular weights of about 100,000 (Levinson et al, 1972) which are found in the cytosol (Munck and Brinck-Johnsen 1968, Beato et al 1970).

The steroid-receptor complex that forms then enters the nucleus where it binds to a specific site on the chromatin of the cell nucleus (Baxter et al, 1972). This binding site is thought to be associated with D.N.A. itself, although chromatin proteins may be

involved. By this means R.N.A. synthesis and ultimately cellular protein and enzyme synthesis are modified (Tomkins and Martin, 1970).

The response depends on the particular steroid compound used and the particular target tissue. Some tissues will have specific receptors for a direct physiologic glucocorticoid response (Kirkpatrick et al, 1971).

Cawson (1968) stated that the mechanisms were primarily related to small blood vessel function consisting of preservation of both vascular tone and endothelium integrity, and the inhibition of capillary permeability increase. This leads to the suppression of cellular diapedesis and transudation of plasma (Cope, 1964). Evidence is available that the corticosteroids have a vaso-constricting action (McKenzie 1962, McKenzie and Stoughton 1962). This action might be brought about by the corticosteroids influencing the degradation of neurotransmitter in the blood vessel wall (Kalsner, 1969).

Corticosteroids suppress leukocyte accumulation at an inflammatory site (Fauci et al, 1976). If leukocytes are already present at the site, these will gradually degenerate and disappear because of their short half-life and whilst the capillary walls are intact, no influx of new leukocytes occurs under the influence of a corticosteroid (Stanley, 1984).

Stanley (1968) also put forward a theory based on the assumption by Thomas in 1965 that lysosomes are bags of fluid enclosed in a semi-permeable membrane. Stanley says these are kept in a stable state by corticosteroids. This has been confirmed by Weissman and Thomas (1963) and Weissman (1972). If the membrane is disrupted, as in inflammation, then the lysosomes release acid

hydrolases which become active and are concerned with autolysis and digestion of cell foodstuffs as well as damage to tissues. There are at least a dozen hydrolases implicated in the process, varying in kind and number from tissue to tissue. The principle enzymes are acid phosphatases, beta-glucuronidases and cathepsin (Stanley, 1968). Granules of polymorphonuclear leukocytes have a similar enzymatic effect and possibly even the same composition as the lysosomes (Grossman, 1978).

Prostaglandins have also been linked to inflammation. There are four groups of prostaglandins: PGE, PGF, PGA and PGB. Generally the individual prostaglandins of a particular group have the same biological action on any one system, but it can differ quantitatively. They may have qualitatively dissimilar actions on different tissues (Feiglin, 1978). PGE has been detected in significantly increased levels in the walls of dental cysts (Feiglin, 1978) and it is known to be related to the inflammatory signs of vasodilation, pain and oedema (Kuehl and Egan, 1980). Corticosteroids are believed to block the production of prostaglandins and thereby block the development of inflammation by the manner shown in Figure A.3-2.

Swerdlow et al (1965) reported that all the characteristics of cell displacement and superficial and deep inflammatory responses were decreased in teeth treated with corticosteroids. Other authors have reported similar findings, including the fibrous changes to the pulp tissue and retardation of connective tissue growth (Cowan 1966, Harris and Bull 1966, Mjör and Nygaard-Östby 1966, Barker and Ehrmann 1969, Sykaras 1972, Harris and Griffin 1972, 1973, Uitto et al 1975, Barker 1975).

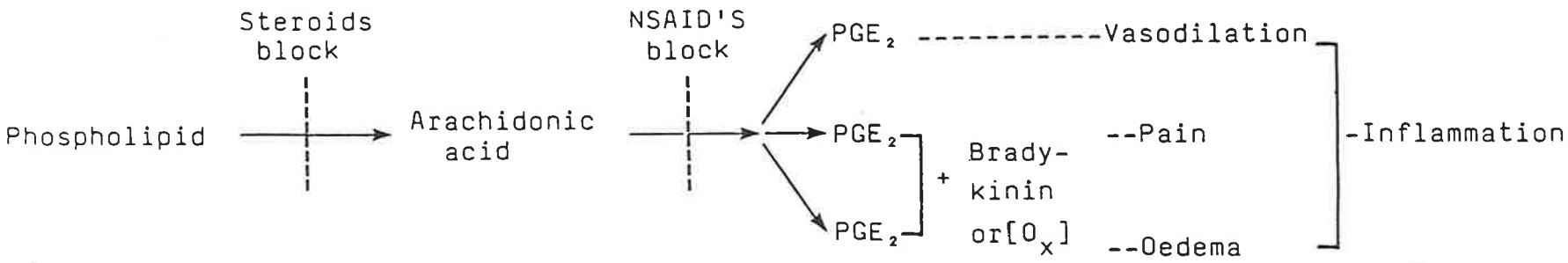


FIG. A.3-2: Relationship of prostaglandins, corticosteroids and inflammation (from Kuehl and Egan, 1980).

De Deus and Han (1967) reported the presence of lymphatic vessels in the pulp. These are believed to be responsible for helping to remove oedema from the pulp, which allows pressure to decrease and thus modifies the symptoms. Leukocytes cannot migrate whilst the capillary walls are intact and further diapedesis is prevented (Stanley, 1984).

Coricosteroids also reduce the permeability of mast cell walls (Mosteller 1962, 1963) and this prevents the escape of histamine and heparin. Other cells will also have the permeability of their walls decreased and therefore the chance of any free histamine affecting them is decreased (Mosteller 1962, 1963, Ehrmann 1964).

Some dispute also exists as to the actual mechanism of the immunological effects of steroids.

Glucocorticoids may inhibit antibody production by inhibiting functions of both lymphoid cells derived from bone marrow (beta cells)[Kirkpatrick, 1973] and thymus-derived "helper" T cells (Atkinson, 1973). The antibody mediated hypersensitivity may be influenced by glucocorticoids in two ways:

1) By suppressing the production of the antibody.

2) By modifying the local or systemic response in sensitised animals.

Walton and Thompson (1975) stated that the glucocorticoids do not prevent the occurrence of the antigen-antibody reaction but they act by protecting the cells from the outcome of this immunological reaction. However, they do not say how they protect the cells.

A.3.4 SYSTEMIC EFFECTS OF CORTICOSTEROIDS

Cortisone is secreted by the adrenal cortex and is then activated in the liver by conversion to cortisol (or hydrocortisone). The glucocorticoids have, in general, two different applications. One is as a replacement of the steroid in patients with adrenal insufficiency (either due to adrenal or pituitary disease). The other, and more common use is in the suppression of inflammatory diseases such as rheumatoid arthritis, eczema, asthma and allergic reactions (Cawson and Spector, 1978).

Below is a summary of the actions of glucocorticoids.

1) Carbohydrate metabolism: gluconeogenesis increases and the peripheral utilisation of glucose may be depressed. The blood sugar is thereby raised and diabetes may be precipitated or exacerbated.

2) Protein metabolism: Anabolism (conversion of amino acids to proteins) is depressed but catabolism (breakdown of living tissue) is not. There is therefore muscle wasting, loss of bone matrix (causing osteoporosis) and increased capillary fragility causing purpura. Healing and fibrosis are also inhibited.

3) Inflammation and allergy: Inflammatory response is suppressed. This can be useful, but may be dangerous since infection may progress unchecked.

Anaphylaxis and other consequences of allergic reactions are suppressed, but the antigen-antibody reaction itself is apparently unaffected. Antibody production is depressed only when large doses are given.

High concentrations of adrenal cortical steroids are lymphocytotoxic. These effects account for the main usage of corticosteroids clinically.

4) Mineral metabolism: Sodium retention is promoted and leads to water retention. Loss of potassium is also promoted. The end result is oedema and raised blood pressure.

5) Fat deposition: Fat is deposited in particular sites, notably the face, shoulders and abdomen. The face becomes "moon-shaped" and is a characteristic of prolonged corticosteroid therapy.

6) Mood changes: A feeling of well-being is not uncommon but may go on to euphoria, or, rarely, psychotic states.

7) Anti-vitamin D action: Absorption of calcium from the gut is impaired and hypercalcaemia in diseases such as sarcoidosis (but not hyperparathyroidism) is reversed.

8) Adrenocortical suppression: Prolonged administration of corticosteroids depresses cortical function by the feedback mechanism. After a time the cortex becomes unable to respond to stressful conditions by production of cortisol and dangerous hypotensive collapse can result. This shutdown of the system usually only occurs with doses higher than 7.5mg/day of hydrocortisone (Cawson and Spector, 1978).

Growth in children may be arrested if shutdown occurs. The overall mechanism is not known, but the epiphyses fuse prematurely and pituitary growth hormone release may be inhibited. Depression of protein formation and calcium absorption are also contributory. The moon-face appearance is accompanied by a complexion of very good colour and this can often mask serious disease.

9) Other reported effects are: peptic ulcer, acne and cataracts.

The contra-indications to the use of corticosteroids in large doses are:

1) Peptic ulceration
2) Infections - especially tuberculosis and herpes simplex (involving the cornea)
3) Diabetes
4) Hypertension or congestive cardiac failure
5) Pregnancy
6) Osteoporosis
7) Psychoses
8) Glaucoma (Meyers et al, 1976).

All these conditions can be precipitated, or exacerbated by corticosteroids. The use of the synthetic hormones, especially triamcinolone, enables a substantial enhancement of the desired action, while at the same time, reducing the less welcome side effects (Schroeder, 1962).

A.3.5 CHEMISTRY OF TETRACYCLINES

The antimicrobial agent used in Ledermix is a tetracycline, demethylchlortetracycline (demeclocycline). The following discussion will be an overall review of this group of antibiotics.

The structure of demeclocycline is shown in Figure 1-2. All of the tetracycline drugs are derivatives of a four-ringed nucleus and differ structurally only with regard to the chemical moieties attached at the 2, 5, 6 and 7 positions of the nucleus. Various derivatives exhibit slightly different pharmacologic properties, such as differences in absorption, protein binding, metabolism, excretion and degree of activity against susceptible micro-organisms (Montgomery, 1985).

The tetracyclines form water-soluble sodium or hydrochloride salts. The anhydrous base and salt forms are relatively stable, but solutions of the tetracyclines undergo decomposition quite rapidly at elevated temperature or alkaline pH (Montgomery, 1985).

A.3.6 MODE OF ACTION OF TETRACYCLINES

The term "broad spectrum" was coined to describe the tetracyclines, as they have the widest antibacterial range of all antibiotics. They are effective against gram-positive and gram-negative bacteria (both aerobes and anaerobes), treponemes, mycoplasma, rickettsia and chlamydia (Cawson and Spector 1978, Montgomery 1985). The only major groups which are completely resistant are the fungi (Cawson and Spector, 1978).

Tetracyclines are bacteriostatic. It is believed that their effect of interfering with protein synthesis is the basis of their antimicrobial actions. They also inhibit phosphorylation.

Great differences exist in the susceptibility of different organisms and the basis of this selectivity may be due to differences

in permeability and concentration of drug by the cell. Susceptible cells concentrate tetracyclines to an extent several times greater than can be found in the environment (Meyers et al, 1976).

A.3.7 RESISTANCE TO TETRACYCLINES

Bacterial resistance to tetracyclines develops in a slow, stepwise fashion similar to that occurring with penicillin derivatives (Montgomery, 1985). Strains of staphylococci, coliform bacteria, some negative bacterial species (especially pseudomonas and proteus) have developed resistance and so the tetracyclines have lost some of their usefulness. Resistance is increasing as a consequence of the intense selection pressure exerted in microbial populations by the widespread use of tetracycline drugs (Meyers et al, 1976).

A.3.8 ABSORPTION AND EXCRETION OF TETRACYCLINES

Absorption from the gastro-intestinal tract is rapid, although somewhat irregular. Some is retained in the bowel and can cause side-effects. The maximal concentration in the plasma is reached in 2 to 4 hours and gradually falls to about half this level in 9 hours and to a very low concentration at 24 hours (Meyers et al, 1976). Demeclocycline has a longer half-life (12 hours) [Accepted Dental Therapeutics, 1979].

Tetracyclines are excreted in the bile and urine, with a variable amount in the faeces. Tetracycline is excreted more rapidly

than demeclocycline, methocycline and doxycycline (Accepted Dental Therapeutics, 1979).

The Accepted Dental Therapeutics (1979) stated that the potency of demeclocycline, on a weight basis, appears to be about twice as great as that of tetracycline against most bacteria. The recommended dose for oral administration of demeclocycline HCl is 150mg every six hours as opposed to 250mg every six hours for tetracycline HCl orally (Accepted Dental Therapeutics 1979, Montgomery 1985). The greater potency and lower dosage may be a result of a longer half-life with slower excretion and/or greater susceptibility of micro-organisms.

A.3.9 SIDE EFFECTS OF TETRACYCLINES

Tetracyclines chelate with calcium ions and therefore can localise in bone and teeth. This is particularly the case in newly formed bone or teeth and can lead to fluorescence, discolouration, enamel dysplasia, deformity or growth inhibition, depending on the stage of development reached when they are administered.

Other side-effects from oral dosages are:

1) Hypersensitivity - uncommon.
2) Gastrointestinal side-effects - e.g. nausea, diarrhoea.
3) Liver toxicity - can impair liver function.
4) Kidney toxicity - can cause renal tubular necrosis, or nitrogen retention.
5) Local tissue toxicity - with intra-venous or intra-muscular injection.

6) Photosensitisation - sensitivity to sunlight or ultraviolet light, especially with demeclocycline.

7) Vestibular reactions - dizziness and vertigo.

8) Superinfection - proliferation of Candida Albicans or Staphylococci (especially Staph. aureus).

(Walton and Thompson 1975, Meyers et al 1976, Cawson and Spector 1978).

These side-effects are not very common and usually only result from long courses of oral medication.

APPENDIX 4

THE VMG-MEDIA

The formulae for the VMG-media 1-4 are (Möller, 1966) :

Sampling fluid VMG 1

a)	Bacto-gelatin, Difco 0143-01	10.0 g
	Tryptose, Difco 0124-01	5.0 g
	Thiotone, BBL 02-108	5.0 g
	Cysteine hydrochloride, Merck 2839	0.5 g
	Thioglycollic acid Light (99%) or Difco 0250-01	0.5 ml
	Glass-distilled water	900.0 ml
b)	Salt stock solution 1	100.0 ml

The ingredients in part a) were dissolved in the distilled water and combined with part b). The pH was adjusted to 7.4 with NaOH,1M. The medium was dispensed in bottles (3-50ml) or in cylinder ampules and autoclaved at 121^{o}C for 20 minutes. It was then stored at room temperature.

Salt stock solution 1

$CaCl_2.6H_2O$ pro anal.	2.4 g
KCl pro anal.	4.2 g
NaCl, Pharm.Sv.Ed.11	10.0 g
$MgSO_4.7H_2O$ pro anal.	1.0 g
Sodium glycerophosphate, Pharm.Sv.Ed.10	100.0 g
Glass distilled water	to 1000.0 ml

The salts were dissolved in about 800ml of the distilled water. The volume was completed with distilled water. Stored at +5°C.

Fluid storage medium VMG 2

a)	Agar, washed	0.1 g
	Glass-distilled water	900.0 ml
	Dissolved by boiling.	
b)	Bacto-gelatin, Difco 0143-01	10.0 g
	Tryptose, Difco 0124-01	0.5 g
	Thiotone, BBL 02-108	0.5 g
	Cysteine hydrochloride, Merck 2839	0.5 g
	Thioglycollic acid Light (99%) or Difco 0250-01	0.5 ml
	Bacteriological charcoal, Oxoid L9	10.0 g
c)	Salt stock solution 2	100.0 ml

The ingredients in part b) were dissolved in part a) after cooling the latter to 50°C. Part c) was added and pH adjusted to 7.5 with

NaOH, 1M. Dispensed in bottles or test tubes and autoclaved at 121°C for 20 minutes. Stored at room temperature.

Salt stock solution 2

Phenylmercuric acetate	0.03 g
$CaCl_2.6H_2O$	2.4 g
KCl	4.2 g
NaCl	10.0 g
$MgSO_4.7H_2O$	1.0 g
Sodium glycerophosphate	100.0 g
Glass-distilled water	to 1000.0 ml

The phenylmercuric acetate was dissolved in about 800ml of the distilled water by gentle heating. Then the other salts were added. The volume was completed with distilled water. Stored at room temperature.

Semifluid - semisolid storage medium VMG 3

a)	Agar, washed	2.0 g
	Glass-distilled water	900.0 ml
	Dissolved by boiling.	
b)	Bacto-gelatin	50.0 g
	Tryptose	0.5 g
	Thiotone	0.5 g
	Cysteine hydrochloride	0.5 g
	Thioglycollic acid	0.5 ml
c)	Salt stock solution 3	100.0 ml

The ingredients in part b) were dissolved in part a) after cooling the latter to 50°C. Part c) was added and pH adjusted to 7.5 with NaOH, 1M. Dispensed in 3 ml screw-capped bottles to the brim and sterilized by tyndallization (100°C, 15 minutes x 3 days) with the screw caps tightly closed. Stored at room temperature.

Salt stock solution 3

Phenylmercuric acetate	0.03 g
$CaCl_2.6H_2O$	2.4 g
KCl	4.2 g
NaCl	10.0 g
$MgSO_4.7H_2O$	1.0 g
Sodium glycerophosphate	100.0 g
Methylene blue	0.02 g
Glass-distilled water	to 1000.0 ml

The phenylmercuric acetate was dissolved in about 800 ml of the water by gentle heating. Then the other salts were added. The volume was completed with distilled water. Stored at room temperature.

Semisolid storage medium VMG 4

a)	Agar, washed	7.0 g
	Glass-distilled water	900.0 ml
	Dissolved by boiling.	
b)	Bacto-gelatin	5.0 g
	Tryptose	0.5 g
	Thiotone	0.5 g
	Cysteine hydrochloride	0.5 g
	Thioglycollic acid	0.5 ml
c)	Salt stock solution 4	100.0 ml

The ingredients in part b) were dissolved in part a) after cooling the latter to 50°C. Part c) was added and the pH was adjusted to 7.5 with NaOH, 1M. Dispensed in 10ml screw-capped test tubes and autoclaved at 121°C for 20 minutes. Rapidly cooled in cold water. Stored at room temperature.

Salt stock solution 4

Phenylmercuric acetate	0.05 g
$CaCl_2.6H_2O$	2.4 g
KCl	4.2 g
NaCl	10.0 g
$MgSO_4.7H_2O$	1.0 g
Sodium glycerophosphate	100.0 g
Methylene blue	0.03 g
Glass-distilled water	to 1000.0 ml

The phenylmercuric acetate was dissolved in about 800ml of the water by gentle heating. Then the other salts were added. The volume was completed with distilled water. Stored at room temperature.

Sampling Vehicles

Charcoal suspension:

Charcoal	10.0 g
VMG 1 sampling fluid	100.0 ml

Cotton swabs on a wooden stick were boiled for 5 minutes in the charcoal suspension.

Absorbent paper points were dipped in the charcoal suspension while stirring.

All vehicles were dried on filter paper and autoclaved at 121°C, the swabs for 45 minutes and the points for 20 minutes.

Table A-4: Properties of the VMG-Media (from Moller, 1966).

Designation	Properties							
	Consistency	Detoxifying substance	Protective colloides		Bacteriostatic substance	Ox-red indicator	Comments	Application
VMG I Rinsing and sampling fluid	Fluid (no agar)	–	Peptone-products 1% Gelatine 1%		–	–	–	Where additional fluid and/or inactivation of antimicrobial agents are needed before sampling
VMG II Storage and transport fluid	Fluid (0.1% agar)	Charcoal in the medium	Peptone products 0.1%	Gelatin 1%	Phenylmercuric acetate	–	Anaerobic storage is necessary	For investigation purposes
VMG III Storage and transport gel	Semisolid in room temperature Semifluid above 30° C (0.2% agar 5% gelatin)	Charcoal in the sampling vehicle		Gelatin 5%		Methylene blue	Medium filled to the brim of the tightly closed vessel. Can be stored for a relatively long time without being oxygenated	For very small samples taken on *e.g.* paper points
VMG III F Storage and transport gel							The medium overlayered with vaseline + paraffin oil. Can be stored without being oxygenated	For storage of stock cultures in the laboratory
VMG IV Transport gel	Semisolid (0.5 – 0.7% agar)			Gelatin 0.5%			When dispensed in ordinary test-tubes oxygenated in a few weeks	Samples taken on swabs

APPENDIX 5

HCMG MEDIUM BASE AND SUPPLEMENTS

HCMG medium base according to Huntoon's method and Supplements Sula, Sulb, Su2 and Su3 (from Möller, 1966).

HCMG MEDIUM BASE

First day

1.	Veal heart meat (apical half)	250.0 g
	Veal meat (lean)	250.0 g
	Distilled water	925.0 ml

Extraneous tissues, e.g. fat, sheath etc. were removed, and the meat minced twice. The well-blended mixture was stored at about +5°C for 24 hours and stirred repeatedly.

Second day

2.	Tryptose	5.0 g
	Thiotone	5.0 g
	Phytone	5.0 g
	Peptonised milk	5.0 g

These ingredients and the meat mixture were mixed and stored at about +5°C for 16-18 hours. Repeatedly stirred.

Third day

3. The meat-peptone mixture was heated to about 50°C and the following ingredients dissolved and mixed:

Glucose	2-10.0 g
NaCl	2.5 g
$NaH_2PO_4.2H_2O$	1.0 g
K_2HPO_4	1.0 g
Yeast extract	3.0 g
Cysteine hydrochloride	0.3 g
Agar	2.0 g
One whipped egg white from hen's egg.	

4. Heated at 68-70°C for 45 minutes (mixture browns).
5. pH adjusted to 7.6 with NaOH, 1M.
6. Heated in an autoclave at 100°C for 30 minutes.
7. Stirred and heated again at 100°C for 15 minutes. Passed through a strainer of stainless steel.
8. pH adjusted to 7.4.
9. Dispensed into centrifuge bottles and stored at +5°C overnight.

Fourth day

10. The medium in the centrifuge bottles was reheated at 100°C for 30-60 minutes and centrifuged when still hot.
11. The clear supernatant was dispensed into test tubes - 9ml in each, autoclaved, and rapidly cooled in cold water.
12. Sterility control after the addition of the supplements.

HCMG-Sula

1.5ml of the fluid part of Sula and a piece of raw potato (Pp) were added to 8.5ml of the HCMG base.

Sula:

Liver extract (L) with 0.6% Cy.	50.0 ml
Yeast autolysate (Ya)	50.0 ml
Horse serum, inactivated (Ser)	50.0 ml

Mixed and sterile-filtered

Piece of potato, raw, sterile-prepared (Pp).

HCMG-Sulb Semifluid Medium

1.7ml of Sulb was added to 8.3ml of the HCMG base.

Sulb:

Liver extract (L)	50.0 ml
Yeast autolysate (Ya)	50.0 ml
Horse serum, inactivated (Ser)	50.0 ml
Potato juice (Pj) with 1.5% Cy.	20.0 ml

Mixed and sterile-filtered.

HCMG-Sulb Solid Medium

HCMG, with 1.5-2% agar	850.0 ml

The melted agar base was cooled to 46-48°C. The following was added and mixed:

Sulb (see above)	170.0 ml

Poured into Petri dishes.

HCMG-Su2 Medium

2ml of Su2 was added to 8ml of the HCMG base.

Su2:

Liver extract (L) with 0.6% Cy	50.0 ml
Horse serum, inactivated (Ser)	150.0 ml

Mixed and sterile-filtered.

HCMG-Su3 Medium

2ml of the fluid part of Su3 and a piece of raw potato (Pp) were added to 8ml of the HCMG base.

Su3:

Liver extract (L) with 0.3% Cy	100.0 ml
Yeast autolysate (Ya)	100.0 ml

Mixed and sterile-filtered

Piece of potato, raw, sterile-prepared (Pp).

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