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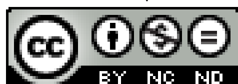

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NEUROTOXIC PROPERTIES OF EUGENOL SOLUTIONS

by

Paul J. Ashkenaz, D.D.S.

A Thesis Submitted to the Faculty of the Graduate School of Loyola University in Partial Fulfilment of the Requirements for the Degree of Master of Science

June
1967

To My Wife--

for the years of

sacrifice, understanding,

and encouragement

LIFE

Paul Joel Ashkenaz was born on February 25, 1941, in Chicago, Illinois. He graduated from Sullivan High School in February, 1959, at which time he entered the University of Illinois, Champaign-Urbana, Illinois.

He attended the University of Illinois from 1959 to 1961. He entered Loyola University School of Dentistry, Chicago, Illinois in September of 1961, and he graduated with the Degree of Doctor of Dental Surgery in June, 1965.

In September, 1965 he began a two year graduate program at Loyola University School of Dentistry leading to a Master of Science Degree in Oral Biology, and a postgraduate Certificate in Endodontics.

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CHAPTER I

INTRODUCTION

While eugenol is commonly used in the practice of dentistry as an anodyne, its use seems to be based more on empiricism than on scientific fact. The purpose of this work is to demonstrate and measure the neurotoxic properties of varying concentrations of eugenol, and its effects on the sciatic nerve of a frog. Ethanol solutions are used to bring the relatively insoluble eugenol into solution, and in this manner it is hoped that a eugenol solution can be developed which manifests profound anodyne properties with relatively low neurotoxic properties. It is hoped that this study will lead to a better understanding of one of the most widely used drugs in the dental profession.

REVIEW OF LITERATURE

Eugenol is the main constituent of oil of cloves and gives to the oil an anodyne quality which has led to the use of both, eugenol and oil of cloves, in the treatment of odontalgia. Molnar (1942), in an extensive work, traced the medical and dental history of cloves, oil of cloves, and eugenol. He stated that the earliest recorded history on the use of cloves for the treatment of a painful tooth was written by the ancient Hindus

in their writings on herbal pharmacy. In this same review, Molnar cited a Portuguese physician, Balascon of Taranta, as being responsible for the first mention of the use of cloves in the cavity of a tooth for the treatment of odontalgia. Balascon advocated the use of clove buds in the decayed tooth once the decay had been cleaned and filed away. He also made a dentifrice of the cloves but recommended its use mainly for the prevention of vomiting.

In the sixteenth century the use of cloves for the treatment of odontalgia became very popular. At the beginning of the century Joannis de Vigo (1516), a Genoa physician, was the author of a book which recommended cloves as the substance to be used in the treatment of painful teeth. Later during the same era, a German dental publication, Zene Artzney (1546), which became very popular, advocated the use of the naturally occurring clove bud, ground up into a powder, for the treatment of odontalgia. Cloves were included in formulae not only for odontalgia but also for the treatment of "mouth odor" and "numb teeth." In the latter part of the sixteenth century, Ambroise Pare, a renowned French physician of the period, wrote on the use of oil of cloves in the adequately enlarged cavity of a painful tooth (Malgaigne, 1840).

At the beginning of the seventeenth century, a medical book written for the laity, The Poor Man's Physician (Vassard 1636),

advocated the use of a mixture containing cloves in the cavity of an aching tooth. F. Friedel (1701), wrote in a thesis on cloves, "Oil of cloves gives excellent results if employed in the cavity of a carious tooth, because its burning principle is not less than actual cauterization, it dries up the humidy and burns the nerve fibers."

In the eighteenth century, Fauchard (1728) published Chirugien Dentiste, probably the first professional work on dentistry. In this book he listed the use of oil of cloves for the treatment of dental decay when the pulp was not involved and mentioned the sedative action of the cloves. Woofendale (1783), during the same era, suggested the use of oil of cloves if the pulp was exposed, and he mentioned for the first time its irritating properties.

At the beginning of the nineteenth century, Bonastre (1837) made the first scientific study of oil of cloves and tested the effects of alkali on the oil. Etting (1834) extracted pure eugenol from oil of cloves by redistillation with either sulphuric or phosphoric acid. The name eugenol was given by Cahours (1858) because of its similarity to alcohol in some chemical reactions.

Peck (1898) evaluated the compatibility of root canal drugs with skin tissue by applying a cotton pellet saturated with a test solution to the skin of the forearm with a rubber cup and

adhesive tape for a period of twenty-four to forty-eight hours. He found oil of cloves produced no tissue irritation and increased the rate of healing of experimentally produced abdominal wounds in guinea pigs.

Coolidge (1929) studied germicides used in the treatment of root canals and among the drugs tested was oil of cloves. This solution was found to be irritating, and it also exhibited a high phenol coefficient. Oil of cloves along with alcohol, phenol, cresatin, and water were found to be surface tension reducing agents, and Coolidge, therefore, assumed that they would penetrate the dentin readily. In this same study, Coolidge also showed that oil of cloves, eugenol, and alcohol form a heavy coagulum when added to egg albumin in a test tube and, therefore, were protein precipitants. Coolidge (1932) described the microscopic reaction of the periapical tissues of pulpless teeth in dogs to various drugs sealed in the canal for twenty-one days. Eugenol and oil of cloves were among the drugs tested. Eugenol produced a severe leukocytic infiltration with associated osteoclastic activity, whereas oil of cloves produced no irritation of the periapical tissues.

Macht (1938) in testing the absorption of various drugs and poisons through the skin and mucous membranes of white mice, found that when a one milliliter dose of oil of cloves was applied to the shaven skin, unconsciousness occurred in twenty minutes, followed by death within two hours and twenty minutes.

This indicated that the drug was absorbed through the skin. He also found a 0.4 milliliter mixture of eugenol and alcohol one to one (1:1), when applied in the same manner, caused coma in one hour with recovery in twenty-four hours. In further studies of the essential oils Macht (1938) found that the essential oils as well as their pure chemical constituents were easily absorbed through both skin and mucous membrane. He further found that although many of the chemicals were quite poisonous, when diluted with alcohol and other solvents they could be used as vehicles for carrying other active drugs into deeper layers of the skin and into the systemic circulation.

Hollander and associates (1947) used 200 milliliters of a 2 percent eugenol-water emulsion to stimulate gastric secretion from the gastric mucosa. Buchbinder (1947) studied the irritating effects of pure eugenol and penicillin on a scratch wound located on the forearm. The test drug was kept on the wound for twenty-four hours, after which the wound was examined for any injury. The wound sites showed no irritation or delayed healing in the presence of either drug.

Hollander (1948) again studied eugenol as a stimulus for gastric mucosal secretion, and he found a 5 percent emulsion to be the most effective of the stimulatory agents tested. It caused the gastric mucosa to yield larger volumes of mucus, and of a higher pH, than the other agents. Sober, Hollander, and

Sober (1950) then determined the LD_{50} of eugenol on rats. Prior to their toxicity studies in rats they performed preliminary experiments on dogs and found a safe dosage to approximate 0.2 grams per kilogram of body weight. Increasing the dosage to 0.25 grams did not produce any fatalities but did induce vomiting in two of the seven animals. At a dosage level of approximately 0.5 grams per kilogram body weight vomiting and ataxia were present in two of six cases and the dogs died in twenty-four hours. In determining the LD_{50} of the drug on rats, pure eugenol was used and the entire experimental dosage was given at once via a catheter for intra-gastric installation. The dosages varied from 1.5-2.2 milliliters per kilogram of body weight. All but two of the deaths occurred within the first two days. The resulting LD_{50} was estimated to be between 1.8 milliliters and 1.93 milliliters per kilogram of body weight. Manley (1948) in the same year reviewed the pulpal reaction to various chemical irritants. He found that the use of zinc oxide eugenol in deep or shallow cavities produced no deleterious effects on the pulp.

Copeland and his associates (1955) in studying the setting process of zinc oxide eugenol pastes found, using a chloroform extraction technique, they could recover 80 percent of the eugenol from a set mix of the paste. This would tend to indicate the presence of free eugenol even in a mixture of zinc oxide eugenol that seems to have hardened completely.

Perreault, Massler, and Schour (1956) studied the reactions of odontoblasts to various medicaments. One of the medicaments tested was eugenol. Cavity preparations were cut at various depths in the rat incisor, varying in depth from fifteen to ninety microns away from the pulp. The medicaments were placed in the preparations for varying lengths of time and the odontoblastic reactions to the pure eugenol, determined by the quantity and quality of reparative dentin produced by these cells, were noted. The only reaction produced by eugenol was in the deep cavity preparation. When eugenol had been in place for ten minutes, it produced only a mild reaction. However, after being sealed in the tooth for two to three days, the effects on the odontoblasts was more severe but the drug had not penetrated the subodontoblastic layer as determined by microscopic examination. Thus, it is still not known how long it would take eugenol to penetrate the dentin and reach the subodontoblastic layer.

Berman (1958) applied eugenol directly to the vital pulp tissue of two teeth and examined the tissue histologically. The sections showed a great deal of pulpal tissue destruction.

Two groups of investigators, Kozman and Burnett (1959) and Pohto and Scheinen (1959), devised similar methods of observing the circulation of blood in the dental pulp of a rat incisor, and what effects certain drugs produced on the pulpal circulation and surrounding tissue. Two of the medicaments tested by

each group of investigators were oil of cloves and eugenol. Kozman and Burnett (1959) placed olive oil on a thin dentinal layer covering the pulp and observed the circulation through this window. Eugenol when applied to the dentin produced no harmful effect on pulpal circulation. The drug was left on the dentin as long as thirty minutes and greatly facilitated visualization of the pulpal vessels. It caused no changes in the size of the vessels, or the rate of flow, and there was no hemorrhage or thrombus formation. Pohto and Scheinen (1959), in addition to eugenol, also applied oil of cloves. They applied the drugs to exposed vital pulp tissue as well as on a thin dentinal layer. When either agent, pure eugenol or oil of cloves, was applied directly to the exposed pulp, severe changes were produced in the tissue; these changes were manifested as a total thrombosis of the entire pulpal circulation within a few minutes following application. Both medicaments applied to a thin dentinal layer produced hyperemia in the underlying tissue with thrombosis occurring in only a few instances. When either liquid was mixed with zinc oxide powder into a paste the reaction was one of hyperemia, and the formation of cell aggregates.

Schilder and Amsterdam (1959), in studying the inflammatory potential of root canal medicaments, found eugenol to be severely irritating when 0.1 milliliters of the drug was injected intradermally. They also placed 0.15 milliliters of eugenol in

the conjunctival sac of a rabbit's eye and evaluated the response on the basis of swelling and hyperemia of the conjunctive, clouding of the cornea, loss of clarity of normal anatomic landmarks, and external swelling and exudation. It was found that eugenol was one of the drugs tested which produced severe inflammation.

Torneck (1961) studied the reaction of hamster connective tissue to drugs used in the sterilization of root canals. The drugs were implanted into the dorsum of the hamster and the animals were sacrificed in two groups, one group was sacrificed at forty-eight hours, and the other group at ninety-six hours. After forty-eight hours eugenol produced a localized area of suppuration and intense inflammation. After ninety-six hours the reaction was less localized, resulting in a moderate to subacute inflammatory response in the adjacent connective tissue with a moderate zone of necrosis and the beginning of muscle tissue degeneration.

Molnar (1964) questioned the usefulness of eugenol in dentistry, and he developed a new liquid to replace eugenol as the liquid in zinc oxide eugenol pastes. He stated, ". . . compounds containing clove oil and eugenol caused hemolysis as well as protein precipitation." Radden (1962) investigated the use of zinc oxide eugenol packs in monkey tooth sockets and found that the pack resulted in a polymorphonuclear response that did not return to normal in a few days, but was a continuing source of

irritation, killing the tissue it contacted, thereby seriously delaying, and in many instances actually arresting the reparative process.

Rothberg and deShazer (1965) were able to demonstrate that eugenol acts as a decalcifying agent on the dentin. They hypothesized that it was the free eugenol in the mixture of zinc oxide eugenol paste that caused the clinically observable phenomenon of soft dentin beneath a zinc oxide eugenol base or temporary filling. In the same year Sayegh (1965) implanted various materials into subcutaneous tissues of rats. A freshly prepared mix of zinc oxide eugenol produced a severe inflammatory reaction in the adjacent connective tissue. Gurney, Pollack, Farchione, and Sawinski (1966) showed eugenol to be exceptionally toxic in both conjunctival sac and periodontal flap tests performed on rabbits.

CHAPTER II

MATERIALS AND METHODS

The materials used in this study were a four channel electrical ink writing recording machine (Physiograph, E and M Instrument Company, Incorporated, Houston, Texas), varying concentrations of eugenol solutions, and frogs as the experimental animals.

The frogs were prepared for the experimental procedure by decapitating them, and then using a sharp pithing needle to destroy the spinal cord. In order to facilitate the operative procedure, after pithing the frogs, the top half of the body was cut away from the lower half by use of a scissors just above the urostyle. The skin was then stripped away from the entire lower half of the body and the muscles of the upper leg cut away to expose the sciatic nerve in its entire length. The tendinous insertion of the gastrocnemius muscle was severed and the muscle then stripped away from the bone.

A silk ligature was tightly secured about the tendon, and then tied to the strain gauge so that any tension developed by contraction of the gastrocnemius muscle, could be recorded as the appropriate writing channel of the Physiograph as the displacement and tension produced by the muscle. The machine was set for a paper speed of 0.5 centimeters per second, and the

time interval marker was set at thirty seconds. The stimulus applied to the nerve was always supramaximal in intensity, and the frequency was set at two per second, with the duration set at two milliseconds. Before the application of any experimental solutions, a control period was established. The control period was that period of time during wnich muscular contraction height remained at a steady level. After a steady contraction height was obtained, a small cotton pellet, saturated with an experimental solution was placed on the sciatic nerve. The pellet was placed on the nerve so that it was located between the stimulating electrodes and the muscle preparation. Time of solution application was appropriately indicated on the recording paper in conjunction with the fixation of the pellet on the nerve. The end point of each experimental trial was the time at which the muscular contraction height had decreased to 10 per cent of its initial height. A supramaximal stimulus was used in all cases to insure the maximal number of neurons were firing at the same time and to standardize the neuro-muscular response to the stimulus.

In order to determine whether nerve damage was permanent or reversible, Ringer's solution was subsequently applied to dilute and to wash away the experimental solutions. The nerve damage was considered reversible if an increase in the measured contractile height was obtained after the test solution had been

washed away.

Eugenol, U.S.P. was used in making the experimental solutions. Since eugenol is relatively insoluble in water, the dilute eugenol solutions were prepared by using various concentrations of ethyl alcohol and water, as shown in Table I.

To evaluate the direct effect of the alcohol on the nerve, controls were run using 35 per cent and 45 per cent aqueous solutions of alcohol. These percentages of alcohol encompass the range used in the eugenol solutions.

Other controls using only Ringer's solution were used in the study.

CHAPTER III

RESULTS AND DISCUSSION

The composition of the various eugenol solutions is shown in Table I. It can be seen that the range of eugenol concentrations used in this study varied from 100 per cent for solution one to 5.45 per cent for solution six. The time for loss of nerve conduction as determined by a 90 per cent decrease in muscular response is shown in Table II and depicted in Figure 1. Failure of the nerve tissue to exhibit recovery after rinsing with Ringer's solution for a period of three minutes, indicates nerve degeneration. Each value plotted on Figure 1 represents the average of four experimental determinations. It should be noted that because of the overlap in values, as shown in Table II, the significance of these points may be questionable. A further study with a sufficient number of samples for statistical analysis is indicated for a more precise evaluation of the experimental results.

In order to determine what effect the alcohol component of the experimental solutions had on the nerve tissue in the experimental range, aqueous alcoholic solutions of 35 per cent and 45 per cent were prepared and used as controls. The time for loss of nerve conduction, under the standard test conditions, for the

alcohol solutions is shown in Table III. The tissue response values in percent, for each alcohol solution respectively, is plotted and shown in Figure 2, each value representing an average of three experimental determinations. Recovery of muscular response (Figure 2) could be demonstrated using the aqueous alcohol solutions. The muscular response stayed constant during the recovery period, which was run for an average of two minutes. It can be seen in Figure 2, that the time for a 90 per cent loss of muscular response for the 35 and 45 per cent alcohol control solutions is approximately three and one-half minutes. In comparison to the experimental eugenol solutions, the time for a 90 per cent drop in muscular response is three to four times longer for the alcohol controls. A comparison of the results in Table I with those of Table II and Figure 2 shows that alcohol in aqueous solutions, a) gives a toxic character to the solution, b) is not the only toxic agent in the experimental eugenol solutions, and c) such toxicity to nerve tissue, under these experimental conditions, is reversible.

The results of the Ringer control solutions are found in Table IV and Figure 3. It can be seen that none of the Ringer controls ever produced a 90 per cent decrease in muscular contraction over the period tested, five to ten minutes. However, it should be noted that the tissue response at the seven to eight minute time interval for nerves exposed to the alcoholic

solutions (Figure 2), and the Ringer control solutions (Figure 3) is nearly identical. This indicates a recovery of the alcohol treated nerve tissue close to the physiologic maximum for this time period, as indicated by the Ringer controls and under these experimental conditions. The recovery response is approximately 90 per cent of the control response.

In Figure 4, the upper curve, a duplicate of Figure 1, is a plot of the average values of nerve degeneration versus eugenol concentration. It can be observed that eugenol toxicity increases with decreasing concentrations to a value of approximately 21 per cent, after which the toxicity appears to decrease. The lower curve in Figure 4 is the plot of alcohol concentration (vertical axis) versus eugenol concentration (horizontal axis). The vertical location of the curve was arbitrarily set so as to show the relationship of alcohol concentration, eugenol concentration and degeneration time simultaneously. From Figure 4 it is clear that as the eugenol concentration decreases to a value of approximately 21 per cent, the alcohol concentration increases to a maximum as does the toxicity. After this point, all three factors--toxicity, eugenol concentration, and alcohol concentration--decrease in value. It, therefore, appears that the alcohol component of the eugenol solutions enhances the toxic action of eugenol in some fashion, perhaps by facilitating penetration of the nerve sheath.

CHAPTER IV

SUMMARY AND CONCLUSION

An investigation into the neurotoxic properties of eugenol solutions was performed using the sciatic nerve of a frog as the test object. The inability of the nerve trunk to conduct enough impulses to produce measurable contraction of the gastrocnemius muscle, along with a failure of the preparation to show recovery were considered as neurotoxic manifestations of the eugenol solutions. The concentrations of eugenol in the solutions varied from 5.45 per cent in the most diluted form, to 100 per cent in the concentrated form.

In comparing aqueous alcohol controls with the eugenol experimental solutions, it was demonstrated that the alcohol present in the experimental solutions was not the cause of the irreversible nerve destruction. Although the alcoholic controls produced a 90 per cent decrease in muscular response, recovery could be demonstrated on the nerves to which the alcohol solutions were applied.

The experimental results indicate that it was the eugenol in the experimental solutions that was responsible for the irreversible nerve damage. The experimental solutions of intermediate eugenol concentrations exhibited neurotoxicity measurably

faster than concentrated or dilute eugenol solutions. It was also demonstrated that the eugenol in the experimental solutions was still a potent tissue damaging agent even at a concentration of 5.45 per cent. At this concentration it can still prevent passage of nerve impulses along the nerve fiber.

Although caution must always be exercised in transferring laboratory results to clinical situations, the implication exists that the clinical usage of eugenol at full strength may be questionable, and that the eugenol-alcohol-water solutions may be as strong a tissue damaging solution as eugenol in its pure form.

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APPENDIX

TABLE I

COMPOSITION OF EXPERIMENTAL SOLUTIONS

Solution No.	Eugenol	Ethyl Alcohol	Water
1	100.00%	0.00%	0.00%
2	37.03	37.03	25.94
3	29.64	39.52	30.84
4	21.55	43.10	35.35
5	9.80	39.21	50.99
6	5.45	36.14	58.41

TABLE II

DEGENERATION TIME FOR EXPERIMENTAL SOLUTIONS

Solution No.	Trial No.	Time for Degeneration	Height A Initial	Height B 10% of A	Recovery Height
1	1	57 secs.	27 mm	2.7 mm	none
	2	44	6	0.6	none
	3	90	5	0.5	none
	4	94	5	0.5	none
Total		285	43	4.3	
Average		71.2	10.7	1.1	
2	1	33.4	22	2.2	none
	2	59.8	25	2.5	none
	3	72.6	25	2.5	none
	4	91.2	4	0.4	none
Total		257.0	76	7.6	
Average		64.2	18	1.8	
3	1	80.0	44	4.4	none
	2	81.8	44	4.4	none
	3	45.2	35	3.5	none
	4	105.4	38	3.8	none
Total		312.4	161	16.1	
Average		78.1	40.2	4.0	
4	1	38.4	8.0	0.8	none
	2	59.0	20.0	2.0	none
	3	59.0	24.0	2.4	none
	4	54.7	23.0	2.3	none
Total		211.1	75.0	7.5	
Average		52.7	18.7	1.8	
5	1	58.9	32	3.2	none
	2	33.4	22	2.2	none
	3	60.4	42	4.2	none
	4	90.4	43	4.3	none
Total		243.1	139	13.9	
Average		60.7	34.7	3.4	
6	1	129.3	21	2.1	none
	2	76.3	50	5.0	none
	3	41.4	37	3.7	none
	4	98.8	30	3.0	none
Total		345.8	138	13.8	
Average		86.5	34.5	3.4	

TABLE III

ALCOHOL CONTROL SOLUTIONS

Solution	Trial	Time for Degeneration	Initial Contraction Height	Minimal Contraction Height	Per cent Decrease in Tissue Response	Recovery Per cent
35 % Alcohol	1	4 min.	20 millimeters	1 millimeter	95	25
	2	2	20	1	95	25
	3	4	13	1	92	100
45 % Alcohol	1	4	23	2.2	90	39
	2	3	22	2.2	90	32
	3	2	12	1.2	90	58

TABLE IV

RINGER CONTROL SOLUTIONS

Solution	Trial	Initial Contraction Height	Minimal Contraction Height	Per cent Decrease in Response	Time Period
Ringer's	1	25 millimeters	4 millimeters	84	8 min.
	2	30	9	70	5
	3	15	10	33	8

FIGURE 1

Eugenol Concentration versus Degeneration Time

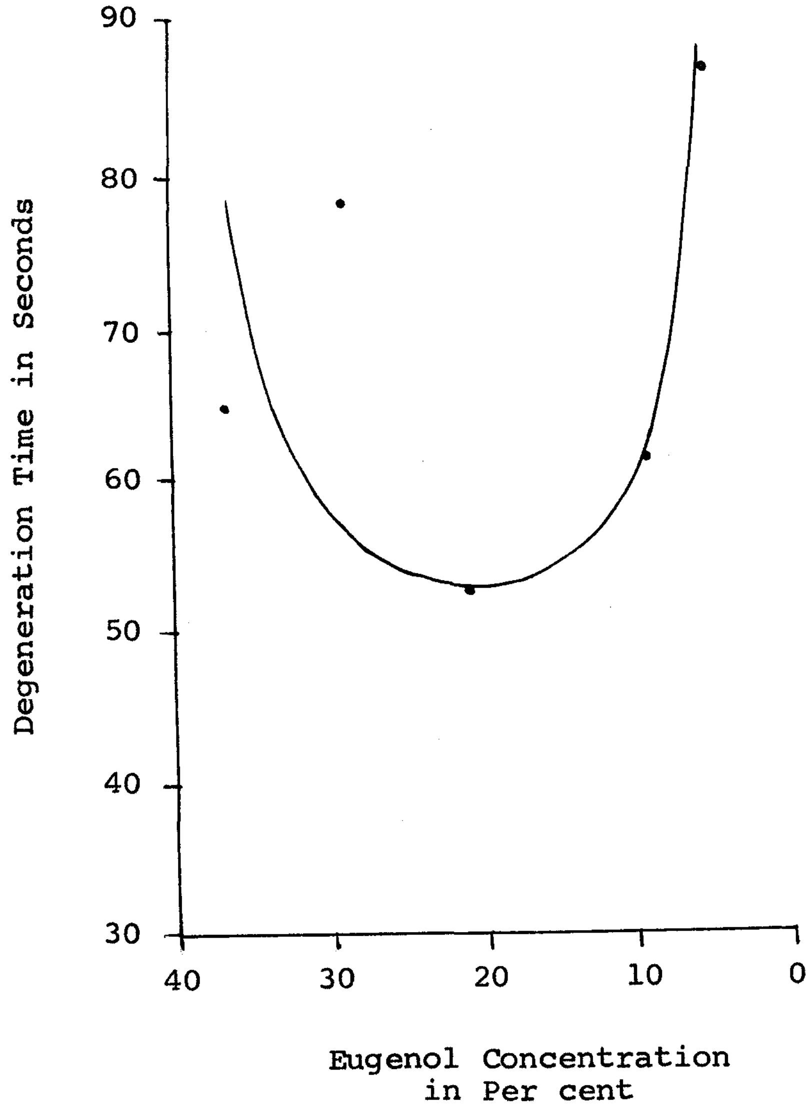


FIGURE 2

Muscle Response versus Time

for Alcohol Solutions

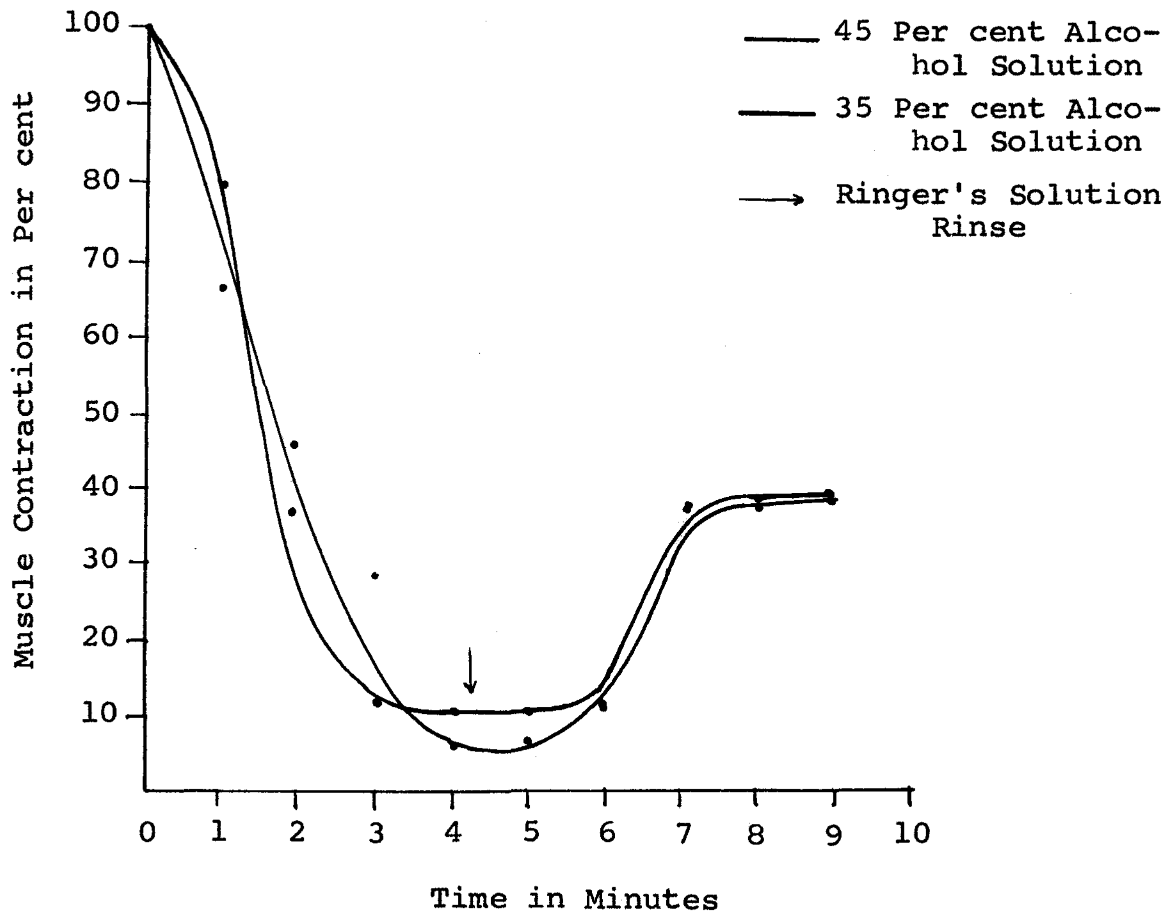


FIGURE 3

Muscle Response versus Time

for Ringer's Solution

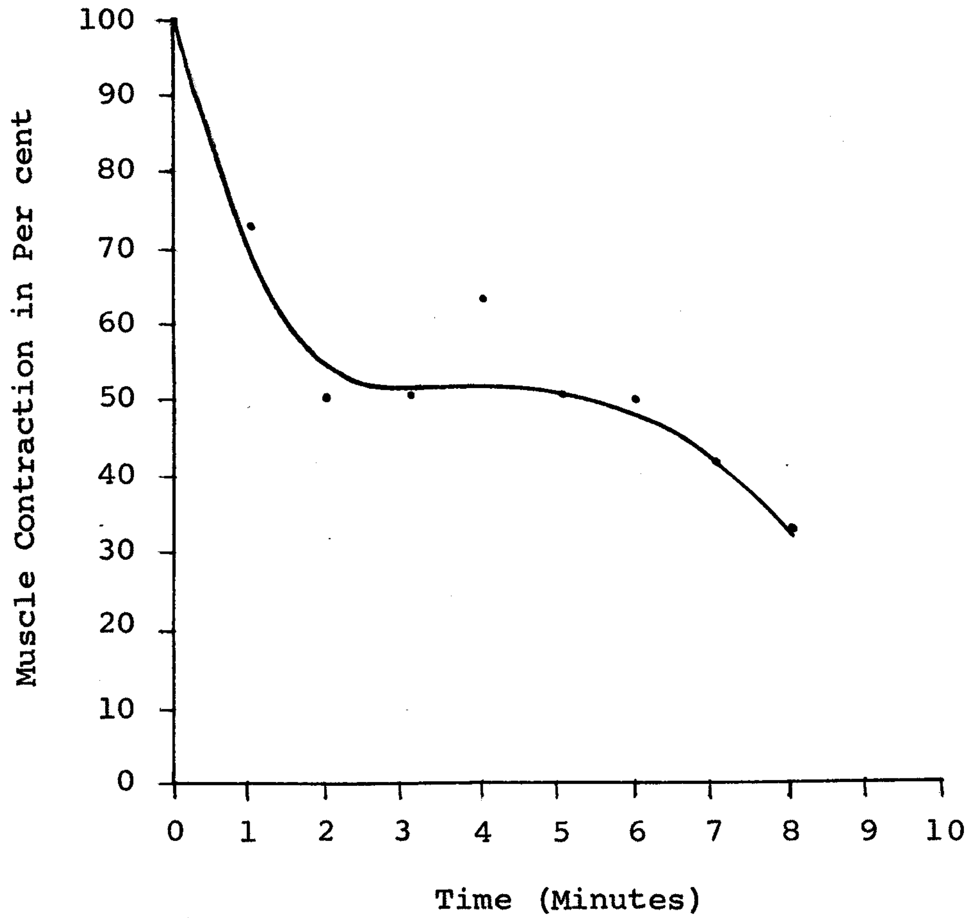
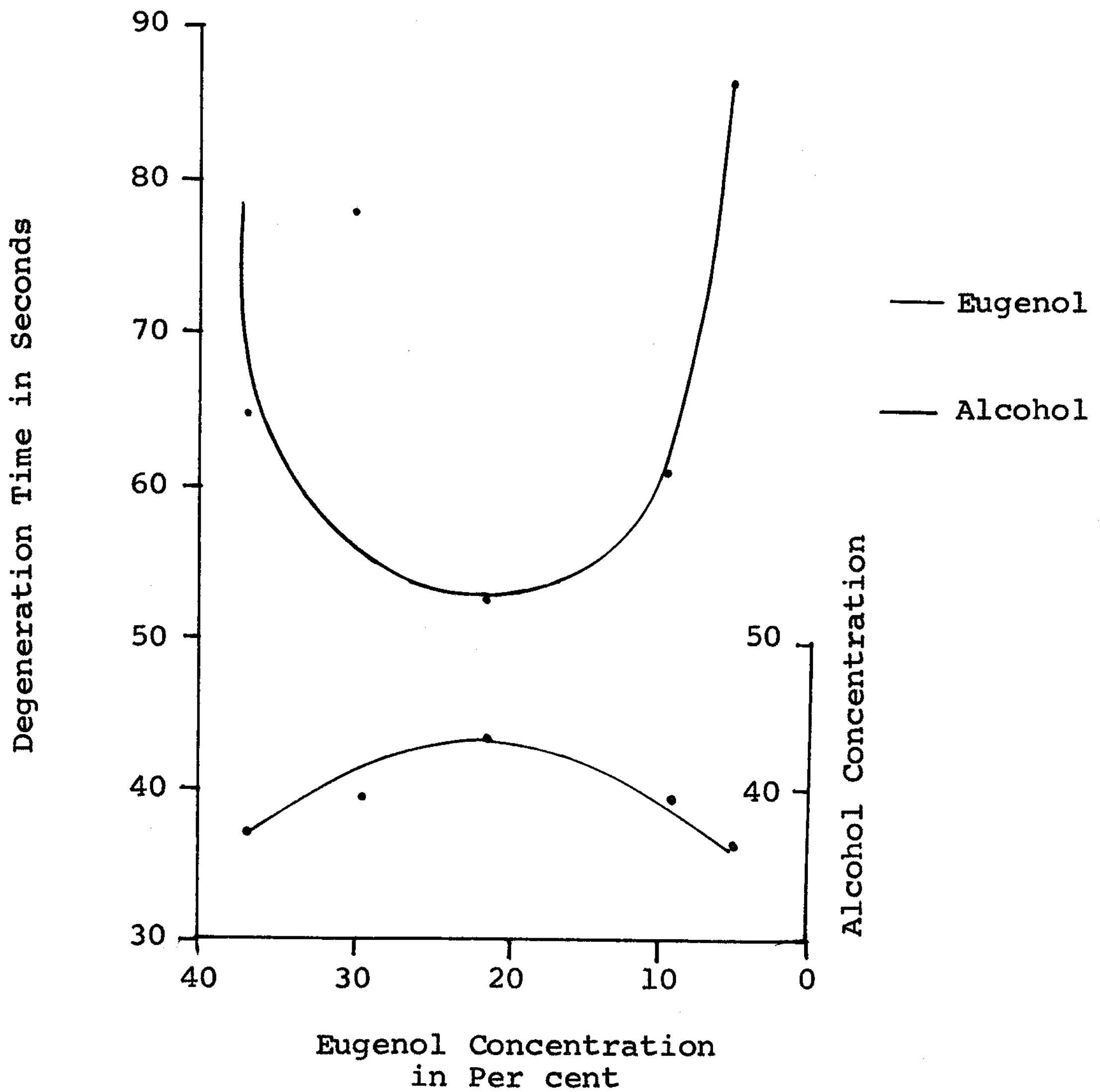
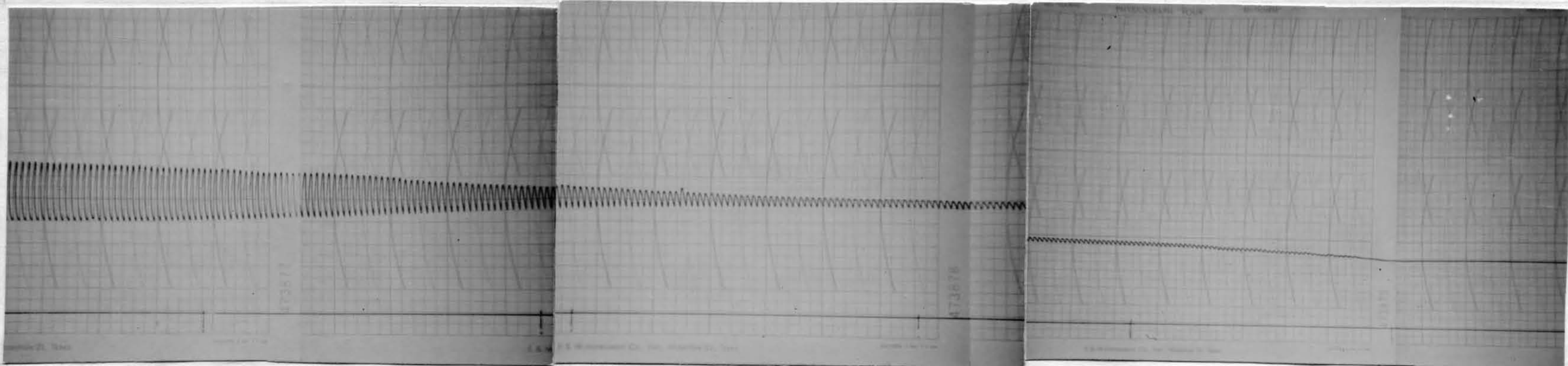


FIGURE 4

Eugenol Concentration versus Degeneration Time

Eugenol Concentration versus Alcohol Concentration



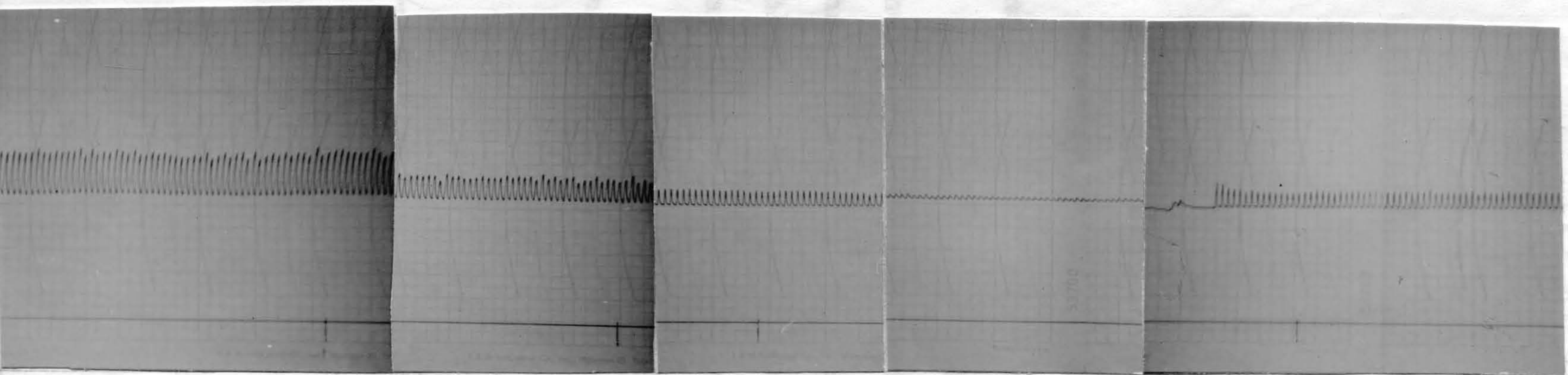


NORMAL | TISSUE RESPONSE TO EUGENOL SOLUTIONS | DEGENERATION

SAMPLE TRACING OF EUGENOL SOLUTIONS

FIGURE 5

SCHOOL OF DENTISTRY LOYOLA UNIVERSITY LIBRARY



NORMAL TISSUE RESPONSE TO ALCOHOL SOLUTIONS RECOVERY

SAMPLE TRACING OF AQUEOUS ALCOHOL SOLUTIONS

FIGURE 6

SCHOOL OF DENTISTRY LOYOLA UNIVERSITY LIBRARY

APPROVAL SHEET

The thesis submitted by Dr. Paul J. Ashkenaz has been read and approved by three members of the Department of Oral Biology.

The final copies have been examined by the Director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the thesis is now given final approval with reference to content, form and mechanical accuracy.

The thesis is therefore accepted in partial fulfillment of the requirements for the Degree of Master of Science.

19 May 1967
Date

B. Franklin Gurney, D.D.S.
Signature of Advisor