14476

# Effectiveness of Urea and of Synthetic Detergents in Reducing Activity of Human Dental Caries.*

ROBERT M. STEPHAN AND BENJAMIN F. MILLER.

*From the Walter G. Zoller Memorial Dental Clinic, and the Department of Medicine, University of Chicago.*

It is generally accepted that dental caries is initiated by the decalcifying action of acids which are produced locally on tooth surfaces by plaques of bacteria. Several methods proposed for the control of caries have been directed toward decreasing this acidity by means of the local application of chemical agents which either reduce production of the acids or neutralize them. It has been shown by one of us that experimental dental caries in the rat can be markedly reduced by adding small quantities of fluoride or iodoacetate to the food.[1] These compounds probably produce this effect by inhibiting the activity of enzymes involved in the production of acid by the bacteria on the teeth. Since both of these substances appeared to us too toxic for prolonged use in the prophylaxis of human dental caries, a search was made for less toxic compounds with similar local action.

Certain synthetic detergents have been shown to be powerful inhibitors of glycolysis in suspensions of oral bacteria.[2,3] In suitable concentrations, they inhibit partially the production of acid in intact dental plaques.[4,5,6] It has also been shown that concentrated solutions of urea exert a double effect on the dental plaques. Urea reacts with the bacterial urease to release sufficient ammonium carbonate to render the plaque alkaline;[7] also in 40% to 50% solution, urea markedly inhibits the production of acid by the micro-organisms in the plaques.[6,8] This paper presents the results of observations made to evaluate the effectiveness of a cationic synthetic detergent, and of urea in the control of human dental caries.

*Procedure.* Young individuals with marked caries activity were selected from patients who had been examined and treated in the Zoller Memorial Dental Clinic. These individnals had been taught the proper use of the tooth brush for home care of the mouth. They were observed during a control period of about 18 months. Full mouth and bite-wing X-rays, as well as complete clinical mouth examinations were obtained several times during this period.

A group of these patients was given a flavored solution of 1:1000 alkyldimethylbenzyl ammonium chloride (Zephiran).† Another group was given a flavored, saturated solution of urea.‡ The patients were instructed to

* This investigation was aided in part by a grant from the Squibb Institute for Medical Research.

1 Miller, B. F., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 389.

2 Miller, B. F., Baker, Zelma, and Harrison, R. W., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 705.

3 Baker, Zelma, Harrison, R. W., and Miller, B. F., *J. Exp. Med.*, 1941, **73**, 241.

4 Miller, B. F., Muntz, J. A., and Bradel, S., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 104.

5 Stephan, R. M., and Miller, B. F., *J. Dent. Res.*, 1943, **22**, 53.

6 Muntz, J. A., and Miller, B. F., *J. Dent. Res.*, 1943, **22**, 73.

7 Stephan, R. M., *Science*, 1940, **92**, 578.

8 Stephan, R. M., *J. Dent. Res.*, 1943, **22**, 63.

† We have referred in the title of this paper to the use of "synthetic detergents" to stress our belief that a number of cationic detergents would be as satisfactory as Zephiran. At the present time we have a number of subjects using other cationic detergents as well as Zephiran.

*Zephiran solution:*

Zephiran (Alba Pharmaceutical Co.) 10 cc of 10% aqueous solution
Oil of wintergreen 0.5 "
Distilled water to 1000 "

‡ *Urea solution:*

| | g |
|---|---|
| Urea (DuPont) | 45.0 |
| Distilled water | 47.2 |
| Alcohol (95% ethyl) | 7.0 |
| Menthol | 0.1 |
| Saccharin | 0.3 |
| Gomagel (thickening agent made by Glyco Products Co., 230 King Street, Brooklyn, N.Y.) | 0.4 |

TABLE I.
Effect of Urea and Zephiran on Dental Caries Activity.

| Case and age* | Period | Months of observation | No. intact surfaces at start† | No. new carious surfaces | No. new carious surfaces per 100 intact surfaces per yr |
|---|---|---|---|---|---|
| | | Urea Cases. | | | |
| E.B. | Control | 19 | 97 | 20 | 13.0 |
| 15 | Urea | 24 | 78 | 4 | 2.6 |
| O.B. | Control | 19 | 115 | 16 | 8.8 |
| 14 | Urea | 21 | 107 | 1 | 0.5 |
| R.D. | Control | 16 | 75 | 29 | 29.0 |
| 15 | Urea | 16 | 43 | 0 | 0.0 |
| J.J. | Control | 34 | 63 | 44 | 25.0 |
| 25 | Urea | 26 | 26 | 0 | 0.0 |
| A.M. | Control | 18 | 118 | 16 | 9.0 |
| 16 | Urea | 25 | 90 | 0 | 0.0 |
| E.T. | Control | 24 | 118 | 27 | 11.0 |
| 14 | Urea | 27 | 92 | 3 | 1.4 |
| | | Zephiran Cases. | | | |
| C.B. | Control | 16 | 90 | 18 | 15.0 |
| 12 | Zephiran | 21 | 90 | 8 | 5.1 |
| R.B. | Control | 24 | 102 | 15 | 7.3 |
| 20 | Zephiran | 18 | 91 | 1 | 0.7 |
| T.C. | Control | 13 | 93 | 12 | 12.0 |
| 13 | Zephiran | 17 | 92 | 7 | 5.3 |
| G.H. | Control | 18 | 97 | 9 | 6.1 |
| 16 | Zephiran | 16 | 88 | 1 | 0.8 |
| C.H. | Control | 19 | 106 | 14 | 8.3 |
| 13 | Zephiran | 24 | 96 | 6 | 3.1 |
| E.R. | Control | 24 | 101 | 36 | 18.0 |
| 13 | Zephiran | 25 | 90 | 6 | 3.2 |
| | | Duplicate Control Cases (No change in dentrifice). | | | |
| W.G. | Control | 21 | 108 | 14 | 7.4 |
| 14 | Duplicate | 21 | 102 | 11 | 6.2 |
| A.H. | Control | 19 | 122 | 16 | 8.3 |
| 15 | Duplicate | 20 | 99 | 14 | 8.5 |
| R.M. | Control | 14 | 116 | 9 | 6.7 |
| 13 | Duplicate | 16 | 104 | 10 | 7.2 |
| J.B. | Control | 19 | 93 | 6 | 4.1 |
| 12 | Duplicate | 19 | 95 | 6 | 4.0 |
| D.A. | Control | 18 | 114 | 12 | 7.0 |
| 16 | Duplicate | 19 | 102 | 15 | 8.4 |
| M.B. | Control | 18 | 81 | 12 | 9.8 |
| 20 | Duplicate | 19 | 66 | 10 | 9.6 |

* Age in years at start of test period.

† Based on counting the mesial, buccal, distal, and lingual surfaces for anterior teeth, and the occlusal surface in addition to these for posterior teeth. Carious and filled tooth surfaces not counted.

apply these solutions with a toothbrush to all accessible tooth surfaces for a period of 4 minutes either before or immediately after breakfast and supper. They were told to make no changes in their dietary habits. Clinical and roentgenological mouth examinations were made at 3 to 4 month intervals during the experimental period and a careful search was made for the development of new carious lesions. The numbers of intact tooth surfaces which became carious during the period in which the solutions were used was compared with the numbers which became carious during the preceding control period.

*Results.* In this paper observations on patients who had used the urea or Zephiran solutions for a period of 16 months or longer and who had had an equivalent control period are reported. It is felt that as long a period of time as this is essential in comparing caries activity rates. In order to secure a quantitative expression of caries rates, we have calculated for each individual the number of new carious lesions which develop per 100 intact tooth surfaces per year.

The degree of caries susceptibility of indi-

vidual tooth surfaces is variable; therefore we have sought to determine whether in young individuals as selected for this study the caries rate would tend to be the same in 2 consecutive periods of observation when no changes were made in the agent used in home care of the teeth. For this purpose we have included a group of patients who after the control period continued the use of their regular dentifrice. The results from 6 patients who used urea, 6 patients who used Zephiran, and 6 patients who continued use of their regular dentifrice are listed in the Table I.

In the first group of 6 subjects the number of new carious lesions appearing during use of the urea solution was only 8 whereas in the preceding control periods 152 new lesions had developed. Individually there was a reduction of from 80 to 100% in the original caries rates which resulted from the use of urea. This represents a great decrease in caries activity.

In the second group of 6 subjects 29 new carious lesions developed while Zephiran solution was being used, whereas in their control periods they had developed 104 new carious lesions. Individually there was a reduction of from 56 to 90% in the original caries rates which resulted from use of the Zephiran solution. This indicates a considerable decrease in caries activity.

In the third group of 6 subjects 71 new carious lesions appeared during the second period (duplicate control) in which no change was made in the dentrifice, and in the preceding control period 69 new lesions had formed. It is apparent that no significant reduction in the caries rate for these individuals occurred during the second period of study when the other subjects were using urea or Zephiran.

An attempt was made to determine the effect of the urea and Zephiran on the progress of carious lesions. A comparison was made of the size of individual lesions as seen in X-rays taken at the beginning, during, and at the end of the study periods. In the urea cases a significant number of the lesions appeared arrested while progress in most of the others was slower than in the control period. In 2 of the Zephiran cases progress in carious lesions appeared to be reduced but in the other 4 cases progress of lesions was about the same as in the control period. However, due to the placing of fillings, and also to inequalities of density and angulation of the X-rays, no exact quantitative expression of caries arrest could be obtained.

*Discussion.* These findings indicate that the rate of formation of new carious lesions can be decreased by the use of certain solutions applied repeatedly to the teeth. Presumably these solutions produce their beneficial effects by reducing the acidity of the dental plaques.[4,5,6,7,8] It is interesting that urea, though less effective *in vitro* as an inhibitor of acid production by suspensions of bacteria than Zephiran, is more effective in these clinical tests. This relationship correlates well with our previous studies showing the greater ability of urea to diffuse into thick dental plaques and inhibit acid formation.[6,8] In addition, the neutralizing power of urea by production of ammonium carbonate probably contributes to its effectiveness.

There were no serious difficulties in getting patients to use the solutions in brushing their teeth. Some subjects using Zephiran developed a thin layer of brown material on the teeth. This could be largely removed by daily brushing with an ordinary dental paste or powder which contains abrasive material. Some patients when first employing the urea solution produced an abrasion of the gingivæ by scrubbing with the tooth brush. This gingival abrasion disappeared when these patients brushed their teeth with the correct "sweeping" technic. The chief difficulty has been in securing daily applications of the solutions for the prescribed length of time. The possibility of lessened caries incidence has not always proved an adequate incentive for this, even though the tastes of the solutions have been generally satisfactory§ and the times for tooth brushing have been arranged for convenience.

The number of cases presented here is small

§ The reaction to the taste of the urea or Zephiran solutions appears to be highly individualized. Some persons find the taste quite pleasant from the beginning, others become accustomed to the taste in a few days, and a few find that the taste is disagreeable.

because of difficulties encountered in maintaining adequate contact with patients over a period of 3 to 4 years. However, we feel that the cases reported have been sufficiently well controlled to indicate that the regular use of the concentrated solution of urea can be very useful in the prophylaxis of dental caries.

*Summary.* Solutions of urea and of synthetic detergents have been employed as dentifrices for approximately 2 years in a small group of patients suffering from severe dental caries. The use of these compounds, especially the urea, resulted in a marked decrease in the incidence of new lesions, and the urea solution also retarded the progress of caries in lesions already present.

The authors wish to express their appreciation to the members of the Walter G. Zoller Memorial Dental Clinic staff for their cooperation in this study.

## 14477 P

## Protective Effect of Vaccination Against Induced Influenza A.*

THOMAS FRANCIS, JR., JONAS E. SALK,† HAROLD E. PEARSON, AND PHILIP N. BROWN.

*From the Department of Epidemiology and the Virus Laboratory, School of Public Health, University of Michigan, and the Ypsilanti State Hospital, Ypsilanti, Mich.*

During the past year from December, 1942, to May, 1943, rather extensive studies were conducted for the purpose of determining the value of subcutaneous vaccination with inactivated influenza virus against the natural disease in man. The anticipated outbreak of influenza did not occur but the opportunity to test the resistance of certain of the vaccinated individuals to induced infection presented itself.

The vaccine represented the allantoic fluid of fertile hen's eggs infected 48 hours previously with either the PR8 strain of influenza virus, Type A, or the Lee strain, Type B. The virus was concentrated by the procedure of Francis and Salk,[1] inactivated with formalin 1:2000, and bottled and tested for sterility by the approved procedures for biological products. Phenyl mercuric nitrate, 1:100,000 was added for bacteriostatic purposes. The final vaccine was of such strength that 1.0 cc represented 5.0 cc of the original Type A fluid and 5.0 cc of Type B fluid.

The subjects were 102 physically active male residents of one ward of the Ypsilanti State Hospital, Ypsilanti, Michigan. On December 21, 1942, 45 received 1.0 cc of the vaccine subcutaneously. On April 21, 1943, 17 of these men again received 1.0 cc of the vaccine as did 21 men not previously vaccinated. There remained 28 men who had been vaccinated 4 months earlier and 36 individuals who had not been vaccinated at any time.

On May 4, 1943, 13 days after the last administration of vaccine, the entire group received an intranasal spray of the Baum‡ strain of Type A virus in allantoic fluid. The material was sprayed into the nostrils from a nebulizer with such fineness that approximately 0.5 cc was delivered in 4 minutes. The subjects were then strictly segregated from the rest of the institution. Oral tempera-

* These investigations were aided through the Commission on Influenza, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

This study was also aided by a grant from the International Health Division of the Rockefeller Foundation.

† Fellow in the Medical Sciences of the National Research Council.

1 Francis, T., Jr., and Salk, J. E., *Science*, 1942, **96**, 499.

‡ The Baum strain was recovered from a patient during the outbreak of 1940-41. Although it is clearly a strain of Type A it is not antigenically identical with the PR8 strain used in the vaccine.