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# DENTAL CARIES AND PERIODONTAL DISEASE IN CHILDREN RECEIVING LONG-TERM PENICILLIN THERAPY

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A thesis submitted in partial requirement for the Diploma of Public Health Dentistry, in the Faculty of Dentistry, University of Sydney

S.C.E. Chan, B.D.Sc.,
June, 1967

## ACKNOWLEDGEMENTS

Throughout this study I was privileged to receive constant supervision, advice, and counselling from Mr. Peter D. Barnard, M.D.S., M.P.H. (Michigan), F.A.C.D.S., F.A.P.H.A., Senior Lecturer in Preventive Dentistry, the University of Sydney. I am greatly indebted to him for arranging final correction, typing and binding of this thesis. I would like to thank Professor Noel Desmond Martin, M.D.S., F.A.C.D., F.A.P.H.A., F.I.C.D., A.I.A.O.P., Professor of Preventive Dentistry, the University of Sydney, for much of the organization behind this study. His enthusiasm and understanding furnished much of my inspiration.

My gratitude is expressed to Professor Thomas Stapleton, M.A., D.M., B.Ch. (Oxford), D.C.H., (R.C.P. & S.), M.R.C.P., Professor of Child Health, the University of Sydney, for his interest in this study, and for his permission to allow me to carry out clinical examination of the mouths of children attending the Cardiac Clinic at the Institute of Child Health, Royal Alexandra Hospital for Children, Sydney. My deep appreciation goes to Dr. Helen Walsh, Paediatrician, and Miss O. Homburg, Social Worker, of the

Institute of Child Health, who were keenly interested in the study and who were always eager to help, and to the staff of the Institute of Child Health for their hospitality.

Mr. C.C. Croker, B.D.S., Superintendent of the United Dental Hospital of Sydney and the staff of the Operative Department were extremely helpful in the provision of patients from the Dental Hospital for the Control Group in this study. Systematic review of the mass of literature on the effect of antibiotics on oral and dental tissues would not have been possible if it had not been for the ready assistance of Miss Dora Hall, Librarian of the Dental Library, the University of Sydney. I was impressed by the staff of the Department of Preventive Dentistry, the University of Sydney, particularly Miss Elizabeth Butcher and Miss Barbara Macintosh, and Miss Carol Dodd who helped prepare the graphs.

The bacteriological investigation was made possible by Mr. Robin Woods, B.D.S., Dental Surgeon of Yass, who went out of his way to carry out bacteriological tests while running a busy dental practice. The hospitality of Mr. and Mrs. Robin Woods will never be forgotten.

Results of the clinical examination were recorded by Miss Diana Macintosh and I express my sincere thanks to her for her never tiring effort, loyalty, and pleasant company. It is to Mrs. Elizabeth Blears that I owe the neat typing and presentation of this report.

It was through the kindness and generous assistance of these teachers and friends that the present study was made possible.

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# INTRODUCTION

"Epidemiologists look upon disease as a breakdown of the balance between agent (cause), host (individual), and environment. Actually, the balance is between the individual and his environment in which there may or may not be a specific, known causative agent." [56]

In dental diseases the oral environment is an important environmental factor. In our present study the emphasis is on the oral environment.

In his studies on germ-free rats Orland[54] has presented conclusive evidence that dental caries does not develop in the absence of microorganisms. This does not imply that microorganisms per se are solely responsible for dental caries production. There is evidence that genetic, physiological, and nutritional factors may all determine production of dental caries.[10]

On the other hand, the evidence also demands that microbial action be recognised as an essential link in the chain of events leading to the production of dental caries. Keyes in 1960 [38] demonstrated the transmissable nature of dental caries in hamsters and Osborne-Mendel rats by exposing the animals to known caries-active animals, and by inoculating the animals with faeces from the caries-active animals.

In the case of periodontal disease evidence suggests that bacteria play an important role in its development. Germ-free studies by Baer and Newton in 1959[2], Fitzgerald and McDaniels[15], Gustafsson and Krasse[26], and Glas and Krasse[21] indicated that formation of dental calculus did not rely on the presence of bacteria.

Theoretically, if bacteria are important in contributing to the production of dental caries, the development of periodontal disease, and/or the formation of dental calculus, then any interference with their growth and metabolism should retard and reduce dental caries, periodontal disease, and dental calculus.

So far the search for a specific causative microorganism which may initiate the production of dental caries has not been successful despite proof of the capacity of the enterococcus (S.faecalis) to induce caries in the germ-free rat[54] and that some strains of streptococcus of human origin caused caries in the hamsters[79].

It has become widely accepted that a host of microorganisms in the oral cavity together with the genetic, physiological, and nutrional factors are responsible for the production of dental caries. It is also believed that dental caries is initiated by acid decalcification of the enamel subsurface, and that the acid is generated by the fermentative process of bacteria acting on carbohydrate substrate.

The studies by Theilade and Fitzgerald[73] and by Richardson[55] inferred that bacteria might influence the formation of dental calculus.

Gibbons[18] proposed that periodontal disease occurred in conditions which permitted proliferation of the oral flora. This would alter the equilibrium between the host and its indigenous micro-organisms in the 'normal' state.

If we accept the previous assumptions, then suppression of the acidogenic and aciduric bacteria as well as a large number of the other microorganisms in the oral cavity should theoretically influence the production of dental caries, the development of periodontal disease, and the formation of dental calculus.

People who are receiving long-term antibiotics offer opportunity to investigate whether bacterma contribute to the production of dental caries, the development of periodontal disease, or the formation of dental calculus because long-term systemic anti-biotics are exerting their influence on the oral environment continuously.

The National Heart Foundation of Australia recommends penicillin as the drug of choice for prevention of subactute bacterial endocarditis. Penicillin is effective against the Gram-positive

organisms. These Gram-positive organisms comprise the majority of the oral flora[11,19,20,22,30,51]. Penicillin is also known for its ability to inhibit acidogenic and aciduric bacteria.

Children who had a history of rheumatic fever attending the Cardiac Clinic at the Institute of Child Health, Sydney, were selected for investigation. They had been receiving long-term prophylactic penicillin therapy for the prevention of subacute bacterial endocarditis.

The purpose of this study is to examine the dental conditions of children with a history of rheumatic fever receiving long-term prophylactic penicillin therapy with respect to :

1. Dental caries
2. Periodontal disease, and
3. General state of oral flora.

An attempt will be made to evaluate the effect of penicillin, if any, on dental caries, the formation of dental calculus, and the development of periodontal disease. A control group was chosen from children attending the United Dental Hospital, Sydney and not receiving long-term prophylactic penicillin therapy.

# REVIEW OF LITERATURE

## 1. ANTIBIOTICS AND DENTAL CARIES

Many studies have been done on animals to investigate the effect of antibiotics on oral and dental tissues, oral microorganisms, and dental caries activity. Dietary penicillin has been shown to exert highly significant retarding effects on the initiation and progression of experimental dental caries under a wide variety of laboratory conditions. In contrast, the use of penicillin in dentifrice or as a prolonged therapeutic agent in children has not been as effective.

### a. Animal Studies :

In their search for evidence to support the chemico-parasitic theory of dental caries McClure and Hewitt in 1946 [52] studied the effect of penicillin on dental caries in rats. Eighty-two rats (forty-three litters), matched with litter-mate controls, received a corn meal caries-inducing diet containing seventy-five units of penicillin per millilitre. After 125 days the rats were sacrificed. No caries appeared in the test (penicillin) rats whereas fifty per cent of the control rats had carious teeth. The plate counts of L. acidophilus for the experimental rats were mostly negative or yielded less than fifty colonies of L. acidophilus organisms. The great majority of the control rats, on the other hand, developed upwards of fifty colonies per plate.

Webman, Hill, and Kniesner in 1949 [75] undertook a study to determine the minimal amount of penicillin in water which could reduce caries incidence in rats in the presence of a caries-producing diet alone, as well as with sucrose in the drinking water. One hundred and twenty-six female rats, twenty- to thirty-days-old, whose molars were just in the process of erupting, were divided at random into seven groups as to drinking water as follows :

| | | |
|---|---|---|
| Group A. | Water | |
| Group B. | Penicillin | 1 unit/ml. in water |
| Group C. | Penicillin | 2 units/ml. in water |
| Group D. | Penicillin | 5 units/ml. in water |
| Group E. | Sucrose | 1.5 per cent in water |
| Group F. | Penicillin | 2 units/ml. in 1.5 per cent aqueous sucrose solution |
| Group G. | Penicillin | 5 units/ml. in 1.5 per cent aqueous sucrose solution |

The rats were fed for 110 days on a Hoppert-Webber-Canniff cariogenic diet containing coarse corn particles. At the completion of the study, before each rat was sacrificed, a qualitative estimate of oral L. acidophilus was obtained by swabbing the teeth and mucosa with a small sterile cotton swab and immediately plating this material on tomato juice agar media. Seventy per cent of the control rats developed dental caries. In the rats receiving

five units of penicillin per c.c. of water supply, fifty per cent had dental caries. Rats receiving additions of 1.5 per cent of sucrose to the water all had dental caries. Of the rats which received five units of penicillin per c.c. and 1.5 per cent of sucrose to the water, sixty-eight per cent had carious teeth. As the concentration of penicillin increased, L. acidophilus present in the oral flora decreased. In the presence of sugar plus penicillin, B. lactis aerogenes replaced the lactobacillus as the predominant organism in the white Rat's mouth.

In view of the different results on the effectiveness of the antibiotics in reducing dental caries, Stephan, Fitzgerald, McClure, Harris, and Jordan in 1952 [70] carried out a study on several antibiotics which had different antibiotic spectra for their ability to prevent experimental caries in rats, and at the same time followed the changes in selected groups of the oral bacteria of the animals. The antibiotics selected included penicillin and bacitracin which chiefly inhibited Gram-positive bacteria, and streptomycin, Aureomycin, and Chloromycetin which inhibited in varying degrees both Gram-positive and Gram-negative microorganisms. Litter-mate rats were evenly distributed into control and test groups.

Twenty-four rats representing twenty-four different litters were placed in each group. The rats, all female, were of the Sprague-Dawley strain, twenty to twenty-two days old, taken at weaning from

the NIH stock colony. This stock was fed Purina Laboratory Chow, kale leaves, and water ad libitum. Each animal was kept on the experiment in individual screened bottom cages. The quantities of antibiotics per 100 grammes of food were as follows :

| | |
|---|---|
| Na Penicillin G | 50,000 units |
| Bacitracin | 5,000 units |
| Aureomycin-HCl | 50,000 units |
| Chloromycetin (Chloramphenicol) | 50,000 units |
| Streptomycin-$CaCl_2$ | 50,000 units |

Bacteriological studies of the oral flora were made before and during the course of the experiment. The rats were fasted overnight prior to these studies. At the end of approximately 122 days the animals were sacrificed. In these experiments, penicillin showed the greatest inhibitory effect. Bacitracin was next in order of effectiveness; Aureomycin and Chloromycetin produced about equal inhibitory effects, while streptomycin produced the smallest reduction in caries.

It is interesting to note that the antibiotics which specifically inhibited the Gram-positive flora (namely, penicillin and bacitracin) proved most effective in preventing caries. Aureomycin, Chloromycetin, and streptomycin which possess a wider spectrum but are less specific for oral streptococci or lactobacilli in vitro were less effective in reducing caries in vivo. However, apart from the bacteriological findings it was difficult to assess this

point with any degree of certainty. The diet employed induced severe caries in all of the control animals. None of the antibiotic groups was completely free of caries at the comparatively high levels of antibiotics which were used. This suggests that the effectiveness of the antibiotics in inhibiting experimental caries in rats depends somewhat on the caries-producing quality of the diet and on other factors which are as yet undetermined.

In the investigation by Stephan, Harris, and Fitzgerald[71] to determine the effect of penicillin and of Terramycin on the development of buccal, labial, proximal, and occlusal surface dental caries in rats, penicillin and Terramycin were added at levels of 0, 20, 100, and 500 units per gramme to a fine particle diet. Four equally distributed litter-mate groups of albino rats, forty-five animals per group, were used for the penicillin experiment and a similar number in the Terramycin experiment, 360 rats in all. The animals were sacrificed and caries scored after seventy-eight days. Samples of the oral flora were taken before and during the experiment. Penicillin reduced lactobacillus counts to almost zero in all concentrations tested, and there was a gradual reduction of streptococci with increasing penicillin concentration. Terramycin had only a gradual reducing effect on lactobacillus counts, but greatly reduced the number and types of streptococci. There was no marked effect on coliform counts. Both penicillin and Terramycin almost completely inhibited dental caries in these animals. It would appear that on the basis of

this study, this effect could not be attributed to a reduction of a single type of microorganism.

In their study of the effects of penicillin and Terramycin on dental caries and certain oral flora, Rosen, Rayheb, Hoppert, and Hunt in 1956 [57] carried out experiments on the Hunt-Hoppert caries-susceptible rats. Eighty-three litter-mate caries-susceptible rats were distributed into two test and one control groups (twenty-eight in the penicillin group, twenty-seven in the Terramycin group, and twenty-eight in the control group). Twenty-seven caries-resistant rats were also selected in order to compare the oral bacteriological changes in antibiotic-inhibited caries with caries inhibited by heredity. The Hoppert, Webber and Canniff cariogenic diet[35] was fed to the rats in the control group. The rats in the test groups were given the same diet containing 500 units of penicillin per gramme of feed and 250 microgrammes of Terramycin per gramme of feed respectively. The rats were observed macroscopically for caries every two weeks. Bacteriorological examinations of litter-mates were made at intervals of one, five, and ten weeks. It was found that Terramycin had retarded caries only slightly, whereas penicillin was extremely effective. Penicillin and Terramycin reduced oral lactobacillus counts with equal effectiveness. Higher numbers of streptococci were recovered from rats receiving Terramycin than those receiving penicillin. However, still

higher streptococcal counts were obtained from caries-resistant rats. Also both test groups had slightly higher coliform counts and slightly lower total counts than their litter-mate controls. These results suggest that organisms other than those considered in this study, which are inhibited by penicillin but not by Terramycin, may play an essential role in the aetiology of dental caries in these animals.

The studies reported by Shaw and Sweeney in 1957 [65] were designed primarily to compare the relative caries-inhibiting activity of different antibiotics and other compounds with pronounced bacteriostatic properties in the intact and desalivated rats as a means to explore the aetiology of caries. Panthenol (300 mg. per Kg. diet and 150 mg. per litre of water both as separate additive to the diet and as a mixture), bacitracin (0.05%), Aureomycin (0.05%), animal protein factor concentrate (1% and 2%) containing Aureomycin, streptomycin (0.05%), penicillin (0.05%, 0.025%, and 0.010%), subtilin (0.01% and 0.05%), Terramycin (0.05%), Chloromycetin (0.05%), tyrothricin (0.05%), and indole (0.5%, 1%, and 2%) were tested as additions to a cariogenic diet for their ability to alter the rate of initiation and progress of carious lesions in cotton rats, intact white rats, and desalivated white rats. Three to twenty rats were used in each experiment for each level of the drugs. Offspring of the white rats were weaned at twenty-one days of age and immediately placed on experiment. The cotton rats were

weaned at fourteen days of age and also distributed among the experimental group according to litter-mates. Wherever intact white rats were used in these experiments, the experimental period was 140 days. The experimental duration among the sialo-adenectomised rats varied from seventy to eighty-five days after operation. The cotton rats in all these experiments were maintained for a period of 100 days on experiment. The supplement of 0.05 per cent penicillin to the diet was the most effective for the intact cotton rats and for the intact and sialo-adenectomised white rats. Concentrations of penicillin as low as 0.025 per cent and 0.01 per cent also gave highly significant decreases in decay. Aureomycin and Aureomycin as an integral component of the animal protein factor concentrate, Chloromycetin, streptomycin, Terramycin, and indole were moderately effective in reducing the incidence of dental caries. Panthenol, tyrothricin, subtilin, and bacitracin appeared to be only slightly effective or were completely ineffective under the circumstances of these trials. In all cases where the influence of a compound was compared in intact rats and in sialo-adenectomised rats, the degree of inhibition produced by a given level of a given compound was very similar for the two experimental situations. There were interesting species difference s in the effectiveness of several of these compounds. The investigation of Shaw and Sweeney[65] tended to emphasise that unknown factors still exist with regard to the effect of antibiotics on experimental caries.

In his study on the dental caries of hamster and Osborne-Medel rats, Keyes[38] demonstrated in two of his experiments that caries activity was markedly reduced in hamsters and rats after the penicillin-sensitive flora in the mouth had been depressed prior to feeding the test diet. He also showed that hamsters, whose oral flora had been depressed, in some cases, produced several generations of progeny with negligable caries activity. In one experiment penicillin or erythromycin suppressed caries activity when present in the caries-test diet at the level of 100 mg. per kg. diet. Females in which the 'cariogenic' flora had been depressed might, in some instances, deliver litters which would continue to show negligable caries activity. The other experiment was carried out to assess the caries activity in litters from females which were inactive as a result of the previous feeding of antibiotics to their mother. The findings of this experiment showed that depression of the penicillin-sensitive oral flora in female breeders resulted in an almost complete loss of caries activity in the offspring.

Shaw, Griffiths, and Terborgh[64] designed an experiment to determine under what circumstances 0.05% per cent penicillin would affect caries activity. Litters of the Harvard caries-susceptible strains of white rats were separated into ten experimental groups at weaning, with fourteen to thirty-four rats in each group. They were maintained on a cariogenic diet throughout an eighty-four day assay period. The rats in nine groups received an

0.05 per cent penicillin supplement in the diet, during a part of, or continuously throughout the assay period. Under different time relationships in this experiment, 0.05 per cent penicillin when fed post-developmentally as a supplement to a cariogenic diet was most effective when available continuously throughout the assay rather than for intermittent periods. The average caries experience was drastically reduced in the former case. It would be very interesting to compare this finding with the effects of penicillin on dental caries experience in persons receiving long-term penicillin therapy.

In another experiment dietary levels of penicillin at 0.02, 0.01, 0.005, and 0.0025 per cent were used by Shaw in 1964 [60] to determine their relative effectiveness against experimental dental caries. Five groups of Harvard caries-susceptible rats were maintained for sixty days after weaning. Highly significant reductions in dental caries incidence occurred in all pencillin-supplemented groups. This dietary level of penicillin as low as 0.0025 per cent was effective in reducing dental caries in rats.

In order to test whether the lesser effectiveness of penicillin to reduce dental caries in man might be attributable to different routes of administration or shorter periods of contact Falla and Shaw[13] conducted two experiments on Harvard caries-susceptible rats. The rats were divided into four groups in the first exp-

eriment and 0.02 per cent penicillin was incorporated in the diet for the first group. Approximately equivalent amounts of penicillin at the level of 0.01% were dissolved in the drinking water for the second group (the rats drank almost exactly twice the volume of water as the weight of diet eaten). The third group was given an equivalent amount of penicillin by daily injection. The last group was the control.

In the second experiment, 4,000, 8,000, 16,000, and 32,000 units of penicillin were injected daily to four separate groups respectively. There was also a control group with no penicillin given. The supplement of 0.02 per cent penicillin in the cariogenic diet caused a typical highly significant reduction in experimental dental caries. The administration of approximately equivalent amounts of penicillin in the drinking water also produced highly significant, though smaller, reduction. The results from the second experiment showed that penicillin could be as effective when injected as when provided in the diet, but that twice as high levels were required. These results clearly indicated differences in the activity of equal amounts of penicillin when provided by these different routes.

König, Guggenheim, and Mühlemann in 1965 [41] inoculated an erythromycin-resistant cariogenic strain of streptococci (OMZ-61) into the oral cavity of rats to investigate any establishment and competition of the inocluated strain with the indigenous and other inoculated microorganisms. When the indigenous Gram-positive bacterial flora

was not depressed at all, inoculation caused an increase in the number of fissure lesions compared with the controls. With increasing time of erythromycin depression of the indigenous Gram-positive flora, there was a decrease in the number of carious fissures and a corresponding increase in the smooth surface involvement. Microorganisms cultured from plaque of rat molars counteracted the establishment of the cariogenic potency of strain OMZ-61, their combined incoculation resulting in low smooth surface as well as low fissure caries count.

Results of the various studies on the effect of penicillin on dental caries and oral flora in animals are summarised in Table 1.

TABLE 1

EFFECT OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN ANIMALS

| Year | Investigator(s) | Animal used | Duration of experiment | Agent | Effect |
|---|---|---|---|---|---|
| 1946 | McClure and Hewitt (52) | Rat | 125 days | Penicillin | Total suppression of caries. Very low L. acidophilus counts. |
| 1949 | Webman, Hill, and Kniesner (75) | Rat | 110 days | Penicillin | 50% reduction in caries with 5 units of penicillin per c.c. of water supply. |
| 1952 | Stephan, et al (70) | Sprague-Dawley Rat | 122 days | Penicillin<br>bacitracin<br>Aureomycin<br>Chloromycetin<br>streptomycin | Reduced dental caries. Penicillin most effective, followed by bacitracin, Aureomycin, Chloromycetin, and streptomycin. |
| 1952 | Stephan, Harris, and Fitzgerald (71) | Albino rat | 78 days | Penicillin and<br>Terramycin | Penicillin suppressed lactobacilli but reduced streptococci only in high concentration.<br>Terramycin greatly reduced streptococci but suppressed lactobacilli only slightly. |

* next page

TABLE 1 (continued)

EFFECT OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN ANIMALS

| Year | Investigator(s) | Animal used | Duration of experiment | Agent | Effect |
|---|---|---|---|---|---|
| 1956 | Rosen et al[57] | Hunt-Hoppert Caries-susceptible rat | 10 weeks | Penicillin and Terramycin | * Both almost completely inhibited caries<br>Penicillin extremely effective, but Terramycin only slightly in retarding caries. Both suppressed lactobacilli and penicillin more effective in reducing streptococci. |
| 1957 | Shaw and Sweeney[65] | Cotton and white rats | 70-140 days | Panthenol, bacitracin, Aueromycin, streptomycin, subtilin, penicillin, Terramycin, Chloromycetin, tyrothricin, and indole. | Penicillin most effective, Aureomycin, Chloromycetin, streptomycin, Terramycin and indole were moderately effective, while panthenol, tyrothricin, subtilin, and bacitracin were only slightly effective in reducing caries. |

3/..

TABLE 1 (continued)

EFFECT OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN ANIMALS

| Year | Investigator(s) | Animal used | Duration of experiment | Agent | Effect |
|---|---|---|---|---|---|
| 1960 | Keyes (38) | Hamster and Osborne-Mendel rat | -- | Penicillin and erythromycin | Caries was markedly reduced. |
| 1962 | Shaw, Griffiths, and Terborgh (64) | Harvard caries-susceptible white rat | 84 days | 0.05% penicillin | Caries drastically reduced when penicillin was administered continuously in the diet. |
| 1964 | Shaw (60) | Harvard caries-susceptible rat | 60 days | Penicillin | Highly significant reduction in caries. |
| 1965 | Falla and Shaw (13) | Harvard caries-susceptible rat | -- | Penicillin | Penicillin in diet caused highly significant reduction in caries, but a lesser reduction when administered in drinking water. Only half as effective when injected. |
| 1965 | König, Guggenheim, and Mühlemann (41) | Rat | -- | Erythromycin | Reduction in carious fissures. |

b. Human Studies :

Topical application of antibiotics

The results of the various investigations of the effectiveness of topical penicillin in depressing the sensitive oral micro-organisms and as an agent to reduce dental caries in man have not been consistent.

The study by Hill and Kniesner in 1949 [32] was undertaken to determine what benefits might be obtained from the use of a penicillin dentifrice by children for one year under conditions comparable to the ordinary non-regimented habits of oral hygiene. One hundred and seventy-six institutionalised boys, aged eight to fourteen years, were examined clinically. Stimulated saliva samples were collected before brushing and before breakfast to determine initial susceptibility. One hundred and eight boys were given tooth powder containing 1,000 units of penicillin per gramme. Sixty-eight boys as a control group used the same type of tooth powder without penicillin. They were instructed to brush their teeth twice each day. At the end of one year, a general reduction in the occurrence of lactobacilli was observed. No significant differences in the number of new carious surfaces nor progress in existent carious teeth could be ascertained from the test and control groups.

In the follow-up of the previous study, White, Kniesner, and Hill[76] observed the effect of penicillin on the oral bacterial flora of the institutionalised children. Paraffin-stimulated saliva was collected from the children in the morning before the teeth were cleaned and before breakfast. There were eighty children in the experimental group and fifty-three children in the control group who did not receive any penicillin from the tooth powder. The children were requested to use the tooth powder once a day without supervision for a period of one year. The number of oral L. acidophilus was reduced at the end of the study. Gram-negative bacilli of the genera Aerobacter and Escherichia increased in occurrence with a large dose of penicillin but were not permanently maintained.

In the 1950 study by Zander[78] two hundred and sixteen school children were given a tooth powder containing 500 units of potassium penicillin per gramme of tooth powder. One hundred and sixty-two children in another school were given the same tooth powder without the penicillin. The children, aged six to fourteen years, brushed their teeth once daily in their classrooms under the supervision of their teachers or the hygienists. They were also instructed to use the tooth powder at home every mnorning and evening. The children were examined at the end of the first year. At the end of the second year, 202 children in the 'penicillin' school and 150 children in the control school were

re-examined. The incidence of caries on previously caries-free surfaces during the first year was 55.3 per cent less in the group using the penicillin dentifrice. The reduction in caries incidence was of about the same order of magnitude for the first and second years.

The experiments by Fitzgerald, Zander, and Jordan[16] incorporated with the previous study by Zander were to determine the effect of continuous use of a 500 units penicillin dentifrice on salivary lactobacillus counts, and to ascertain whether the use of such a dentifrice would result in an increased resistance to penicillin by the lactobacilli. This phase of the study included 129 children in the control school and 181 children in the experimental school. For the lactobacillus counts paraffin-stimulated salivas were diluted one to five in dextrose infusion broth of pH 5.0. In the case of the experimental school four such plates were inoculated for each child : a control, and three plates containing 1.0, 10.0, and 50.0 units respectively of sodium penicillin G per ml. of agar. It was established that a concentration of 1.0 unit per ml. of sodium penicillin G would prevent the growth of all but a small percentage of the lactobacilli from normal salivary samples. For the control school, two plates were made for each child : a control and one containing 1.0 unit of penicillin per ml. of agar. The plates and the broth dilutions were incubated for four days at 37°C.

Gram stain smears were made of the broths from samples which were negative for lactobacilli on the plate counts to determine if any L. acidophilus were present. Two sets of counts were made; the first after the children had been using the dentifrice for a year and a half, and the second after two years. Use of the dentifrice was omitted on the morning of the day on which saliva was collected. These investigators found that after the penicillin dentifrice had been in use for eighteen months or longer, there was no difference in the L. acidophilus counts which could be ascribed to its use. The L. acidophilus did not develop a resistance to the penicillin.

Lind and Zander in 1951 [45] conducted a clinical study on penicillin resistance of streptococci and staphylococci from the use of a penicillin dentifrice by school children. One hundred and ninety children were given a tooth powder containing 500 units per gramme of tooth powder. One hundred and fifty-four children in another school were given the same powder without penicillin. The children brushed their teeth once daily, under supervision of the teacher or the hygienist, with the tooth powder they were given. After the children had been brushing their teeth with the respective dentifrices for approximately two years, throat swabs were taken. The throat swabs were planted directly into a sterile tube containing 2 ml. of brain heart infusion broth. After incubation for two to four hours at 37°C. a single blood agar plate was streaked to isolate the colonies. The serial tube dilution method for penicillin G

sensitivity were run immediately. In this method 0.5 c.c. of 1:1000 dilution of a 24-hour broth culture was added to 0.50 c.c. of decreasing concentrations of penicillin, starting with 10 units per ml. followed by two-fold dilutions, taken out to 0.0011 unit per ml. for every organism tested. Staphylococcus aureus (Oxford strain) was the organism used for control, and was sensitive to 0.078 units of penicillin per ml. The tube containing the least amount of penicillin and showing complete inhibition was selected as that amount to which the organism was sensitive. In both groups the sensitivity of the organisms was well within the range normally found for these organisms. Most of the organisms were inhibited at the concentration of approximately one unit of penicillin G. The predominant organisms most frequently isolated in both groups were alpha-hemolytic streptococcus, pneumococcus, non-hemolytic staphylococcus, and beta-hemolytic streptococcus in that order. Penicillin did not induce an acquired resistance in the groups of streptococci and staphlyococci isolated from the throats.

Ludwick, Fosdick, and Schantz in 1951 [49] carried out a screening test to determine the probably effectiveness of dentifrices modified with antibiotics or enzyme inhibitors in the prevention of dental caries in naval personnel. All 780 subjects (from seventeen to twenty-five years) were maintained on a rigidly uniform schedule, including diet, rest, and exercise. Paraffin-

stimulated saliva specimens were collected from each subject after the subjects arose at 5.30 a.m. prior to smoking, ingestion of food, water or the institution of oral hygiene procedures. Oral L. acidophilus counts (Hadley[27]) and colorimetric determinations for caries activity (Snyder[69]) were ascertained on each of the collected specimens, and these results became the pretreatment values for the group. A compounded dentifrice, which had been modified with an antibiotic or an enzyme inhibitor, was supplied to each subject. The paraffin-stimulated saliva specimens were again collected during the sixth or seventh week of the test, and L. acidophilus counts and colorimetric tests for caries activity were again determined on each specimen. Of all the thirteen potentially therapeutic dentifrices tested, the one containing 0.07 per cent penicillin was by far the most effective in the reduction of the lactobacillus counts (from a mean L. acidophilus count of 60,000 to 4,000).

Walsh and Smart (1951 [74]) used an experimental tooth powder with a concentration of 100 units of penicillin per gramme of powder to compare the incidence of new caries under standardized conditions of fifty-five children in four orphanages. The children ranged in age from five to fifteen years, the average being slightly under ten years. The penicillin powder was distributed to thirty children, the control powder to the other twenty-five children. Each child was instructed to brush their teeth twice daily, after breakfast and

before retiring, and this was generally supervised by the orphanage staff. After two and a half years the children were re-examined and new carious lesions were assessed. The findings showed that the difference in new caries for the control and the experimental groups was not significant. The penicillin and control powders, considered together, caused a fifty-three per cent decrease in new caries when compared to the attack rate before the study. The result was thought to be due to improved oral hygiene mainly.

Brudevold and Hawes[7] took intraoral measurements of the fall in pH in dental plaques following sucrose rinses over a seven-week period in a group of dental hygienist students who used :

(a) A dental powder containing 500 units penicillin per gramme of powder (eleven students)

(b) A dental paste containing 1,000 units per gramme (thirteen students)

(c) A control paste without penicillin (twenty-one students)

After a five-week period of brushing the groups differed in acid production in saliva collected before tooth brushing and eating. Bacteriological examinations of saliva showed that the penicillin dentifrices produced a slight reduction in Gram-positive organisms, and an increase in resistant forms such as the coli-aerogenes group.

The numbers of yeasts (monilia albicans) and micrococci did not seem to be affected by the penicillin dentifrices.

Slanetz and Reynolds[67] evaluated, by in vivo methods, the antibacterial action of Cepacol solution, Cepacol troches, penicillin troches (5,000 units per troche), and Cepacol-penicillin troches on oral bacteria. Listerine and Aureomycin troches were also included for comparative purposes. Paraffin-stimulated saliva samples were collected from each subject. All samples were plated in the tryptose glucose blood agar using dilutions of 1:10,000, 1:100,000, and 1:1000. For L. acidophilus counts, dilutions of 1:100 and 1:1000 were prepared in tomato juice agar, and the plates were placed in jars in an atmosphere of ten per cent carbon dioxide. Dilutions of 1:50 and 1:100 were employed for the estimation of the number of fusiform bacteria, and the plates incubated in jars under complete anaerobic conditions. All cultures were incubated at 35°C. for 48 hours. Before plating, all saliva samples were adjusted first to a total volume of 20 ml., using a phosphate buffer solution containing Tweed 80 and lecithin. The subjects ranged from seventeen to forty-five years. The antiseptics and antibiotics were used daily for a five-day period.

There was a marked reduction in the number of oral bacteria, including the alpha streptococci, lactobacilli, and fusiform bacilli. When penicillin was used, yeast and penicillin-resistant bacteria, such as Aerobacter aerogenes, Neisseria, and Serratia marcescens

appeared in the mouth, sometimes in large numbers.

In order to find out whether there was any difference between a. regimented and unregimented programme when investigating the effectiveness of penicillin dentifrice Hill, Sims, and Newman[34] conducted a second experiment (first report in 1949 [32]) which was patterned after the programme used by Zander in 1950 [78]. The dentifrice used was a paste containing approximately 1,000 units per gramme of the procaine salt of penicillin. There were 347 children in the experimental group and 145 children in the control group. The children brushed their teeth in school each day under the direct supervision of the teachers. Two salivary L. acidophilus counts were made at the beginning and again at the end of the experiment after one year. There was a slight reduction in the DMF surfaces. The difference between the experimental and the control groups in the L. acidophilus counts was not significant either at the beginning or at the end of the experiment.

In the previous study Hill and others[34] employed a dentifrice containing approximately 1,000 units per gramme of penicillin in the control of dental caries in school children. After one year's use of the dentifrice, a follow-up sensitivity study was made by Hill, Rasch, and Wollpert[33] to determine if there had been an increase in the prevalence of organisms resistant to this antibiotic. Tests were carried out on 814 organisms isolated from

the saliva of the 150 children chosen at random, 50 children in the control group and 100 children in the experimental group. Each salivary specimen was diluted 1:10 in sterile saline solution and streaked on a blood agar plate. After incubation the organisms were transferred from the blood agar plate to tryptose agar slants, incubated, then stored in a refrigerator. After incubation each of these cultures was inoculated into six tubes of tryptose broth with two per cent blood cells. These tubes of broth contained, respectively, 0.000, 0.005, 0.020, 0.100, 0.500, and 1.000 unit procaine penicillin per ml. Growth was determined by the hemolysis of red blood cells. There was a high percentage of Streptococcus viridans which required 0.5 unit or more of penicillin to inhibit in the penicillin group. There were similar increases in the percentage of organisms other that Streptococcus viridans, predominately Gram-positive cocci, which required concentrations of 1.0 unit or more of penicillin per ml. to inhibit in the experimental group.

Lunin and Mandel in 1955 [50] undertook a study to observe the general oral effect of a dentifrice containing 600 units of potassium penicillin per gramme of tooth powder, when used by school children without supervision. There were 161 children from two schools in this study, 77 in the experimental group and 84 in the control group. The acid-producing potentiality of

the oral flora was studied by subjecting saliva samples to the Snyder test[69]. Samples of fasting-stimulated saliva were collected at three to four month intervals throughout the study for eighteen months. In neither school was the difference in caries incidence between the control and experimental group statistically significant. There was no change in the character of the oral flora with regard to acid production in both control and experimental groups. No oral or dermatological lesions were observed. There appears to be no development of a resistance to penicillin by the acidogenic flora considered in toto.

Shiere (1957 [66]) evaluated the effectiveness of toothbrushing with a tyrothricin dentifrice in the control of dental caries in hamsters and the capacity of this dentifrice for clinical control of human dental caries. Six dentifrices, one control and five containing tyrothricin of 0.01, 0.025, 0.05, 0.1, and 0.5 per cent respectively, were evaluated for their effect in reducing hamster caries, as a preliminary to study for their effect on the incidence of human caries. The dentifrices were all in paste form. Two hundred and forty Syrian hamsters, three to four weeks old, were divided into six groups. Three-fourths were litter-mates and were distributed to provide litter-mate control. An equal number of male and female were present in each group. The animals were maintained five to a cage, and fed a caries-producing diet.

They were sacrificed after ninety days. A paste with insoluble sodium metaphosphate-dicalcium phosphate as polishing agent plus 0.05 per cent tyrothricin proved to be the most effective, giving 25.6 per cent reduction in carious surfaces. In the clinical study, a total of 425 children, seven to thirteen years of age, were divided into two groups of similar age and sex distributions. Both groups were given identical dentifrices except that the dentifrice used by the experimental group contained 0.05 per cent U.S.P. tyrothricin. The polishing agent was a combination of insoluble sodium metaphosphate and dicalcium phosphate. During the two-year brushing period the experimental group had a mean of 7.7, and the control group had a mean of 10.4 new decayed and filled surfaces. Brushing with the dentifrice containing 0.05 per cent tyrothricin resulted in about 26 per cent reduction in the incidence of new decayed and filled surfaces.

To determine the merit of bacitracin mouth-wahes, Law, Wallace, and Spitz[44] conducted a study on 912 children, ranged in age from six to fourteen years. One hundred and seventy-nine children used 3/4 ounce of mouth-wash within half an hour after their arrival for the morning session, and an equal quantity after the lunch period. Two hundred and seventy-seven children did their mouth washing only once daily, in the morning. In all instances, children retained the solution in their mouths for one minute.

Ninety per cent of the children in the first group used the mouth-washes for 140-154 days. In the second group 55 per cent followed the procedure for 140-154 days and an additional 40 per cent for 125-139 days. The solution prepared for use by the children in the study group contained 750 units of zinc bacitracin per ounce. In the formula used by the control group, an equivalent weight of sodium chloride was substituted for bacitracin, resulting in approximately 8 mg. of sodium chloride per ounce of solution. The difference in dental caries incidence between study and control groups was not significant statistically, whether the mouth-wash was used once or twice daily.

Williams in 1963 [77] analysed the specific relationships between selected bacteria cultured from saliva samples that had been collected by chewing paraffin before, during, and after the administration of 20,000 units penicillin in lozenges to five subjects or 15 mg. oxytetracycline (Terramycin) lozenges to one subject. The lozenges were allowed to dissolve slowly in the mouth and lasted for 30-45 minutes. Penicillin was given for seven days. Streptococcus salivarius markedly decreased during this seven-day period, and re-established in the oral cavity with the withdrawal of the antibiotic, but the coliforms increased at that time and decreased later. With the use of oxytetracycline (Terramycin) there was a reduction of the lactobacilli, the coliforms, and Streptococcus salivarius, in that order. There was

a steady increase in the number of yeasts. These data indicated that prolonged topical use of tetracyclines in the oral cavity was likely to induce undesirable changes in the quality of the oral flora.

Results of the various studies on the effect of topical application of antibiotics and enzyme inhibitors on dental caries and oral flora in humans are summarised in Table 2.

TABLE 2

EFFECT OF TOPICAL APPLICATION OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN HUMANS

| Year | Investigator(s) | Duration of study | Agent | Effect |
|---|---|---|---|---|
| 1949 | Hill and Kniesner (32) | one year | Penicillin dentifrice | General reduction of lactobacilli. No effect on dental caries. |
| 1949 | White, Kniesner, and Hill (76) | one year | Penicillin dentifrice | L. acidophilus reduced. Temporary increase of Gram-negative bacilli. |
| 1950 | Zander (78) | two years | Penicillin tooth powder | 55% reduction of caries |
| 1950 | Fitzgerald, Zander, and Jordan (16) | 18 months | Penicillin tooth powder | No reduction in L. acidophilus. No resistance developed. |
| 1951 | Lind and Zander (45) | two years | Penicillin tooth powder | No resistance developed in streptococci and staphylococci |
| 1951 | Ludwick, Fosdick, and Schantz (49) | | Penicillin or each of 12 other antibiotics and enzyme inhibitors in dentifrice | Penicillin most effective in reducing caries. |
| 1951 | Walsh and Smart (74) | $2\frac{1}{2}$ years | Penicillin tooth powder | Both penicillin and control dentifrices reduced caries. |
| 1952 | Brudevold and Hawes (7) | 5 weeks | Penicillin dentifrices | A slight reduction in Gram-positive organisms, and an increase in the coli-aerogenes group. No effect on monilia and micrococci. |

TABLE 2 (continued)

EFFECT OF TOPICAL APPLICATION OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN HUMANS

| Year | Investigator(s) | Duration of study | Agent | Effect |
|---|---|---|---|---|
| 1952 | Slanetz and Reynolds (67) | 5 days | Cepacol solution and troches of Cepacol, penicillin, Cepacol-penicillin, listerine, and Aureomycin | Marked reduction in streptococci, lactobacilli, and fusiform bacilli. An increase in yeast, Aerobacter aerogenes, Neisseria, and Serratia marcescens when penicillin was used. |
| 1953 | Hill, Sims, and Newman (34) | one year | Penicillin dental paste | A slight reduction in DMF surfaces. No significant effect on L. acidophilus. |
| 1953 | Hill, Rasch, and Wollpert (33) | one year | Penicillin dental paste | An increase of Streptococcus viridans and Gram-positive cocci |
| 1955 | Lunin and Mandel (50) | 18 months | Penicillin tooth powder | No difference in caries incidence between experimental and control groups. No change in oral flora. |
| 1957 | Shiere (66) | two years | Tyrothricin dental paste | 26% reduction in new decayed and filled surfaces. |

3/..

TABLE 2 (continued)

EFFECT OF TOPICAL APPLICATION OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN HUMANS

| Year | Investigator(s) | Duration of study | Agent | Effect |
|---|---|---|---|---|
| 1961 | Law, Wallace, and Spitz [44] | 125-154 days | Bacitracin mouth-wash | Difference in caries incidence not significant between experimental and control groups. |
| 1963 | Williams [77] | 7 days | Penicillin and Terramycin lozenges | A decrease of Streptococcus salivarius and an increase of coliforms with penicillin.<br><br>A reduction in lactobacilli, coliforms, and Streptococcus salivarius with Terramycin.<br><br>A steady increase of yeasts. |

Systemic administration of antibiotics

The clinical dental caries studies of the relationship of the effectiveness of antibiotics in reducing dental caries progression in man as well as their effects on the oral flora are rather interesting.

Long in 1947 [47] reported the changes in the flora of the mouth in sixty patients treated systemically with penicillin given by intramuscular injection. There was an initial phase of reduction of the penicillin-sensitive organisms of the mouth and a later phase of invasion by Gram-negative bacilli. Penicillin excretion in the saliva probably occurred only when a dosage of over 500,000 units in 24 hours was employed. It would be demonstrable only during the initial phase of reduction of bacteria, before the organisms of the Bacterium group had established themselves.

Kraus (1951 [43]) investigated the antibiotic levels in human saliva. Twenty dental students were each given 3 gm. of Aureomycin HC1 in capsules. Five hundred mg. were administered every four hours. Blood and unstimulated saliva were collected and assayed two and a half hours after both the initial and final doses, and again 24 hours later.

The results were :

| | 2½ hr. after initial dose | 2½ hr. after final dose | After 24 hrs. |
|---|---|---|---|
| Mean plasma level (mcg./ml.) | 0.63 (0.25-2.0) | 4.3 (1.0-16.0) | 0.11 (⁄ 0.063-0.25) |
| Mean saliva level (mcg./ml.) | 0.09 (⁄0.063-0.25) | 0.45 (⁄0.25-2.0) | 0.09 (⁄0.063-0.25) |

The pooled parotid and submaxillary salivas from four medicated subjects each contained detectable concentrations of Aureomycin. One 15 mg. Aureomycin troche was dissolved in the mouth of each of six subjects, and, while the mean salivary concentration declined rapidly within the first thirty minutes, it was still, after three hours, equal to almost one hundred times the highest mean salivary concentration of the systemically administered antibiotics. However, both the excreted and the dissolved antibiotic in the saliva were comparable in their reduction of oral bacterial population in eight subjects.

Smith, Skinner, and Erikson (1952 [68]) studied thirty-six children who had had an attack of rheumatic fever within the preceding five years to determine the effectiveness of a daily prophylactic dose of 100,000 units of oral penicillin. Throat smears were obtained with dry swabs. These were streaked on ten per cent human blood agar plates and also inoculated into blood difusion broth. The cultures were read the following day and, as indicated, were

transferred to other media for further isolation and identification. The study lasted three months. The prevalence of positive cultures for beta hemolytic streptococci was significantly less for rheumatic children. The hemolytic staphylococci appeared to be more common in those on penicillin. There was an increase in Gram-negative bacilli in the group taking penicillin.

Bender, Pressman, and Tashman in 1953 [3] measured and compared the concentrations of antibiotics in the blood serum and in the saliva after their parenteral administration. A single dose, consisting of a mixture of one gramme of dihydrostreptomycin and 400,000 units pencillin (100,000 units crystalline sodium penicillin and 300,000 units procaine penicillin), was administered intramuscularly to each patient. For purposes of checking, a few patients were given the 400,000 units of penicillin without the streptomycin. A third group of subjects received no antibiotic therapy and were used as controls. Samples of blood serum and stimulated saliva, approximately 5 ml. of each, were collected at 0.5, 1, 2, 4, 6, and 8 hours after administration of the antibiotics. One hour after the administration of the penicillin-streptomycin mixture, the number of units of penicillin per ml. of blood serum was as follows :

(a) Average for thirty-four patients, 2.84

(b) Highest, 4.20

(c) Lowest, 0.40

The peak level was reached in the first hour; it was sustained for two hours. At the end of the fourth hour, there was about a ten per cent drop. At the end of the eighth hour, the average was 0.575 units of penicillin per ml. One half hour after administration of the penicillin-streptomycin mixture, no penicillin could be detected in the saliva of most of the patients.

At the end of one hour, the concentration of penicillin in units per ml. of saliva was as follows :

(a) Average for thirty-one patients, 0.029

(b) Highest, 0.062

(c) Lowest, 0.0125

The peak level was reached in the first hour; after that there was a considerable drop. Detectable amounts of penicillin were present at the end of the six and eight hours. The rate of destruction of penicillin depended on the concentration, being greater at lower concentrations. At the peak concentration of 0.062 unit per ml. 50 to 55 per cent of the penicillin was destroyed by the end of the second hour. The rate of destruction, however, was no faster in saliva than in water. This suggested, therefore, that penicillin was not affected by penicillinase-producing organisms or other enzyme action. One hour after administration of penicillin without streptomycin to a small group of patients, the concentration of penicillin in the saliva was about the same as it was for the group receiving both penicillin and streptomycin. One hour after administration, the number of

micrograms of streptomycin per ml. of blood serum was as follows :

(a) Average for thirty-four patients, 19.3

(b) Highest, 32.0

(c) Lowest, 4.0

The peak level was sustained for two hours. At the end of the fourth hour, there was a fifty per cent drop. At the end of the eighth hour, four micrograms per ml. were still present. Concentrations of streptomycin in saliva were almost as high at the end of one half hour as they were at the end of one hour. One hour after administration, the number of micrograms of streptomycin per ml. of saliva was as follows :

(a) Average for thirty-one patients, 2.9

(b) Highest, 4.3

(c) Lowest, 1.1

Peak levels were obtained in the first hour. At the end of the second hour, there was a drop of about forty per cent. No correlation between penicillin levels in blood serum and saliva was observed. Similarly, no relationship was observed between concentrations of streptomycin in blood serum and saliva.

In one of a series of studies on human saliva as affected by antibiotics Bender, Pressman, and Tashman[4] investigated the effects of penicillin, streptomycin,chloramphenicol, and a combination of penicillin and streptomycin on the bacterial population of the mouth after a single parenteral injection. Stimulated saliva samples were collected before injection and at the optimal level after injection. Bacterial counts were made on the saliva samples. Antibiotics excreted into the saliva were assayed.

Administration of the antibiotics was as follows :

| Antibiotic | Dosage | Route | No. of patients |
|---|---|---|---|
| Penicillin (Crystalline Na penicillin Procaine penicillin | 400,000 units 100,000 units 300,000 units) | I.M. | 10 |
| Dihydrostreptomycin | 1.0 Gm. | I.M. | 10 |
| Chloramphenicol in acetyldimethylamine | 1.0 Gm. | I.V. | 20 |
| Dihydrostreptomycin and penicillin | 1.0 Gm. and 400,000 units | I.M. | 20 |

An 0.1 ml. specimen of saliva was diluted with 0.9 ml. of a brain heart infusion broth containing 2.5 per cent of penicillinase and 0.033 per cent of sodium poly-anethol sulfonate. Specimens were diluted using a 'virus technique'. Two 0.1 ml. samples of the appropriately diluted material were transferred to two blood agar

plates. Plates were incubated at 37°C. for eighteen hours, one of them under anaerobic condition using ten per cent carbon dioxide, the others using aerobic condition. There was no significant reduction in bacterial population count one hour after injection of a single dose of penicillin. Streptomycin had no effect on the bacterial population count of the mouth one hour after injection of a single dose. One half hour after a single intravenous injection of one gramme of chloramphenicol, the aerobic population count was reduced about forty per cent; the aerobic count was reduced about thirty per cent. One hour after a single I.M. injection of a mixture of one gramme of dihydro-streptomycin and 400,000 units of penicillin, the aerobic and the anaerobic counts were each reduced about sixty-five per cent. Concentration of streptomycin in saliva was about the same whether it was administered by itself (2.7 mcg. streptomycin per ml. of saliva) or in a mixture with penicillin (2.8 mcg. streptomycin per ml. saliva). Concentration of penicillin in saliva was actually less when the penicillin was administered by itself (0.014 unit penicillin per ml. saliva) than when it was administ-ered in the mixture (0.030 unit penicillin per ml. saliva).

As part of a joint venture in an investigation to evaluate anti-biotic agents Ludwick, Bass, and Jay in 1953 [48] studied the control of L. acidophilus counts by these agents amongst 320 male naval enlistees, ranged in age from seventeen to twenty-five years, with

an average age of eighteen and a half years. Three kinds of capsules, containing respectively a placebo, 100,000 units of procaine penicillin, or 250 mg. of Aureomycin, were used in the study. Each man received one capsule daily (prior to breakfast) for six weeks. L. acidophilus counts were made weekly according to the Hadley method[27] from saliva specimens collected prior to administration of the agents. The daily ingestion of 100,000 units of procaine penicillin or 250 mg. of Aureomycin failed to reduce or control the L. acidophilus counts. These antibiotic agents did not produce any sensitivity reactions in the gingival tissues nor was there any evidence that the gingivitis was reduced.

Carter, White, and Bass (1953 [9]) discussed the controversial relationship between dental caries and oral L. acidophilus counts. But they pointed out that at the time of their investigation the L. acidophilus count stood as the best means of measurement for caries by laboratory methods. They were interested in the germicidal power of the test penicillin troches and peroral tablets on oral lactobacilli. Tomato juice agar was used for the culturing of the L. acidophilus. Paraffin-stimulated saliva specimens were collected upon arising in the morning from patients before the teeth were cleaned and before breakfast. Lactobacillus counts were determined by the Hadley method[27]. Following shaking for three minutes in a Kahn shaker, one c.c. of saliva was trans-

ferred to four c.c. of Jay's infusion broth and 0.1 c.c. of the 1:5 dilution streaked on tomato juice agar and Littman medium. Further dilutions of 1:100,000 and 1:500,000 were made in sterile saline and 0.1 ml. streaked to blood plates. The tomato agar and Littman medium were incubated for four days, and the blood plates forty-eight hours at 37°C. before enumeration. The subjects ranged in age from seventeen to thirty years. Twenty-four subjects received for one day one troche containing 20,000 units of potassium penicillin G and 50 units of bacitracin every two hours until ten troches were assimilated (total 200,000 units of penicillin). Ten subjects from this group received troches for a second day. Twenty subjects received two-hourly another troche containing 50 units of bacitracin only for one day, and nine of them went on for a second day. Fifteen subjects received every two hours a third troche containing potassium penicillin G (5,000 units), cetylpyridinium chloride in a ratio of 1:1,500, and 0.3 per cent bezyl alcohol for one day (total 50,000 units), while eight of them continued for two days (100,000 units total). Twenty-two subjects were given a troche of similar base material but contained no antibiotic or other additive on a two-hourly schedule for a day. Ten of them received placebo for a second day. The remaining subjects received peroral tablets containing 200,000 units of potassium penicillin G (buffered) for a two-day period. Six subjects took one tablet per day, an equal number of subjects took two tablets per day, and another six of subjects

took three tablets per day. The study showed that L. acidophilus organisms were sensitive to the action of penicillin. There were reductions of 75 per cent or more in oral L. acidophilus with both a 5,000 unit and a 20,000 unit penicillin troche. The inhibitory action of the penicillin troches was quite transitory. It persisted for a period for less than twenty-four hours. The penicillin troches were also effective in reducing Streptococcus viridans, and there was almost complete inhibition of non-hemolytic staphylococci, hemolytic and non-hemolytic streptococci. These organisms, along with the Gram-negative bacteria, required longer periods to regenerate their respective populations once inhibited. An increase in yeast in the saliva was noted. There was no inhibitory effect demonstrated with the peroral penicillin tablets for L. acidophilus at these dosage levels.

In their investigation report in 1961 on the effects of long-term parenteral administration of antibiotics on the oral flora Handelman, Hawes, and Yap[29] found that in general there were no profound differences amongst the mean counts of organisms cultured and that the subjects had had no shift in bacterial flora even after continuous long-term antibiotic therapy.

The subjects in this study were grouped as follows :

1. Group I.

   Ninety-two children who had had rheumatic fever and received 250,000 units of penicillin daily by mouth.

2. Group II.

   Sixty-five siblings of Group I children as untreated control.

3. Group III.

   Thirty-five children who received from 1,000,000 to 3,000,000 units of penicillin and/or one gramme of tetracycline daily.

4. Group IV.

   Twenty-one children who had completed therapy, as in Group III, one year ago.

5. Group V.

   Thirty-two siblings of Groups III and IV subjects as untreated control.

Paraffin-stimulated saliva samples were collected and inoculated into different media suitable for estimating the numbers of 'total' aerobes, 'total' anaerobes, streptococci, micrococci, lactobacilli, veillonella, coliforms, and candida. The resistance of organisms in saliva to two concentrations of penicillin and tetracycline on antibiotic test discs was determined. Subjects receiving antibiotics showed slightly narrower zones of inhibition.

Littleton and White (1964 [46]) compared findings from dental examinations in a group of children given 200,000 units of oral penicillin daily over an extended period with findings for public school children who were without intensive antibiotic therapy. Three hundred and sixty-two children in the control group and seventy-three children in the experimental group, aged six to thirteen years, were included in the study. Age at start of daily penicillin therapy for the seventy-three hospital children varied from less than one year up to ten years. Average age at start of medication was 5.7 years. Dental caries experience was consistently less for hospital children than for public school children. The mean periodontal index scores (Russell's) tended to be slightly lower for hospital children. Hospital children had a slightly better general level of oral cleanliness (using Oral Hygiene Index of Greene and Vermillion).

Handelman and Hawes in 1965 [28] reported the relationship of antibiotic administration to changes in the salivary flora. The salivary flora of 204 children and adults who received systemic antibiotics by mouth over a long period of time was compared to 140 siblings and spouses who had not. Forty-three adults with a mean age of thirty years and six months and 106 children with a mean age of twelve years and eleven months received 200,000 units of penicillin daily for the prophylaxis of recurrent rheumatic fever. Another group of fifty-five children with a mean age of

twelve years nine months received one to three million units of penicillin daily plus one gramme of tetracycline occasionally for the treatment of chronic respiratory disease. The average length of therapy was one and one half years for the lower dosage group and four years for the higher dosage group. Approximately 5.0 ml. of paraffin-stimulated saliva was collected from each subject immediately upon rising; before eating, drinking or brushing the teeth. Suitable serial dilutions were prepared using sterile broth. Cultures were incubated for seventy-two hours at 37°C. Anaerobic cultivation was done in an atmosphere of ninety-five per cent nitrogen and five per cent carbon dioxide in Brewer's jars. The numbers of viable bacteria from representative salivary microbial categories were compared using selective and enriched media. There was little or no difference in the total cultivable flora on aerobic and anaerobic incubation, the Veillonella, lactobacilli, salt-tolerant staphylococci, and Candida organisms. The facultative streptoccocal population was 24 per cent less for patients receiving antibiotics than those who did not, and was the same for subjects receiving antibiotics on the two dosage levels. The reduction in the streptococcal population was attributed to Streptococcus salivarius.

Handelman, Mills, and Hawes (1966 [31]) assessed the effects of continuous, long-term systemic antibiotic administration on dental caries incidence for 175 children who received treatment for the

prevention of recurrent rheumatic fever (RF) and for 75 children who received treatment for chronic respiratory disease (CRD). The findings were compared to those from 144 untreated siblings. The RF group subjects received 200,000 units of oral penicillin daily. The CRD group patients received one to three million units of oral penicillin daily and occasionally one gramme of tetracycline. The mean length of therapy was 2.2. years for the RF group and 3.9 years for the CRD group. Regression analysis was used to determine the magnitude and significance of antibiotic therapy on dental caries incidence. The caries increment during antibiotic administration was approximately two thirds less than the general caries increment. The effect of antibiotic administration tended to increase with increased time on antibiotics. There appeared to be a residual effect following antibiotic therapy. Children receiving high dosages of antibiotics tended to have lower caries increments than did children on lower dosages.

Results of the various studies on the effect of systemic antibiotics on dental caries and oral flora in humans are summarised in Table 3.

TABLE 3

EFFECT OF SYSTEMIC ADMINISTRATION OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN HUMANS

| Year | Investigator(s) | Duration of administration | Agent | Effect |
|---|---|---|---|---|
| 1947 | Long (47) | 24 hours | Penicillin (I.M.) | Reduction of penicillin-sensitive organisms and an increase of Gram-negative bacilli. |
| 1951 | Kraus (43) | 24 hours | Aureomycin | Reduction of bacterial population by systemic Aureomycin was comparable to topical application. |
| 1952 | Smith, Skinner, and Erickson (68) | 3 months | Prophylactic oral penicillin daily | A decrease in hemolytic streptococci and an increase in hemolytic straphylococci and Gram-negative bacilli. |
| 1953 | Bender, Pressman, and Tashman (4) | one hour | Penicillin, streptomycin, and chloramphenicol | Penicillin and streptomycin separately had no effect on bacterial population.<br>Chloramphenicol reduced aerobic population by 40% and anaerobic count by 30%.<br>Penicillin plus streptomycin reduced both aerobic and anaerobic counts respectively by 65%. |

2/..

TABLE 3 (continued)

EFFECT OF SYSTEMIC ADMINISTRATION OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN HUMANS

| Year | Investigator(s) | Duration of administration | Agent | Effect |
|---|---|---|---|---|
| 1953 | Ludwick, Bass, and Jay (48) | 6 weeks | Penicillin and Aureomycin | No effect on L. acidophilus |
| 1953 | Carter, White, and Bass (9) | 2 days | Penicillin and bacitracin | Penicillin troches reduced Streptococcus viridans and 75% of L. acidophilus. Almost complete inhibition of non-hemolytic straphylococci, hemolytic and non-hemolytic streptococci by penicillin troches. |
| 1961 | Handelman, Hawes, and Yap (29) | | Prophylactic penicillin and tetracycline daily | An increase in yeast. No inhibitory effect by oral penicillin tablets. |
| | | | | No shift in bacterial flora. |

3/..

TABLE 3 (continued)

EFFECT OF SYSTEMIC ADMINISTRATION OF ANTIBIOTICS ON DENTAL CARIES AND ORAL FLORA IN HUMANS

| Year | Investigator(s) | Duration of administration | Agent | Effect |
|---|---|---|---|---|
| 1964 | Littleton and White (46) | | Prophylactic oral penicillin daily | A reduction in dental caries. |
| 1965 | Handelman and Hawes (28) | 1½ to 4 years | Tetracycline and prophylactic oral penicillin daily | A reduction in streptococcus salivarius. |
| 1966 | Handelman, Mills, and Hawes (31) | 2 to 4 years | Tetracycline and prophylactic oral penicillin daily | About 66% reduction of caries increment. |

## 2. ANTIBIOTICS AND DENTAL CALCULUS

### Animal and Human Studies :

It appears that bacteria do not play an important part in the formation of dental calculus. Baer[1] stated that under certain circumstances the bacteria play a role but that their presence is not essential for the formation of dental calculus.

Germ-free studies [2,15,21,26] have shown that dental calculus can form on the molar teeth of germ-free animals.

König and Mühlemann[42] found that topically applied penicillin had no effect on calculus formation in rats.

Fitzgerald, Jordan, Scott, and McCann (1960[14]) observed extensive calcareous deposits on the teeth of rats receiving a non-cariogenic diet. In their study three groups of twenty-four Sprague-Dawley females rats received distilled water and a non-cariogenic diet ad libitum from weaning. Chloramphenicol was mixed in the diet of one group at a level of 50 mg./kg. The second group received the same level of chlortetracycline, and the third served as control. A parallel series of animals, similarly treated, received a cariogenic coarse particle diet. After 110 days all surviving animals were sacrificed. In every animal in each of the groups receiving

the non-cariogenic diet hard calcareous deposits were noted on the molar teeth. Neither chloramphenicol nor chlortetracycline, antibiotics capable of inhibiting a broad spectrum of micro-organisms, exerted any inhibitory effects on the deposition of calculus in the animals receiving the non-cariogenic diet. The same level of these drugs in a cariogenic diet, whilst not appreciably altering the slight degree of calculus deposition, markedly inhibited the development of dental caries.

Dossenbach and Muhlemann (1961 [12]) carried out experiments in humans to determine the effect of penicillin lozenges on calculus formation. They observed no difference between the treated group and the control group.

Gressly in 1963 [24] reported the use of a high phosphate non-cariogenic diet which contained 3.5 per cent $KH_2PO_2$ ; he reported that a concentration of 100 mg. chlortetracycline per kg. markedly reduced calculus formation.

Theilade and Fitzgerald[73] designed an experiment to obtain more information as to the effect of addition of antibiotics to the diet on calculus formation in the white rat. Weaning female Sprague-Dawley rats were randomly divided into eight experimental groups of twelve animals each and one control group of six animals. The rats were housed two in a cage. Their age at the start of the

experiment was twenty-six days. Erythromycin at a level of 50 mg. per kg. was incorporated into a coarse and a fine particle diet respectively with or without the substitution of corn oil (20 gm. per hundred grammes of diet) at the expense of the starch in the diet. One further group of six animals was kept on the stock diet of Purina Chow laboratory pellets. Food and water was available ad libitum to all groups. The experiment was run for eight weeks at the end of which period the animals were sacrificed. Incorporation of erythromycin in the diet at a level of 50 mg. per kg. of diet resulted in a much diminished frequency and severity of calcified deposits in all groups regardless of fat content or physical consistency of the diet.

In his attempt to elucidate the relative importance of various factors influencing calculus formation Richardson (1965 [55]) administered antibiotics to cats daily for eighteen weeks by intramuscular injection. Thirty-five cats were divided equally and at random into seven groups. The antibiotics used and the dosages per cat were :

1. Group I.

   0.5 ml. sterile saline

2. Group II.

   30,000 units of procaine penicillin G plus 90,000 units of benzathine penicillin G every 21 days

3. Group III.

   50 mg. of dihydrostreptomycin

4. Group IV.

   50 mg. of tetracycline (as a capsule and placed down the throat).

5. Group V.

   125 mg. of chloramphenicol

6. Group VI.

   25 mg. of erythromycin

7. Group VII.

   A mixture that contained 30,000 units of procaine penicillin G and 50 mg. of dihydrostreptomycin.

The greatest reduction in the formation of dental calculus, 66 per cent, and the only reduction that was statistically significant ($P = 0.04$), was observed with erythromycin. Penicillin and dihydrostreptomycin caused moderate reductions of 43 and 35 per cent respectively. These were nearly significant ($P = 0.07$ and 0.06 respectively). Penicillin and dihydrostreptomycin in combination inhibited 20 per cent of the calculi, and this percentage approached significance ($P = 0.06$). Chloramphenicol and tetracycline caused reductions of 31 and 43 per cent that were not significant ($P = 0.30$ and 0.20, respectively). The inhibition by saline was 8 per cent and not significant statistically.

## 3. ANTIBIOTICS AND PERIODONTAL DISEASE

### Animal and Human Studies :

Although Baer and Newton[2] observed the occurrence of periodontal disease in germ-free white Swiss mice, there is considerable evidence which indicates that bacteria play an important role in periodontal disease (Gibbons[18]).

1. Antibiotics, such as penicillin, are effective in alleviating acute ulcerative gingivitis in man, and also in preventing the progression of periodontal disease in experimental animals[25,39].

2. Good oral hygiene which entails the physical removal of bacteria or the removal of sites for their colonization is effective in treating periodontal disease.

3. The organisms present in the gingival crevice have pathogenic potential.

Keyes and co-workers[37,39] showed that a form of periodontal disease in the hamster could be communicable.

After reviewing the literature on the subject of bacteriology and periodontal disease at that time, Gibbons[18] concluded that it would appear that periodontal disease occurred when conditions permitted an overall proliferation of and increase in mass of the entire gingival crevice microbiota. This would result in an increase in the overall tissue destructive capacity of the microbiota which would alter the equilibrium existing between the host and its indigenous microorganisms in the 'normal' state.

Strock (1944 [72]) noted that in 198 patients who were treated with from 80,000 to 9,000,000 units of penicillin for various pathological conditions, amongst which were gonorrhoea, syphilis, osteomyelitis, septicaemia, subacute bacterial endocarditis, and brain abscess, the gingivae were remarkable in tone and free from inflammation despite a history in thirty-seven instances of ulceration and spontaneous bleeding at the time penicillin treatment began, or a history of bleeding gums. He made an attempt to verify this influence of penicillin under controlled conditions in a study of fifteen patients with acute ulcerative gingivitis. All patients were male, aged eighteen to fifty years. Neither tooth brushing, mouth irrigations, nor oral hygiene measures of any kind were allowed. Penicillin was administered in varying amounts from 1,250,000 units intramuscularly to 5,000 units placed into the mouth and held at rest for lengths of time ranging from one hour to continuous bathing except during eating and sleeping periods. In all

cases there was prompt improvement. After definite early favourable changes in the gingivae, healing progressed despite the withdrawal of the penicillin. The duration of the treatment was not disclosed in the report.

Mitchell and Johnson (1956 [53]) conducted a study to examine the true nature of the gingival plaque material in the hamster. Eleven hamsters which were maintained on a high carbohydrate diet for three months developed a grossly apparent white plaque at the palato-gingival area of the upper molars. When these animals were fed laboratory chow (non-cariogenic) for two weeks, the plaque disappeared. After two subsequent weeks of a high carbohydrate diet, the plaque reappeared. By feeding 500 units of sodium penicillin G per gramme of diet, and 100 units per c.c. in the drinking water with the high carbohydrate diet for two weeks, the plaque was made to disappear. The plaque was determined to consist in large part of aciduric microorganisms.

To explore the effects of penicillin and streptomycin on the initiation and progression of periodontal lesions in rice rats which were susceptible to periodontal disease, Gupta, Auskaps, and Shaw[25] conducted four experiments on two hundred and fourteen rice rats. All rats were housed in individual wire-bottom cages with their own water bottles and food cups. Supplements of 0.05 per cent streptomycin to a cariogenic diet throughout the twenty-one-week experimental period caused major reductions in the number and

extent of soft tissue lesions but much smaller reductions in the amount of alveolar bone resorption. A supplement of 0.01 per cent penicillin to the diet was also highly effective in the prevention of periodontal lesions, while a comparable supplement of streptomycin was much less effective. Supplements of 0.05 per cent penicillin or 0.05 per cent of streptomycin to the diet during the last seven weeks of the experimental period were much less effective. Penicillin caused a moderate amount of healing of existing lesions of the soft tissues, while streptomycin did not encourage healing but did prevent further progression of soft tissue lesions.

In an effort to understand more fully the role of the antibiotics in the periodontal syndrome in rice rats, Shaw, Griffiths, and Auskaps (1961 [63]) evaluated polymyxin B sulphate, erythromycin glucoheptonate, and a benzyl penicillin preparation at various levels in a cariogenic diet on a preventive basis. In the same study a benzyl penicillin preparation, streptomycin sulphate, and oxytetracycline hydrochloride were tested for their curative ability. Three hundred and sixty-two rats were used on the study for twelve to twenty weeks. A benzyl penicillin preparation and erythromycin glucoheptonate were highly effective in the prevention of the periodontal syndrome, even at levels as low as 0.005 per cent in the diet. Polymyxin B sulphate was effective at high levels but ineffective at comparatively low levels. In curative trials, a 0.05 per cent benzyl penicillin preparation

resulted in a regression of the soft tissue lesions but was able only to retard the further progress in alveolar bone resorption. Oxytetracycline hydrochloride and a combination of a benzyl penicillin preparation and streptomycin sulphate were less effective than a benzyl penicillin preparation alone in the curative trials.

Observations made by Keyes and Jordan[40] over a period of five years in several thousand hamsters which had been used primarily for studies of experimental dental caries revealed some findings related to an infectious and transmissible component in periodontal lesions in the Syrian hamsters. The customary procedure for tests was to place three to five newly weaned animals weighing about 30 gm. in screen-bottom, stainless steel cages and to provide a high carbohydrate low fat diet and distilled water ad libitum plus a weekly supplement of fresh vegetables. An active type of periodontal disease developed in the golden and cream animals when they were fed the appropriate diet but it did not develop in the albino hamsters tested under similar conditions. However, the disease could be readily induced in the 'noninfected' albino hamsters by an inoculation of scrapings of subgingival plaque from the affected animals. Once acquired, either by direct inoculation or other contamination, the periodontal disease could be transmitted from generation to generation. Filamentous bacteria had been recovered from cultures of the plaque material in high numbers. Keyes and

Jordan concluded that periodontal lesions could be produced separately or together with enamel caries because different bacterial components were apparently associated with the diseases.

Jordan and Keyes in 1964 [36] reported that in studies up to that time the primary infectious agent responsible for the spontaneous periodontal syndrome in hamsters had been a Gram-positive filamentous organism indigenous to certain lines of hamsters. This disease was characterised by a heavy, adherent, subgingival plaque and accompanied the feeding of a high carbohydrate diet. Uninfected albino hamsters were obtained as weanling animals approximately twenty days of age and 30 gm. in weight. They were randomly distributed and caged in groups of three to four. Each animal in a group was immediately inoculated orally with 0.2 ml. of a broth culture of a single bacterial strain, and about 5 ml. of the broth culture was also added to the drinking water. This procedure was repeated in the same manner five days later. In each series of tests one cage of hamsters was retained as a control and was not inoculated. The experimental period was 90 to 100 days. All animals including the controls were fed a high carbohydrate diet, normally used to produce dental caries in hamsters. Pure cultures of aerobic branching filaments isolated from the plaque induced the disease when inoculated orally into unifected albino hamsters. Other plaque organisms including streptococci and various unidentified Gram-negative rods did not induce the disease. A filamentous

strain 'labelled' by making it resistant to terramycin was used to induce the disease and to trace implantation, persistance, and transfer of the organisms. The 'labelled' strain was recovered in high numbers from all hamsters infected with this strain and its transfer from infected mothers to offspring was observed.

Simultaneous inoculations with the aerobic filament and a specific streptococcus induced both periodontal disease and dental caries in the same animal. Jordan and Keyes pointed out that since their work was not done with a germ-free or gnotobiotic system, bacterial interactions could still be present but unrecognized.

In their findings from a preliminary study of seventy-three children receiving long-term penicillin therapy, Littleton and White reported in 1964 [46] that gingivitis scores (using Russell's Periodontal Index) were only slightly lower in the penicillin group. These were associated with a somewhat better level of oral hygiene.

Earlier studies by Gupta, Auskaps, and Shaw[25] and by Shaw, Griffiths, and Auskaps[63] had shown that the inclusion of varying amounts of certain antibiotics in the diet of rice rats caused major reductions in the initiation and progression of periodontal syndrome. Shaw[61] devised additional experiments to define the circumstances under which optimal benefits could be obtained from minimal usage of the effective antibiotics. Rice rats were weaned at 21 days of age and distributed as uniformly as possible among the several groups in each

of the six experiments. These rice rats had a high susceptibility to the development of the periodontal syndrome when they were fed a periodontal syndrome-producing diet. They were maintained in screen-bottom cages and fed the appropriate diet and water ad libitum. After 84 days the rats were sacrificed. Preliminary periods of four to twenty-eight days administration of 0.05 per cent penicillin (Procaine penicillin G and buffered crystalline penicillin G for aqueous suspension) in the diet of the rice rats before the usual 84 day assay period on periodontal syndrome-presenting diet caused highly significant reductions in the prevalence of the periodontal syndrome. Continuous administration in the same diet of 0.01 or 0.05 per cent oxytetracycline or chlortetracycline or of as little as 0.0025 per cent penicllin caused highly significant decreases in the periodontal syndrome. Intermittent feeding of the diet supplemented with either 0.01 or 0.05 per cent penicillin as frequently as one day in seven also caused highly significant reductions in the periodontal syndrome.

Jordan and Keyes in 1965[37] reported their further attempts to isolate additional bacterial components from hamster periodontal plaque and to assess their disease inducing potential in uninfected animals. In addition to the indigenous microorganisms, certain strains of gingival organisms obtained from the rat and human being were also tested for pathogenicity in the hamster. Pure cultures of the various bacterial strains from infected animals were inocul-

ated into the mouths of young albino hamsters as soon as the animals were started on the test regimen and again one week later. Each animal received 0.2 c.c. of a broth culture, and 4 to 5 c.c. of the broth was also added to the drinking water. Animals weighing 20 to 30 gm. were caged together in groups of two to four and fed the same high carbohydrate low fat diet used for studies of experimental dental caries. A puree of fresh vegetables was supplied once a week and distilled water was always available. Animals were examined periodically over a period of 42 to 84 days for evidence of gingival plaque and also for signs of dental caries. Intensive survey of plaque organisms failed to uncover organisms other than the aerobic, branching filamentous type with a primary role in the disease. Leptotrichia usually were present in the plaque but did not induce the disorder. Fusobacteria were not isolated from the plaque. Bacteriodes melaninogenicus was present in low numbers in about half the animals sampled but did not induce the plaque formation under the conditions used. Aerobic branching filaments similar to the hamster organisms were isolated from periodontal plaque in Sprague-Dawley rats, and these also induced the disease in hamsters. Various types of filaments isolated from the human gingival crevice and a direct inoculation of human periodontal plaque failed to induce periodontal disease in hamsters.

Shaw and Dick (1966 [62]) tested the effectiveness of penicillin in their experiment by different routes of administration. There were four groups of littermate-matched rice rats. The first group, eleven female and thirteen male, served as control and was maintained on tap water and a periodontal syndrome-producing diet. The second group, fifteen female and fourteen male, received tap water and the same diet supplemented with 0.05 per cent penicillin. The third group, eleven female and twelve male, was given unsupplemented diet plus water supplemented with 0.025 per cent penicillin, a level which provided approximately the same amount of penicillin per rice rat per day to that in the second group. The fourth group received injections of penicillin suspension subcutaneously daily except Sunday at a level of 4 mg. per 100 gm. of body weight, which was approximately equivalent to that consumed in the diet for the second group. Penicillin either in the diet or injected subcutaneously resulted in an almost complete prevention of lesions of the gingivae or other soft tissues. Penicillin in the drinking water did not result in complete prevention of the syndrome. In all three experimental groups a slow rate of progression of alveolar bone resorption was observed. The duration of the experiment was not mentioned.

## 4. SUMMARY

From the various studies (Table 1) it appears that penicillin, when incorporated into the diet, is effective in reducing dental caries and suppressing lactobacilli in rats.

The effect of topical application of penicillin and other antibiotics in the form of dentifrices, troches, and lozenges, on human dental caries was not consistent (Table 2). Thus while Zander[78] reported a fifty-five per cent reduction of caries, and Ludwick, Fosdick, and Schantz[49] found that penicillin was effective in reducing dental caries, findings from other investigators (Table 2) were not in agreement. Walsh and Smart[74] observed that both the penicillin and control dentifrices in their study reduced dental caries. There was a slight reduction in DMF surfaces in the study by Hill, Sims, and Newman[34]. A study by Shiere[66] showed a twenty-six per cent reduction in new decayed and filled surfaces. Penicillin had no effect on dental caries according to the results of Hill and Kniesner[32]. There was no difference in caries incidence between the experimental and control groups in the study by Lunin and Mandel[50].

Studies with human subjects receiving long-term penicillin therapy showed that penicillin was effective in reducing dental caries.

Reduction in caries was observed in the study by Littleton and White[46]. Handelman, Mills, and Hawes[31] also reported about sixty-six per cent reduction in caries.

On calculus formation, results of studies by König and Mühlemann[42], Fitzgerald, Jordan, Scott, and McCann[14], and Dossenbach and Muhlemann[12] showed that penicillin, chloramphenicol, or chlortetracycline had no inhibitory effect in rats. However, Gressly[24] found that chlortetracycline markedly reduced calculus formation, and Theilade and Fitzgerald[73] also observed that erythromycin reduced the frequency and severity of calcified deposits in white rats, while Richardson[55] reported a sixty-six per cent reduction in calculus formation in cats with erythromycin, and moderate reductions with penicillin and dihydrostreptomycin (forty-three and thirty-five per cent reduction respectively).

All reported studies on the effect of antibiotics on periodontal tissues showed that antibiotics appeared to be beneficial both in the prevention and treatment of periodontal syndrome. Strock[72] observed a prompt improvement in the gingivae when people with bleeding gums were treated with penicillin. Studies by Gupta, Auskaps, and Shaw[25] showed that supplement of penicillin to the diet of rice rats was highly effective in the prevention of periodontal lesions, and it also caused a moderate amount of healing of the existing soft tissue lesions. Using erythromycin as well as

penicillin, Shaw, Griffiths, and Auskaps[63] confirmed the results of the study by the previous investigators. In the study by Littleton and White[46], children receiving long-term penicillin therapy had slightly lower gingivitis scores than children in the control group. Tetracyclines and penicillin caused a highly significant reduction in periodontal syndrome in rice rat according to the study by Shaw[61]. In another study, Shaw and Dick[62] found that penicillin almost completely prevented lesions of the gingivae or other soft sissues in rice rats.

Results of studies on the effect of penicillin on lactobacillus, streptococcus, yeast (monilia), or on the bacterial population as a whole in the oral cavity were contradictory. A study of oral flora in rats by McClure and Hewitt[52] showed that there was a very low lactobacillus count with penicillin. Stephan, Harris, and Fitzgerald[71] and Rosen et al[57] found that penicillin suppressed both lactobacilli and streptococci in rats, but a higher concentration of penicillin was required to reduce streptococci in the former study.

Lactobacilli in the oral cavity were reduced by topical application of penicillin in the studies with human subjects by Hill and Kniesner[32], White, Kniesner, and Hill[76], and Slanetz and Reynolds[67]. However, Fitzgerald, Zander, and Jordan[16], and Hill, Sims, and Newman[34] observed that topical application of penicillin had no effect on the lactobacilli.

Findings from Slanetz and Reynolds[67] and Williams[77] showed that topical penicillin suppressed streptococci and there was an increase in the yeast population. In their study, Hill, Rasch, and Wollpert[33] found that there was an increase of Streptococcus viridans with the use of topical penicillin. Brudevold and Hawes[7] reported that topical penicillin had no effect on monilia. There was no change in the oral flora in the study by Lunin and Mandel[50] using penicillin tooth powder.

Systemic administration of penicillin to human subjects caused a reduction of streptococci in the studies by Long[47], Smith, Skinner, and Erickson[68], Carter, White, and Bass[9], and by Handelman and Hawes[28]. There was also an increase in yeast in the study by Carter, White, and Bass[9]. Systemic penicillin had no effect on Lactobacillus acidophilus according to the results of Ludwick, Bass, and Jay[48]. There was no shift in the oral bacterial flora with systemic administration of penicillin in the studies by Bender, Pressman, and Tashman[4] and Handelman, Hawes, and Yap[29].

It is with the results of these various studies on the effect of antibiotics, particularly penicillin, on dental caries, calculus formation, periodontal syndrome, and on oral flora in mind that the present study was formulated and carried out. Results of this study are to be compared with those by previous investigators.

## EXPERIMENTAL STUDY - METHOD AND DESIGN

Children who had a history of rheumatic fever attending the Cardiac Clinic at the Institute of Child Health, Royal Alexandra Hospital for Children, Sydney, were examined. They had been receiving twice daily 200,000 units of oral Penicillin V (Potassium phenoxmethyl penicillin, LPV tablets 125 mg., Commonwealth Serum Laboratory) over a long period as a prophylactic measure against the recurrence of rheumatic fever. The group of children used as control had not received any antibiotic therapy and they had been attending the United Dental Hospital of Sydney for dental treatment.

There were 83 children in each group and they were matched according to age, sex, and the number of teeth present. Socio-economic factors were in general comparable in both groups. The children were divided into four age groups, namely, 7-9 years, 10-12 years, 13-15 years, and 16-19 years, respectively. (Table 4 shows the age, sex distribution of the two groups.) Mean age of the children in the Experimental Group was 13 years and that of the children in the Control Group was 12 years 9 months (Table 9 and Table 11).

Children in the Experimental Group were examined over a period from July to October 1966. Only those who had been receiving penicillin therapy continuously for more than 12 months were selected.

TABLE 4

DISTRIBUTION OF CHILDREN BY AGE AND SEX

| Age (years) | Experimental Group | | | Control Group | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| 7 | 2 | 2 | 4 | 2 | 2 | 4 |
| 8 | 1 | 2 | 3 | 1 | 2 | 3 |
| 9 | 2 | 4 | 6 | 2 | 4 | 6 |
| 10 | 5 | 4 | 9 | 7 | 4 | 11 |
| 11 | 5 | 2 | 7 | 3 | 2 | 5 |
| 12 | 6 | 3 | 9 | 6 | 3 | 9 |
| 13 | 6 | 8 | 14 | 6 | 10 | 16 |
| 14 | 6 | 6 | 12 | 8 | 4 | 12 |
| 15 | 5 | 3 | 8 | 3 | 3 | 6 |
| 16 | 0 | 2 | 2 | 4 | 2 | 6 |
| 17 | 3 | 0 | 3 | 2 | 0 | 2 |
| 18 | 2 | 2 | 4 | 1 | 2 | 3 |
| 19 | 2 | 0 | 2 | 0 | 0 | 0 |
| All ages (7-19) | 45 | 38 | 83 | 45 | 38 | 83 |

Duration of therapy varied from one year to twelve years. The average duration was five years. Age at commencement of daily penicillin therapy for the 83 children in the Experimental Group varied from 1 year to 13 years (Table 5).

All dental examinations were carried out by the one examiner. A portable dental chair, portable dental light (Planet light), and standard dental mirrors (No.4), and sickle-shaped explorers (Explorer PRO FT 54 Ash England Lustra) were used. Dental caries experience in deciduous teeth (for the age group 7-9 years only) was estimated clinically using the dmft and dfs indices. The DMFT and DMFS indices were used for the permanent dentition. Criteria used for these indices were :

1. Decayed teeth (dt or DT) include not only teeth with caries but also filled teeth with carious lesions or defective fillings.
2. Missing teeth (mt or MT) include only teeth lost as a result of dental caries.
3. Filled teeth (ft or FT) include only teeth with satisfactory fillings.
4. DMFT or dmft is the sum of these three categories.
5. One missing permanent tooth (MT) has five missing surfaces (MS).

TABLE 5

DISTRIBUTION OF CHILDREN IN THE EXPERIMENTAL GROUP BY AGE WHEN DAILY PENICILLIN THERAPY COMMENCED

| Age at examination (years) | Age in years at time penicillin therapy started | | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
| 7 | - | - | - | 1 | 2 | 1 | - | - | - | - | - | - | - | 4 |
| 8 | - | - | - | - | 1 | - | 2 | - | - | - | - | - | - | 3 |
| 9 | - | - | - | - | - | 4 | - | 2 | - | - | - | - | - | 6 |
| 10 | 2 | - | - | - | - | 1 | 3 | 2 | 1 | - | - | - | - | 9 |
| 11 | - | - | - | - | - | 1 | - | 2 | - | 4 | - | - | - | 7 |
| 12 | - | 1 | 1 | 1 | - | 2 | 2 | 1 | - | - | 1 | - | - | 9 |
| 13 | - | - | - | - | 1 | 3 | 2 | 3 | 1 | 2 | 2 | - | - | 14 |
| 14 | - | 1 | - | 2 | - | 2 | 1 | - | 2 | 2 | - | 1 | 1 | 12 |
| 15 | - | - | 2 | 1 | - | 2 | 1 | 1 | 1 | - | - | - | - | 8 |
| 16 | - | - | - | - | - | 1 | - | 1 | - | - | - | - | - | 2 |
| 17 | - | - | - | - | - | - | - | - | 1 | 2 | - | - | - | 3 |
| 18 | - | - | - | - | - | 1 | - | 1 | - | - | - | 1 | 1 | 4 |
| 19 | - | - | - | - | - | - | 1 | - | - | - | 1 | - | - | 2 |
| All ages (7-19) | 2 | 2 | 3 | 5 | 4 | 18 | 12 | 13 | 6 | 10 | 4 | 2 | 2 | 83 |

A tooth was counted as carious if there was an actual break of surface continuity demonstrable with the explorer, a softened cavity floor detected on slight explorer pressure, visual evidence of backward decay of the enamel, or visual evidence of deterioration of the pit or fissure wall. In the present study, subsurface decalcification of the enamel (white spot) was not considered as clinical caries.

The Periodontal Index of Russell[58] was used to record the clinical condition of the periodontal tissues. The Oral Hygiene Index of Greene and Vermillion[23] was used to score the presence and extent of oral debris and calculus deposits.

Findings were recorded by an assistant on the Examination Chart as used by the Department of Preventive Dentistry, the University of Sydney (Figures 1 and 2).

Saliva samples were taken from 18 children randomly selected in the Experimental Group and from 20 children approximately matched by age and sex in the Control Group.

Two (2) c.c. of paraffin-stimulated saliva (stimulated for five minutes) were introduced into 98 c.c. Ringer's solution. One half (0.5) c.c. of the diluted saliva was spread onto a petri dish of tomato juice agar. The plate was incubated at 37°C. for 72 hours. Monilia and lactobacillus colonies were counted at the end of 72 hours.

# UNIVERSITY OF SYDNEY

## DEPARTMENT OF PREVENTIVE DENTISTRY

### Examination Chart

Telephone 211-4322

Name HURLEY, Julie (Miss)

~~Address~~ School 51 MOUNT ST., PYRMOUNT.

Date of Birth 6.3.1957

Group _____

Age - Years 9 Months 84 Date of Examination 6.7.66

Sex F (b) Examiner _____ (a) Examiner S.C.

| | C. Incisor | L. Incisor | Cuspid | D. Molar 1 / Bicuspid 1 | D. Molar 2 / Bicuspid 2 | Molar 1 | Molar 2 | Molar 3 |
|---|---|---|---|---|---|---|---|---|
| Upper Left | S | S | S | $D_4$ X 4 | $D_4$ X | $S_4$ X O | | |
| Upper Right | S 6W | (1) | S – | $D_4$ L – | D – | $D_9$ X 3 | $S_4$ X O | |
| Lower Left | S | S | S – | S – | $S_4$ X | $S_4$ X | | |
| Lower Right | S | S – | O – | S – | △ | $S_4$ X | | |

Debris 5.65 Calculus ~~0.67~~ 0.68 Oral Hygiene ~~6.32~~ 6.32

Periodontal Index Russell 15/22 = 0.68 Stain _____

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| S/Teeth: | Hypoplasia | (6) | ___ | (6F) | ___ | 6 | ___ | 6F | ___ | (6) | 6 | ___ | (6F) | 6F | ___ |
| | Opacity | 6W | ✓ | 6WF | ___ | 6B | ___ | 6BF | ___ | 6W | 6B | ___ | 6WF | 6BF | ___ |
| D/Teeth: | Hypoplasia | (6) | ___ | (6F) | ___ | 6 | ___ | 6F | ___ | (6) | 6 | ___ | (6F) | 6F | ___ |
| | Opacity | 6W | ___ | 6WF | ___ | 6B | ___ | 6BF | ___ | 6W | 6B | ___ | 6WF | 6BF | ___ |

Remarks: Tooth brushing 2/daily.

Fluorosis: Norm. ✓ Quest. ___ V.Mild ___ Mild ___ Mod. ___ Severe ___

Ortho No. _____ X-Ray No. _____ Photo No. _____

| DEBRIS | | | | | CALCULUS | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Right | Anterior | Left | Total | | Right | Anterior | Left | Total |
| Upper | 3/3 | 3/3 | 3/3 | 9/9 | Upper | / | / | / | / |
| Lower | 3/3 | 1/3 | 3/3 | 7/9 | Lower | / | 1/3 | / | 1/3 |
| Sub-Total | 6/6 | 4/6 | 6/6 | 16/18 | Sub-Total | / | 1/3 | / | 1/3 |

P/Index Russell 15/22 = 0.68

Debris 34/6 = 5.65

Calculus 4/6 = 0.67

O/Hygiene 38/6 = 6.32

Stain .....

Angle: Cl.1 _____ Cl.II/I _____ Cl.II/II _____ Cl.III _____ Orthodontic Index ____

Orthodontic: Normal _____ Mild _____ Moderate _____ Severe _____

Remarks: _____

_____

Duration of Penicillin treatment 13/12.

10. 11. 65 31.4 Kg. Steroid

Penicillin V 200,000 units b.i.d.

The results were expressed as :

1. Monilia or lactobacilli count per c.c. of the undiluted saliva samples.

2. The mean monilia or lactobacillus count.

   (a) As a mean of the entire group. (Experimental or Control Group)

   (b) As a mean of those samples in which monilia or lactobacilli occurred.

3. The prevalence of occurrence of monilia or lactobacilli in each group.

Another 0.5 c.c. of the diluted saliva was transferred into 5 c.c. of nutrient broth (pH 7.0) containing :

1. 0.5 per cent Peptone (" L 37 Oxoid").
2. 0.5 per cent brain heart infusion
3. 1.0 per cent glucose.

The broth was incubated at 37°C. in a water bath. The pH of the medium was observed and graphed in relation to time. The time taken for the medium to reach pH 6.7 from a pH of 7.0 was noted. (At pH 6.7 the $H^+$ concentration is double that at pH 7.0 .) This time taken to reach pH 6.7 is a measure of relative degrees of anaerobic metabolism taking place and consequently is an indicator of the streptococcal activity. The terminal pH of each sample tested was also recorded. The pH was determined colorimetrically using the indicators Bromocresol purple and Bromocresol green.

# RESULTS

The results from the dental examination of 83 children who had been taking penicillin daily for the prevention of recurrent rheumatic fever (Experimental Group) and of 83 children who had been attending the United Dental Hospital for dental treatment but had not received any antibiotic therapy (Control Group) are presented. The mean age of the children in the Experimental Group was 13 years 0 months (male 13 years 1 month and female 12 years 11 months). In the Control Group the average age of the children was 12 years 9 months (male 13 years 0 months and female 12 years 6 months).

## 1. PERIODONTAL DISEASE

In both groups periodontal disease was limited, with one exception, to gingival inflammation. The exception was a boy in the Experimental Group, aged 19 years 4 months, with pocket formation in 24 teeth out of the 27 teeth present.

The mean Russell Periodontal Index for the Experimental Group was $1.02 \pm 0.019$ and that for the Control Group was $1.44 \pm 0.007$ (Table 6). The difference in the mean Russell Periodontal Index between the two groups was clearly significant statistically ($p < 0.001$).

TABLE 6

MEAN PERIODONTAL INDEX AND ORAL HYGIENE SCORES

(By group, age and sex)

| Group | Sex | N | Russell Index | Debris Index | Calculus Index | Oral Hygiene Index |
|---|---|---|---|---|---|---|
| Experimental | | | | | | |
| 10-12 years | M | 16 | 0.83 | 2.98 | 0.25 | 3.23 |
| | F | 9 | 1.13 | 3.21 | 0.24 | 3.41 |
| | M+F | 25 | 0.94 | 3.06 | 0.23 | 3.30 |
| 13-15 years | M | 17 | 0.98 | 3.11 | 0.20 | 3.30 |
| | F | 17 | 0.94 | 2.82 | 0.14 | 2.95 |
| | M+F | 34 | 0.96 | 2.97 | 0.16 | 3.13 |
| 16-19 years | M | 7 | 1.71 | 3.26 | 0.38 | 3.64 |
| | F | 4 | 0.84 | 3.58 | 0.09 | 3.68 |
| | M+F | 11 | 1.39 | 3.38 | 0.27 | 3.65 |
| 10-19 years | M | 40 | 1.05 | 3.08 | 0.25 | 3.33 |
| | F | 30 | 0.98 | 3.04 | 0.15 | 3.18 |
| | M+F | 70 | 1.02 ±0.019 | 3.06 | 0.21 | 3.27 ±0.022 |
| Control | | | | | | |
| 10-12 years | M | 16 | 1.37 | 3.21 | 0.08 | 3.30 |
| | F | 9 | 1.34 | 2.89 | 0.07 | 2.96 |
| | M+F | 25 | 1.36 | 3.10 | 0.08 | 3.18 |
| 13-15 years | M | 17 | 1.51 | 3.38 | 0.17 | 3.54 |
| | F | 17 | 1.44 | 3.10 | 0.04 | 3.14 |
| | M+F | 34 | 1.48 | 3.24 | 0.10 | 3.34 |
| 16-19 years | M | 7 | 1.41 | 3.29 | 0 | 3.29 |
| | F | 4 | 1.63 | 3.83 | 0.08 | 3.92 |
| | M+F | 11 | 1.49 | 3.48 | 0.03 | 3.51 |
| 10-19 years | M | 40 | 1.44 | 3.30 | 0.10 | 3.40 |
| | F | 30 | 1.44 | 3.13 | 0.06 | 3.19 |
| | M+F | 70 | 1.44 ±0.007 | 3.23 | 0.08 | 3.31 ±0.014 |

## 2. ORAL HYGIENE :

The mean Oral Hygiene Index was similar and high for both groups of children (3.27 ± 0.022 for the Experimental Group and 3.31 ± 0.014 for the Control Group). Children in the Experimental Group aged 10-19 years had a higher mean Calculus Index (0.21 ± 0.005) than that for the children in the Control Group (0.08 ± 0.003). (Table 6). This difference was clearly significant statistically. ($p < 0.001$).

## 3. DENTAL CARIES EXPERIENCE :

The mean number of deciduous teeth present for children aged 7-9 years in the Experimental Group was 10.22, with 1.23 teeth missing due to caries (Table 7). 11.46 teeth had erupted and not exfoliated. Extensive caries involving the pulp had caused 0.08 teeth per child to be due for extraction. Thus eventually 1.31 teeth would be lost as a result of caries.

The dft per child 2.84 ± 0.035, the dmft per child 4.07 ± 0.028, and the number of df surfaces per child 4.69 ± 0.070 (Table 8). 18.1 per cent of the total dmf teeth was restored.

For children aged 7-9 years in the Control Group the mean number of deciduous teeth present was 8.77 teeth, with 3.00 teeth missing due to caries. 11.76 teeth had erupted. For each child 0.08

TABLE 7

MEAN NUMBER OF DECIDUOUS TEETH PRESENT, MISSING, ERUPTED, DUE FOR EXTRACTION, AND PERCENTAGE OF FILLED TEETH OF dmf TEETH

(By group and sex)

| Group | Sex | N | Deciduous teeth present | mt | Total* erupted | et | mt + et | ft / dmft % |
|---|---|---|---|---|---|---|---|---|
| Experimental | | | | | | | | |
| 7-9 years | M | 5 | 12.80 | 1.20 | 14.00 | 0.00 | 1.20 | 47.1 |
| | F | 8 | 8.63 | 1.25 | 9.88 | 0.13 | 1.37 | 0.0 |
| | M+F | 13 | 10.22 | 1.23 | 11.46 | 0.08 | 1.31 | 18.1 |
| Control | | | | | | | | |
| 7-9 years | M | 5 | 8.00 | 3.20 | 11.20 | 0.20 | 3.40 | 31.4 |
| | F | 8 | 9.25 | 2.88 | 12.12 | 0.00 | 2.88 | 28.3 |
| | M+F | 13 | 8.77 | 3.00 | 11.76 | 0.08 | 3.08 | 29.5 |

* Includes missing teeth (mt) or teeth lost for reasons other than exfoliation, but does not include those deciduous teeth which could have exfoliated.

mt = Teeth missing because of caries

et = Teeth due for extraction because of extensive caries involving the pulp.

TABLE 8

AVERAGE dft, dmft, AND dfs SCORES

(By group and sex)

| Group | Sex | N | df | ft | dft | mt | dmft | ds | fs | dfs |
|---|---|---|---|---|---|---|---|---|---|---|
| Experimental | | | | | | | | | | |
| 7-9 years | M | 5 | 1.20 | 1.80 | 3.00 | 1.20 | 4.20 | 1.80 | 3.20 | 5.00 |
| | F | 8 | 2.75 | 0 | 2.75 | 1.25 | 4.00 | 4.50 | 0 | 4.50 |
| | M+F | 13 | 2.15 | 0.69 | 2.84 ±0.035 | 1.23 | 4.07 | 3.46 | 1.23 | 4.69 ±0.070 |
| Control | | | | | | | | | | |
| 7-9 years | M | 5 | 1.80 | 2.40 | 4.20 | 3.20 | 7.40 | 2.80 | 4.00 | 6.80 |
| | F | 8 | 2.88 | 1.00 | 3.87 | 2.87 | 6.75 | 4.75 | 1.75 | 6.50 |
| | M+F | 13 | 2.46 | 1.54 | 4.00 ±0.046 | 3.00 | 7.00 | 4.00 | 2.62 | 6.62 ±0.042 |

teeth were due for extraction because of extensive caries involving the pulp (Table 7). With the missing teeth this gives a total of 3.08 teeth which would be lost from caries consequently.

The dft per child was 4.00 $\pm$ 0.046, the dmft per child 7.00 $\pm$ 0.091, and the number of df surfaces per child 6.62 $\pm$ 0.042 (Table 8).

29.5 per cent of the total dmf teeth was restored.

The difference in the mean dft per child between the two groups was clearly significant statistically ($p < 0.001$). The differences in the mean dmft per child and dfs per child were probably significant ($p < 0.01$ and $p < 0.05$ respectively).

The mean number of permanent teeth present for the Experimental Group aged 7 to 19 years was 23.01 teeth, with 0.81 $\pm$ 0.042 teeth missing due to caries (Table 9). A total of 23.82 teeth had erupted and 0.14 teeth were due for extraction because of extensive caries involving the pulp, Thus eventually 0.95 teeth would be lost as a result of caries.

The mean number of DMF teeth per child for the Experimental Group was 8.04 $\pm$ 0.292, and that of DMF surfaces per child was 14.63 $\pm$ 0.563 (Table 10). The percentage of teeth at risk affected by decay, expressed as DMF teeth per 100 teeth erupted, was 32.9 $\pm$ 0.51 per cent. A proportion of 32.9 per cent of the total DMF

teeth was restored (Table 9). For each child 0.43 ± 0.041 teeth which had previously been restored had recurrent caries.

For children aged 7 to 19 years in the Control Group the mean number of permanent teeth present was 21.69 teeth, with 1.97 ± 0.172 teeth missing due to caries (Table 11) and a total of 23.67 teeth had erupted. An average of 0.11 teeth per child was due for extraction because of extensive caries involving the pulp. Together with the teeth missing this gives a total of 2.08 teeth which will be lost from caries consequently.

The mean number of DMF teeth per child for the Control Group was 11.80 ± 0.544 and the number of DMF surfaces per child was 26.10 ± 1.482 (Table 12). The percentage of teeth at risk, expressed as DMFT per 100 teeth erupted, was 47.4 ± 1.27 per cent. The FT comprised 44.9 per cent of the total DMF teeth index (Table 11) not counting 0.58 ± 0.052 teeth which had previously been restored and had recurrent caries at time of examination.

The differences between the groups in the mean number of missing teeth, DMF teeth per child, DMF surfaces per child, and the percentage of teeth at risk expressed as DMF teeth per 100 teeth erupted between the two groups were clearly significant statistically ($p < 0.001$).

TABLE 9

MEAN NUMBER OF PERMANENT TEETH PRESENT, MISSING, ERUPTED, FILLED BUT DECAYED, DUE FOR EXTRACTION, AND PERCENTAGE OF FILLED TEETH OF DMFT

(Experimental Group by age and sex)

| Group (Years) | Sex | N | Age* | Teeth present | MT | Teeth erupted | (D+F)T | XT | M+X | $\frac{FT}{DMFT}$ % |
|---|---|---|---|---|---|---|---|---|---|---|
| 7-9 | M | 5 | 8.3 | 9.40 | 0 | 9.40 | 0 | 0 | 0 | 0 |
| | F | 8 | 8.7 | 14.38 | 0 | 14.38 | 0 | 0.13 | 0.13 | 25.0 |
| | M+F | 13 | 8.5 | 12.46 | 0 | 12.46 | 0 | 0.08 | 0.08 | 15.4 |
| 10-12 | M | 16 | 11.7 | 21.41 | 0.38 | 21.80 | 0.50 | 0.19 | 0.56 | 46.5 |
| | F | 9 | 11.5 | 21.62 | 1.44 | 23.10 | 0.55 | 0.22 | 1.67 | 19.5 |
| | M+F | 25 | 11.6 | 21.50 | 0.76 | 22.23 | 0.52 | 0.20 | 0.96 | 36.8 |
| 13-15 | M | 17 | 14.5 | 27.03 | 0.94 | 28.00 | 0.29 | 0.18 | 1.12 | 29.8 |
| | F | 17 | 14.3 | 26.59 | 1.12 | 27.70 | 0.24 | 0.12 | 1.24 | 37.2 |
| | M+F | 34 | 14.4 | 26.80 | 1.03 | 27.82 | 0.26 | 0.15 | 1.18 | 33.5 |
| 16-19 | M | 7 | 18.0 | 29.00 | 0.57 | 28.58 | 1.14 | 0 | 0.57 | 50.3 |
| | F | 4 | 17.4 | 25.50 | 2.25 | 27.75 | 1.50 | 0.25 | 2.50 | 29.6 |
| | M+F | 11 | 17.9 | 27.08 | 1.18 | 28.25 | 1.27 | 0.09 | 1.27 | 42.8 |
| 7-19 | M | 45 | 13.1 | 23.25 | 0.58 | 23.82 | 0.47 | 0.13 | 0.71 | 35.6 |
| | F | 38 | 12.11 | 22.74 | 1.08 | 23.81 | 0.39 | 0.16 | 1.24 | 29.6 |
| | M+F | 83 | 13.0 | 23.01 | 0.81 ±0.042 | 23.82 | 0.43 | 0.14 | 0.95 | 32.9 |

* = Mean age in years and months

TABLE 10

MEAN NUMBER OF DECAYED, MISSING, AND FILLED PERMANENT TEETH AND TOOTH SURFACES

(Experimental Group by age and sex)

| Group (Years) | Sex | N | DT | MT | FT | DMFT | DMFT / 100 T. % | DS | MS | FS | DMFS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7-9 | M | 5 | 2.00 | 0 | 0 | 2.00 | 19.2 | 3.00 | 0 | 0 | 3.00 |
| | F | 8 | 2.63 | 0 | 1.13 | 3.76 | 28.9 | 4.38 | 0 | 1.63 | 6.01 |
| | M+F | 13 | 2.39 | 0 | 0.59 | 3.08 | 25.2 | 3.85 | 0 | 1.00 | 4.85 |
| 10-12 | M | 16 | 3.63 | 0.38 | 2.50 | 6.51 | 30.1 | 4.75 | 1.82 | 4.25 | 10.88 |
| | F | 9 | 4.78 | 1.44 | 1.56 | 7.78 | 33.3 | 7.66 | 7.22 | 2.34 | 17.21 |
| | M+F | 25 | 4.04 | 0.76 | 2.16 | 6.96 | 31.3 | 5.80 | 3.80 | 3.56 | 13.15 |
| 13-15 | M | 17 | 5.65 | 00.94 | 3.12 | 9.71 | 34.7 | 7.41 | 4.12 | 4.70 | 16.22 |
| | F | 17 | 4.47 | 1.12 | 3.71 | 9.29 | 33.6 | 5.95 | 5.59 | 6.11 | 17.64 |
| | M+F | 34 | 5.06 | 1.03 | 3.41 | 9.50 | 34.1 | 6.67 | 4.85 | 5.40 | 16.95 |
| 16-19 | M | 7 | 4.29 | 0.57 | 5.86 | 10.71 | 37.4 | 5.43 | 2.86 | 11.12 | 19.42 |
| | F | 4 | 7.00 | 2.25 | 4.50 | 13.75 | 49.5 | 9.50 | 11.24 | 7.00 | 27.75 |
| | M+F | 11 | 5.27 | 1.18 | 5.36 | 11.82 | 41.8 | 6.91 | 5.90 | 9.65 | 22.45 |
| 7-19 | M | 45 | 4.31 | 0.58 | 2.98 | 7.87 | 31.8 | 5.66 | 2.66 | 5.02 | 13.35 |
| | F | 38 | 4.42 | 1.08 | 2.74 | 8.24 | 34.2 | 6.40 | 5.40 | 4.36 | 16.15 |
| | M+F | 83 | 4.36 | 0.81 | 2.87 | 8.04 $\pm$0.292 | +32.9 $\pm$0.51 | 6.00 | 3.91 | 4.72 | 14.63 $\pm$0.563 |

TABLE 11

MEAN NUMBER OF PERMANENT TEETH PRESENT, MISSING, ERUPTED, FILLED BUT DECAYED, DUE FOR EXTRACTION, AND PERCENTAGE OF FILLED TEETH OF DMFT

(Control Group by age and sex)

| Group (Years) | Sex | N | Age | Teeth present | MT | Teeth erupted | (D+F)T | XT | M+X | $\frac{FT}{DMFT}$% |
|---|---|---|---|---|---|---|---|---|---|---|
| 7-9 | M | 5 | 8.5 | 12.60 | 0 | 12.60 | 0 | 0 | 0 | 65.0 |
| | F | 8 | 8.5 | 12.00 | 0.13 | 12.12 | 0 | 0 | 0.13 | 21.8 |
| | M+F | 13 | 8.5 | 12.25 | 0.08 | 12.30 | 0 | 0 | 0.08 | 38.5 |
| 10-12 | M | 16 | 11.4 | 20.80 | 0.50 | 21.30 | 0.25 | 0.13 | 0.63 | 37.6 |
| | F | 9 | 11.4 | 22.22 | 1.00 | 23.20 | 0 | 0 | 1.00 | 50.9 |
| | M+F | 25 | 11.4 | 21.32 | 0.68 | 22.00 | 0.16 | 0.08 | 0.76 | 42.4 |
| 13-15 | M | 17 | 14.3 | 25.08 | 2.35 | 27.42 | 1.41 | 0.41 | 2.76 | 50.6 |
| | F | 17 | 13.11 | 24.90 | 3.06 | 28.00 | 0.82 | 0 | 3.06 | 46.9 |
| | M+F | 34 | 13.8 | 25.05 | 2.70 | 27.74 | 1.12 | 0.21 | 2.91 | 48.8 |
| 16-19 | M | 7 | 16.11 | 24.55 | 3.86 | 28.25 | 0.43 | 0 | 3.85 | 62.1 |
| | F | 4 | 17.2 | 21.25 | 6.75 | 28.00 | 0.75 | 0 | 6.75 | 18.6 |
| | M+F | 11 | 17.0 | 23.35 | 4.91 | 28.25 | 0.55 | 0 | 4.91 | 46.3 |
| 7-19 | M | 45 | 13.0 | 22.21 | 1.67 | 23.78 | 0.69 | 0.20 | 1.87 | 49.4 |
| | F | 38 | 12.6 | 21.18 | 2.34 | 23.53 | 0.45 | 0 | 2.34 | 39.6 |
| | M+F | 83 | 12.9 | 21.69 | 1.97 ±0.172 | 23.67 | 0.58 | 0.11 | 2.08 | 44.9 |

TABLE 12

MEAN NUMBER OF DECAYED, MISSING, AND FILLED PERMANENT TEETH AND TOOTH SURFACES

(Control Group by age and sex)

| Group (Years) | Sex | N | DT | MT | FT | DMFT | DMFT / 100 T. % | DS | MS | FS | DMFS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7-9 | M | 5 | 1.60 | 0 | 2.80 | 4.40 | 35.2 | 2.00 | 0 | 5.20 | 7.20 |
| | F | 8 | 2.88 | 0.13 | 1.00 | 4.00 | 33.5 | 4.75 | 0.63 | 1.87 | 7.25 |
| | M+F | 13 | 2.38 | 0.08 | 1.69 | 4.15 | 34.1 | 3.70 | 0.38 | 3.16 | 7.24 |
| 10-12 | M | 16 | 4.19 | 0.50 | 2.50 | 7.12 | 33.4 | 5.62 | 2.50 | 5.62 | 13.75 |
| | F | 9 | 4.00 | 1.00 | 4.55 | 9.55 | 40.1 | 4.23 | 5.00 | 8.22 | 17.45 |
| | M+F | 25 | 4.12 | 0.68 | 3.24 | 8.00 | 35.8 | 5.12 | 3.40 | 6.55 | 15.08 |
| 13-15 | M | 17 | 5.35 | 2.35 | 8.12 | 15.80 | 57.4 | 8.18 | 11.77 | 15.18 | 35.15 |
| | F | 17 | 4.76 | 3.06 | 6.82 | 15.22 | 54.4 | 7.17 | 15.30 | 11.77 | 34.22 |
| | M+F | 34 | 5.06 | 2.70 | 7.48 | 15.50 | 55.9 | 7.68 | 13.52 | 13.49 | 34.65 |
| 16-19 | M | 7 | 2.58 | 3.86 | 11.70 | 18.15 | 63.6 | 3.57 | 19.30 | 21.58 | 44.49 |
| | F | 4 | 7.75 | 6.25 | 3.25 | 17.75 | 63.4 | 12.50 | 33.79 | 5.00 | 51.30 |
| | M+F | 11 | 4.45 | 4.73 | 8.64 | 18.00 | 63.6 | 6.82 | 24.55 | 15.55 | 47.00 |
| 7-19 | M | 45 | 4.07 | 1.67 | 6.09 | 11.80 | 47.3 | 5.86 | 8.34 | 11.67 | 25.85 |
| | F | 38 | 4.50 | 2.29 | 4.69 | 11.80 | 47.5 | 6.53 | 11.71 | 8.14 | 26.40 |
| | M+F | 43 | 4.26 | 1.95 | 5.45 | 11.80 ±0.544 | 47.4 ±1.27 | 6.16 | 9.88 | 10.03 | 26.10 ±1.482 |

4. BACTERIOLOGY :

There was no difference in the mean Lactobacillus count between the two groups. The mean Lactobacillus count for the Experimental Group was 4,660 per c.c. and for the Control Group 5,380 per c.c. Lactobacilli were present at a concentration of greater than 100 per c.c. in sixty-seven per cent of the samples examined in the Experimental Group, and fifty-five per cent of the samples in the Control Group.

Monilia was present at a concentration greater than 100 per c.c. in sixty-seven per cent of the samples in the Experimental Group, compared to only thirty-five per cent in the Control Group.

The mean Monilia count was 3,620 per c.c. for the Experimental Group compared to 375 per c.c. for the Control Group. Monilia were present both in greater concentration and in a greater proportion of children in the Experimental Group.

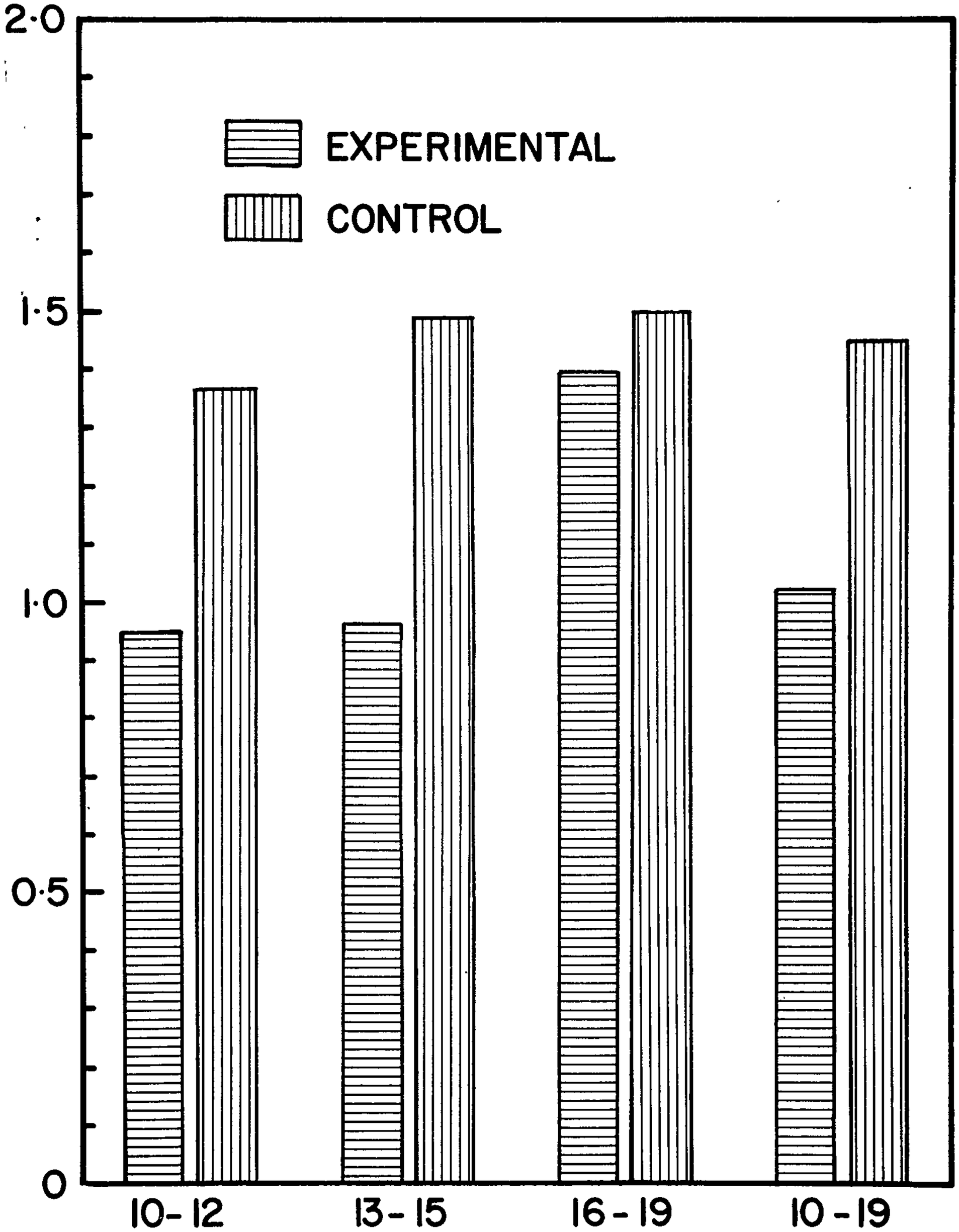
The overall streptococcal population as determined by the method outlinedwas greater in the Control Group than that of the Experimental Group. The mean time for 1/100 c.c. of the saliva sample from the Control Group (when cultured as described) to reach pH 6.7 from pH 7.0 was $4.55 \pm 0.13$ hours compared to $6.00 \pm 0.301$ hours for the Experimental Group. This difference in the mean time between the two groups was clearly significant statistically ($p < 0.001$).

## DISCUSSION

Throughout this study every effort was made to attain comparibility. The number of children in both groups was small. Ninety children who had been taking penicillin and 113 children who did not receive any antibiotics were examined. All dental examinations were carried out by the one examiner. Finally 83 children in each group were matched as well as possible according to age, sex, and the number of teeth present. The mean age of the children for the Experimental Group was 13 years and for the Control Group it was 12 years 9 months. Socio-economic factors were in general comparable in both groups. The water in Sydney was not fluoridated at the time of the study.

The abnormal clinical conditions of the periodontal tissues in both groups was limited mainly to gingival inflammation. The Control Group had a higher Russell Periodontal Index Score (1.44 $\pm$ 0.007) than the Experimental Group (1.02 $\pm$ 0.019). Figure 3, which was prepared from the data of Table 6, shows these differences in the periodontal indices. According to Russell (1960 [59]) most persons with clinically diagnosed gingivitis had scores ranging from 0.1 to 1.0 and those with frankly established destructive disease from 1.5 to 5.0

Figure 3. Russell Periodontal Index for Experimental and Control Groups by Age.



All reported studies on the effect of antibiotics on periodontal tissues showed that antibiotics appeared to be beneficial both in the prevention and treatment of periodontal syndrome (Strock 1944 [72]; Gupta, Auskaps, and Shaw 1957 [25]; Shaw, Griffiths, and Auskaps 1961 [63]; Littleton and White 1964 [46]; Shaw 1965 [61]; Shaw and Dick 1966 [62]). Results from this study confirm findings of these investigators.

The Oral Hygiene Index was similar for both groups (Table 6 and Figure 4). The Calculus Index scores for the Experimental Group were higher than those for the Control Group as shown in Figure 5. ($0.21 \pm 0.005$ and $0.08 \pm 0.003$ respectively, $p < 0.001$). This shows that penicillin has no inhibitory effect on the formation of calculus. This is in agreement with the findings of König and Mühlemann (1959 [42]), Fitzgerald, Jordan, Scott, and McCann (1960 [14]), and Dossenbach and Mühlemann (1961 [12]). In fact, the calculus deposition was greater in the Experimental Group than in the Control Group. However, Gressly (1963 [24]), Theilade and Fitzgerald (1963 [73]), and Richardson (1965 [55]) observed that antibiotics suppressed the deposition of calculus.

In the animal studies by McClure and Hewitt (1946 [52]), Webman, Hill, and Kniesner (1949 [75]), Stephan et al (1952 [70]), Stephan, Harris, and Fitzgerald (1952 [71]), Rosen et al (1952 [57]), Shaw and Sweeney (1957 [65]), Keyes (1960 [38]), Shaw, Griffiths, and Terborgh (1962 [64]),

Figure 4. Oral Hygiene Index for Experimental and Control Groups by Age.

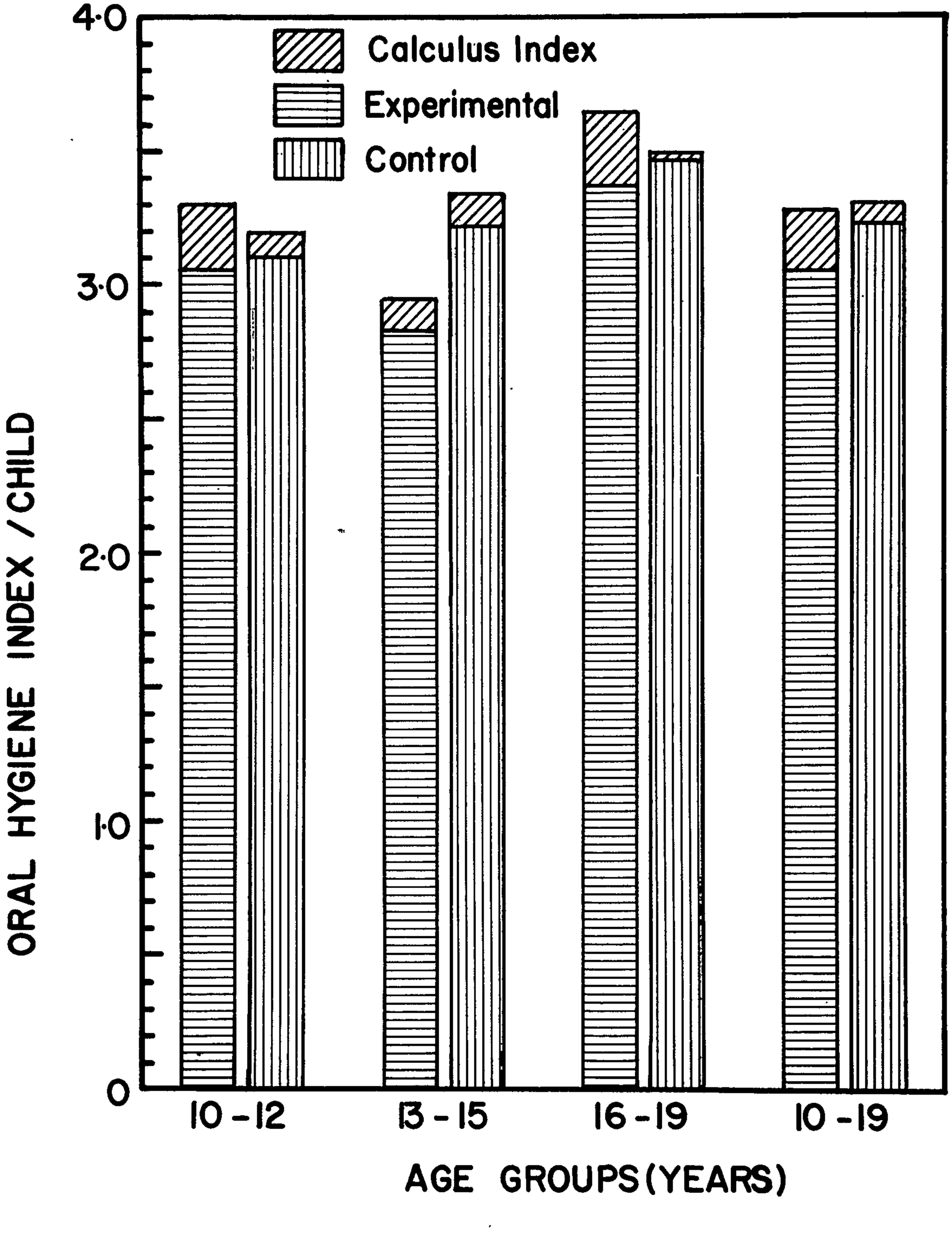
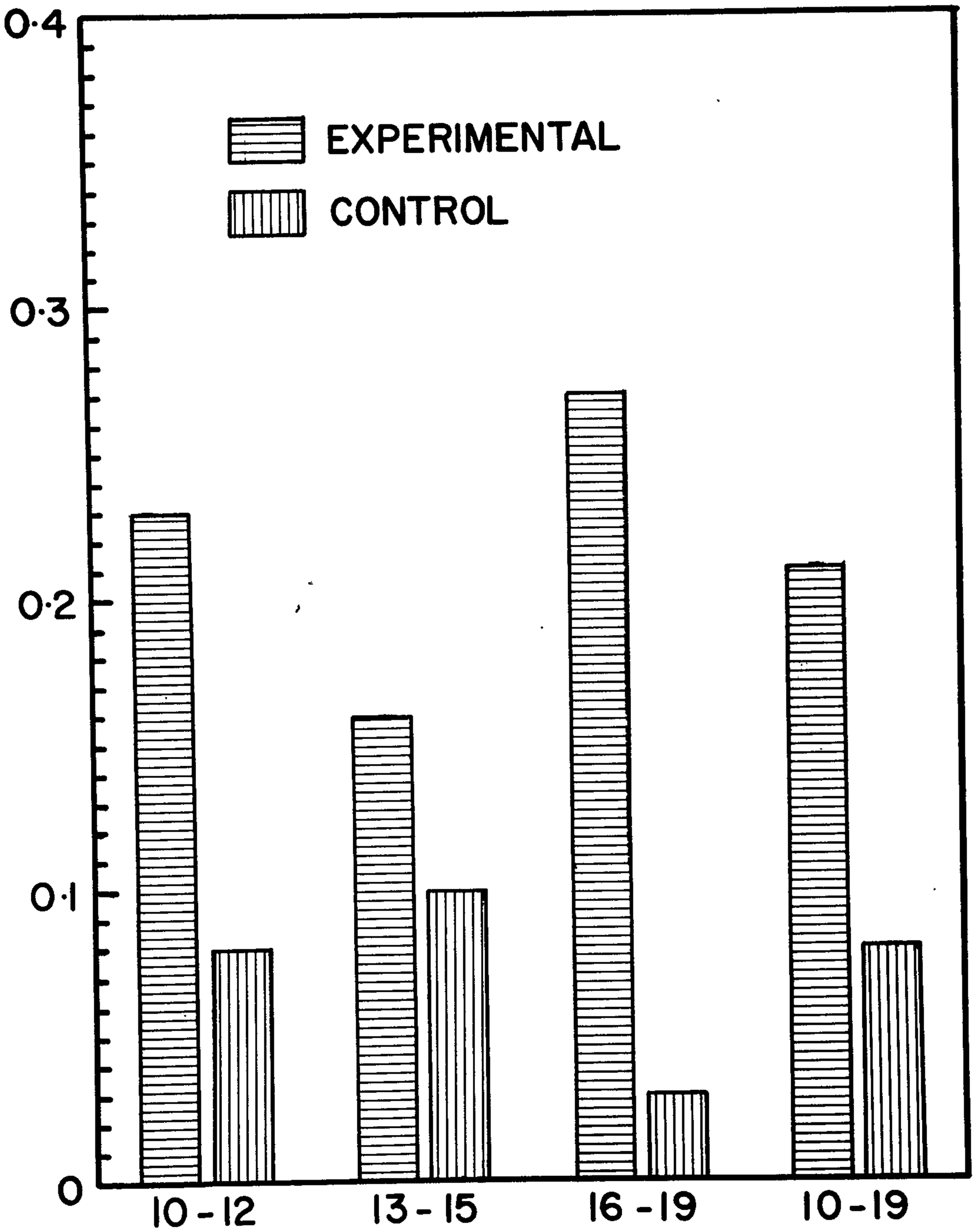


Figure 5. Calculus Index for Experimental and Control Groups by Age.



Shaw (1964 [60]), Falla and Shaw (1965 [13]), and by König, Guggenheim, and Mühlemann (1965 [41]), it was found that penicillin and other antibiotics were effective in reducing dental caries when incorporated into the diet of animals.

The effect of topical application of penicillin and other antibiotics on human dental caries was not consistent. Zander (1950 [78]) and Ludwick, Fosdick, and Schantz (1951 [74]) observed that penicillin had a beneficial effect on human dental caries. Walsh and Smart (1951 [74]) reported that both the penicillin and the control dentifrices in their study reduced dental caries. There was a slight reduction in DMF surfaces in the study by Hill, Sims, and Newman (1953 [34]), and Shiere (1957 [66]) found a twenty-six per cent reduction in new decayed and filled surfaces. According to the results of Hill and Kniesner (1949 [32]) and Lunin and Mandel (1955 [50]) penicillin had no effect on dental caries.

The studies with human subjects receiving long-term penicillin therapy by Littleton and White (1964 [46]), and Handelman, Mills, and Hawes (1966 [31]) showed that penicillin was effective in reducing dental caries.

Results of the present study are summarised in Table 13. For the deciduous dentition the Control Group had an average of 3.00 $\pm$ 0.045 teeth missing while the Experimental Group had an

TABLE 13

DENTAL FINDINGS FOR THE EXPERIMENTAL AND CONTROL GROUPS

| Index | N | Experimental Group (± S.E.) | Control Group (± S.E.) | Statistical Significance of the Difference | |
|---|---|---|---|---|---|
| mt | 13 | 1.23 ± 0.007 | 3.00 ± 0.045 | p < 0.001 | |
| mt + et | 13 | 1.31 ± 0.024 | 3.08 ± 0.073 | p < 0.001 | |
| dft | 13 | 2.84 ± 0.035 | 4.00 ± 0.046 | p < 0.001 | |
| dmft | 13 | 4.07 ± 0.028 | 7.00 ± 0.091 | p < 0.010 | |
| ft/dmft % | 13 | 18.13 ± 6.621 | 29.49 ± 0.444 | p < 0.200 | NS |
| dfs | 13 | 4.69 ± 0.070 | 6.62 ± 0.042 | p < 0.050 | |
| MT | 83 | 0.81 ± 0.042 | 1.97 ± 0.172 | p < 0.001 | |
| (D+F)T | 83 | 0.42 ± 0.041 | 0.58 ± 0.052 | p < 0.025 | |
| M + X | 83 | 0.95 ± 0.014 | 2.08 ± 0.175 | p < 0.001 | |
| DMFT | 83 | 8.04 ± 0.292 | 11.80 ± 0.544 | p < 0.001 | |
| FT/DMFT % | 83 | 32.87 ± 0.894 | 44.89 ± 0.423 | p < 0.001 | |
| DMFT/100 teeth | 83 | 32.9 ± 0.51 | 47.4 ± 1.27 | p < 0.001 | |
| DMFS | 83 | 14.63 ± 0.563 | 26.10 ± 1.482 | p < 0.001 | |
| R.I. | 70 | 1.02 ± 0.019 | 1.44 ± 0.007 | p < 0.001 | |
| C.I. | 70 | 0.21 ± 0.005 | 0.08 ± 0.003 | p < 0.001 | |
| O.H.I. | 70 | 3.27 ± 0.022 | 3.31 ± 0.014 | p < 0.100 | NS |

average of 1.23 ± 0.007 teeth missing. Children in the Control Group would eventually lose 3.08 ± 0.073 teeth (sum of the average number of teeth missing and teeth due for extraction because of extensive caries involving the pulp) compared with 1.31 ± 0.024 teeth for children in the Experimental Group. The average number of decayed and filled teeth (dft) per child for the Control and Experimental Groups was 4.00 ± 0.046 and 2.84 ± 0.035 respectively. The average number of decayed, missing, and filled teeth (dmft) per child for the two groups was 7.00 ± 0.091 (Control Group) and 4.07 ± 0.028 (Experimental Group) respectively, while the average number of decayed and filled surfaces (dfs) per child was 6.62 ± 0.042 (Control Group) and 4.69 ± 0.070 respectively. The Control Group had higher scores in the dft, dmft, and dfs counts. The amount of dental care received for the deciduous teeth was possibly greater for the Control Group as shown by the percentage of filled teeth over the decayed, missing, and filled teeth (ft/dmft %) but this was not significant statistically.

The average number of permanent teeth missing because of caries was 1.97 ± 0.172 teeth for the Control Group and 0.81 ± 0.042 teeth for the Experimental Group. This may be due to the fact that children in the Control Group received more dental care as they were attending the United Dental Hospital regularly. The percentage of filled teeth over the decayed, missing, and filled teeth (FT/DMFT %) was also higher for the Control Group. Yet the unmet needs for

restorative dental care were similar in both groups, as there was no difference in the average number of decayed teeth or decayed surfaces between the two groups (Tables 10 and 12). Children in the Control Group would eventually lose 2.08 $\pm$ 0.175 teeth due to caries (sum of the average number of teeth missing and teeth due for extraction because of extensive caries involving the pulp) compared with 0.95 $\pm$ 0.014 teeth for children in the Experimental Group (Figure 6). The average number of filled teeth with recurrent caries, i.e. (D + F)T, was similar for both groups. The average number of decayed, missing, and filled teeth (DMFT) per child for the Control and Experimental Groups was 11.80 $\pm$ 0.544 and 8.04 $\pm$ 0.292 respectively (Figure 7); the mean number of decayed, missing, and filled surfaces per child (DMFS) for the Control and Experimental Groups was 26.10 $\pm$ 1.482 and 14.63 $\pm$ 0.563 respectively (Figure 8). Both the DMFT and DMFS indices showed significant differences in the dental caries experience of the two groups. The percentage of teeth at risk, expressed as DMFT per 100 teeth erupted was 47.4 $\pm$ 1.27% and 32.9 $\pm$ 0.51%, respectively for the Control and Experimental Groups (Figure 9).

In this study the mean age of the 83 children in the Experimental Group was 13 years. The average duration of penicillin therapy was five years. There were 65 children who started penicillin therapy before the age of 10 years (Table 5). This represented

Figure 6. Number of missing permanent teeth(M) plus teeth due for extraction(X) because of caries for Experimental and Control Groups by Age.

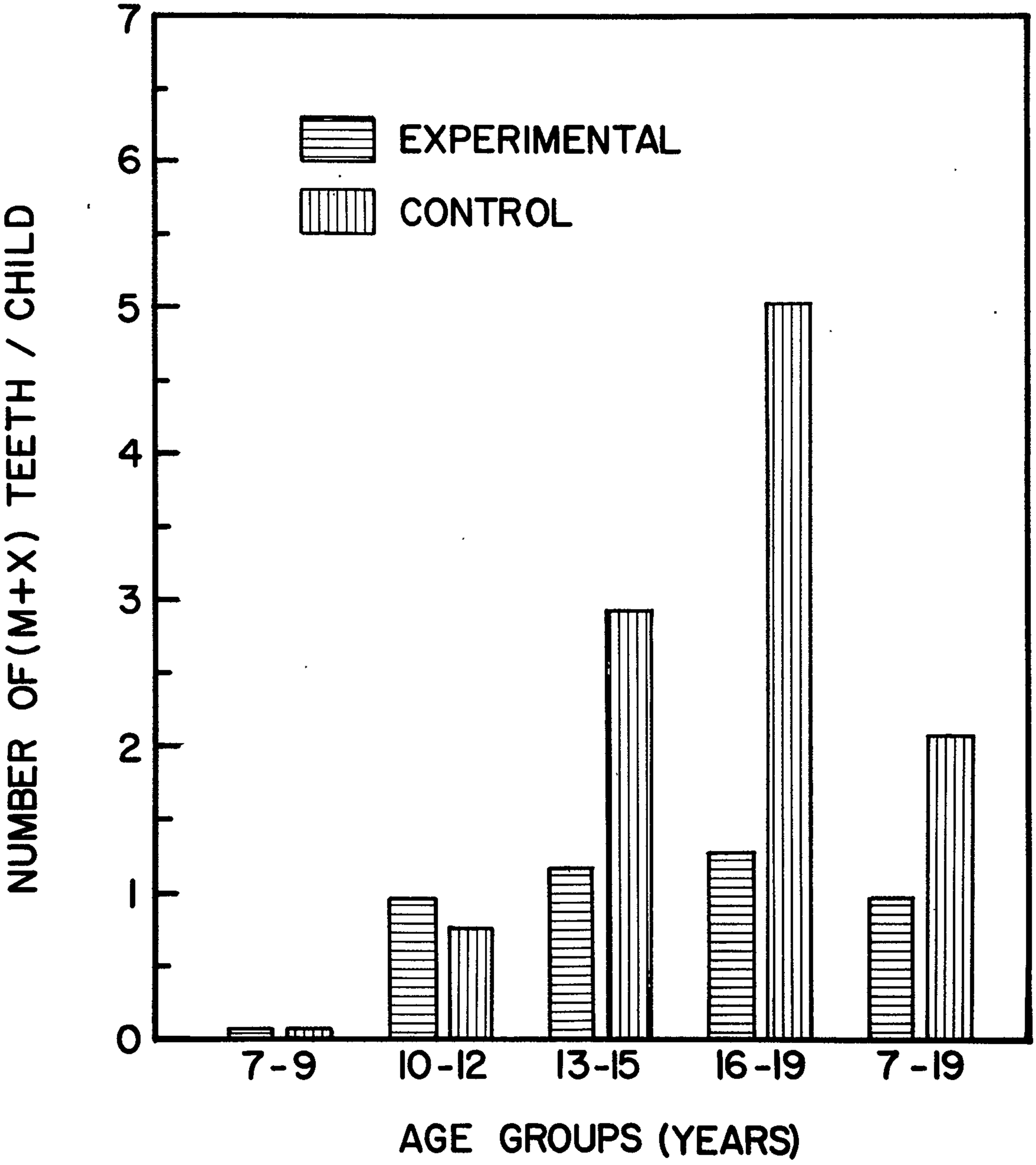


Figure 7. Number of DMF teeth for Experimental and Control Groups by Age.

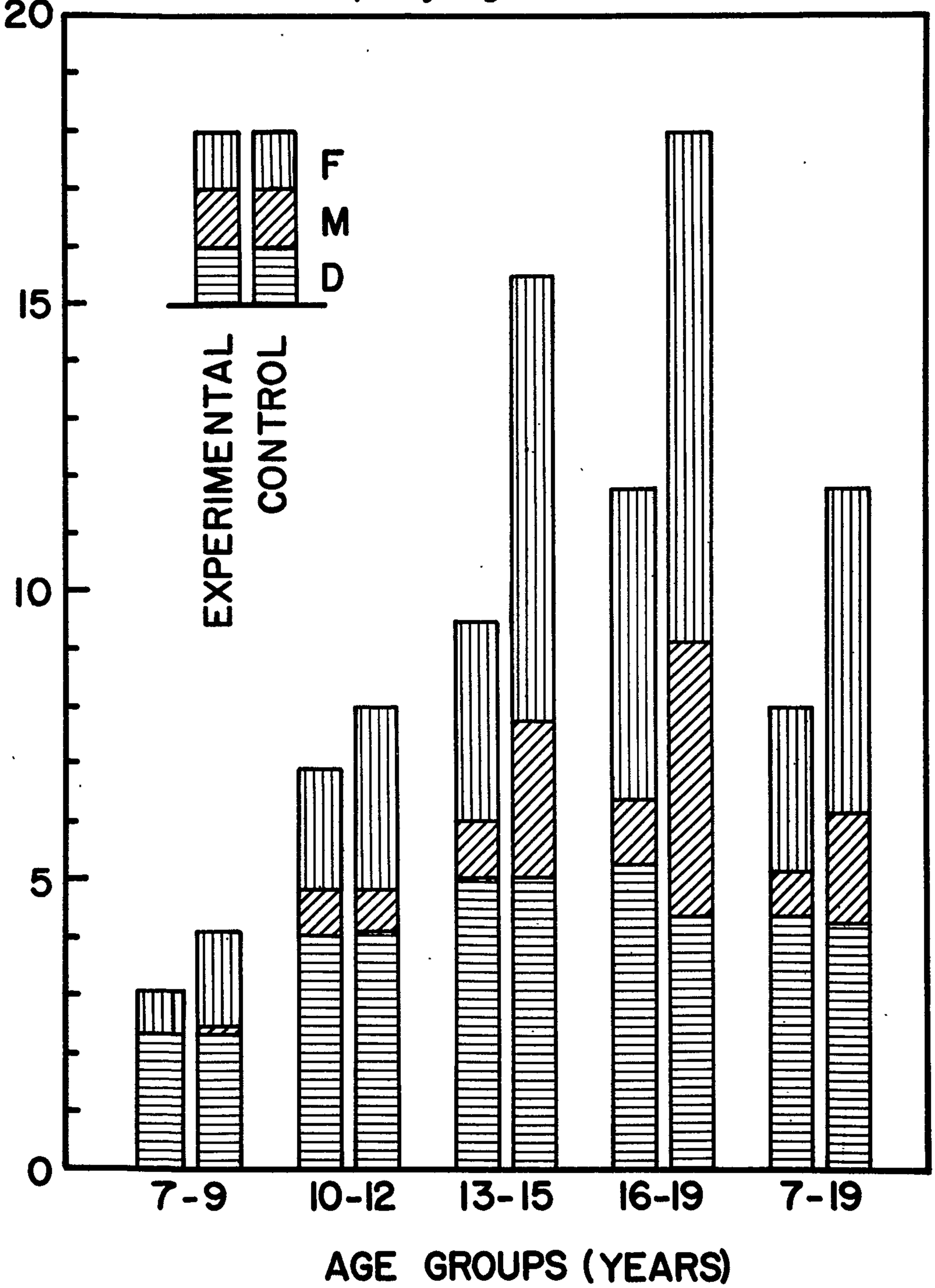


Figure 8. Number of DMF surfaces for Experimental and Control Groups by Age.

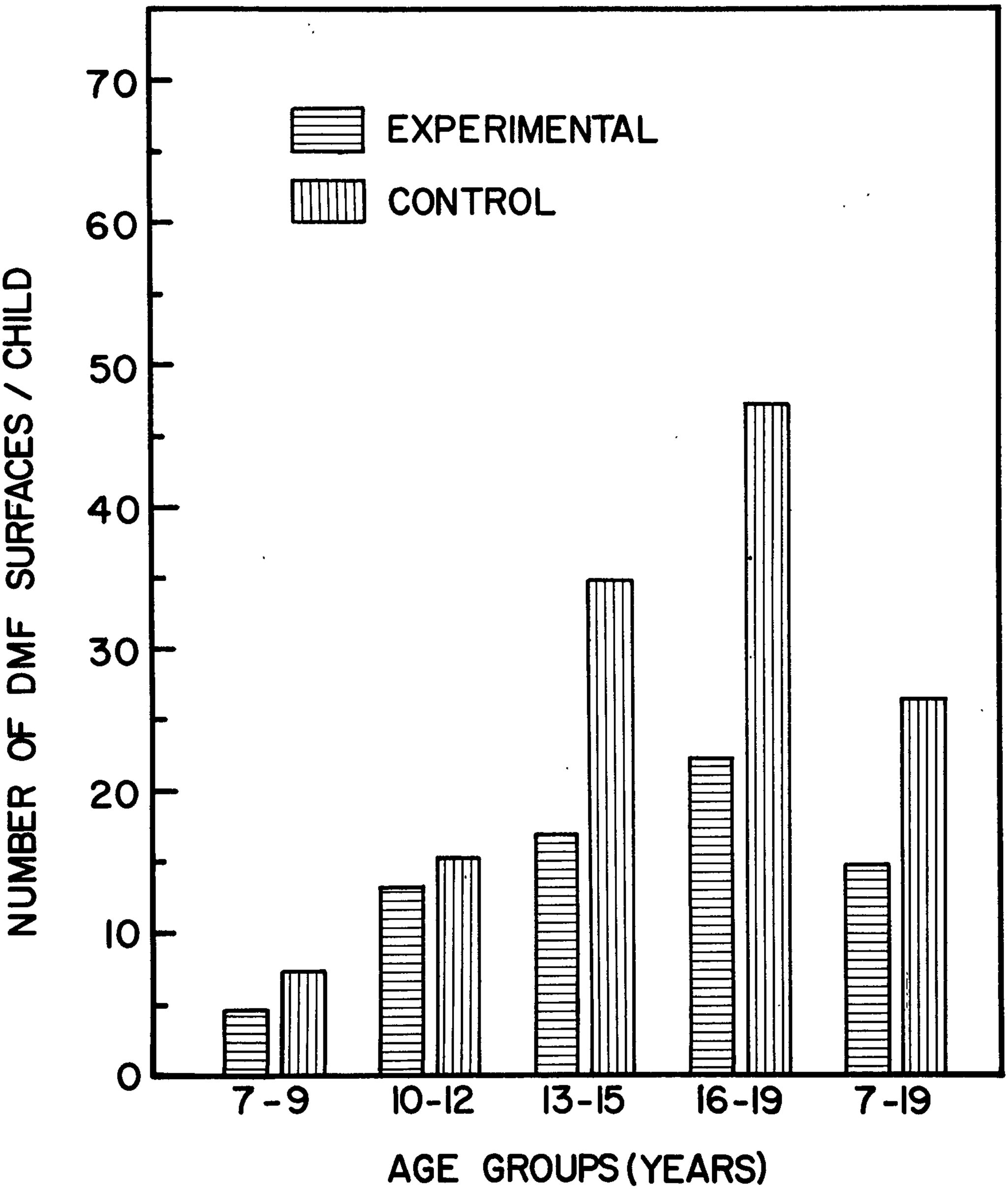
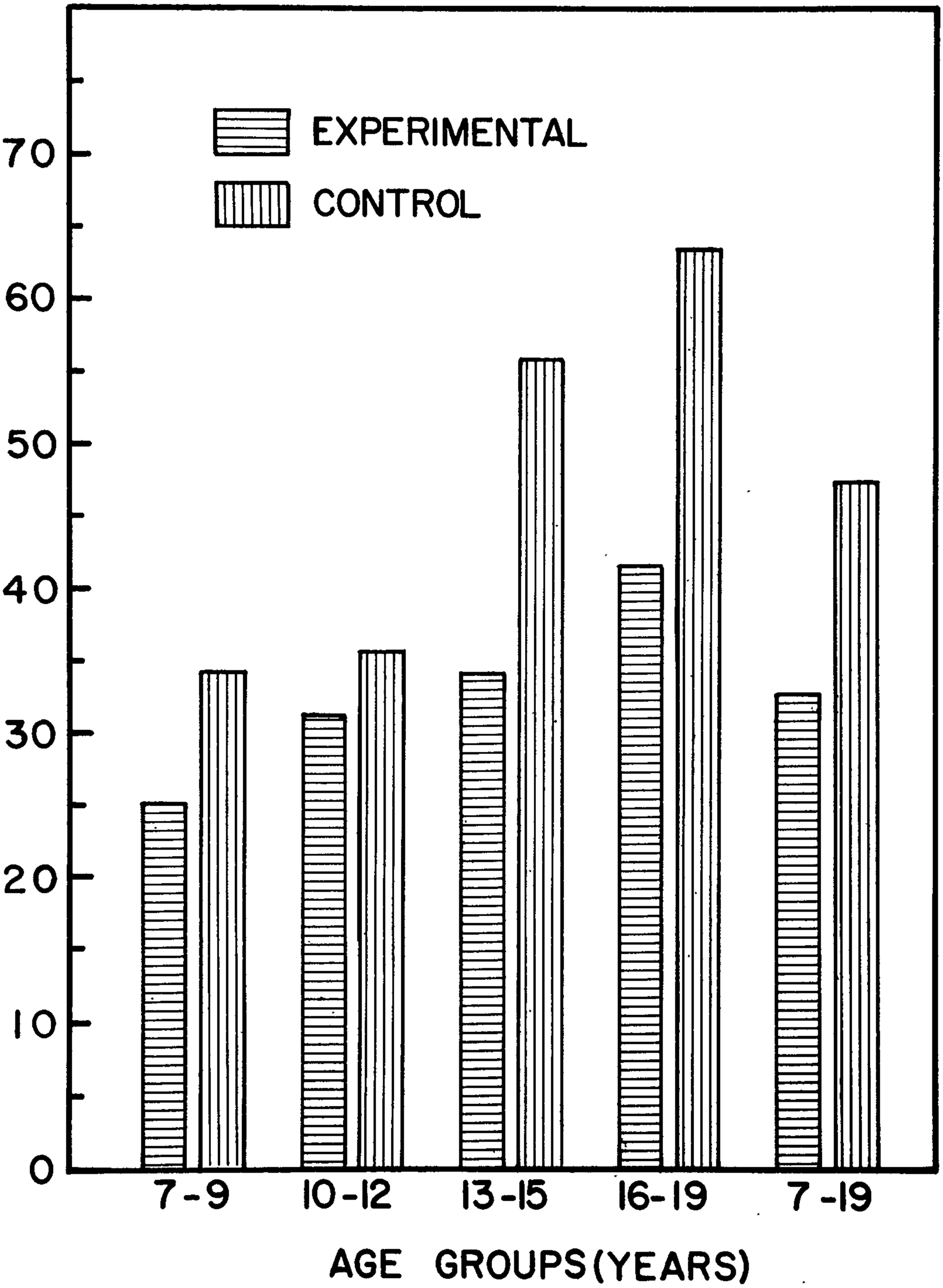


Figure 9. Per cent of teeth at risk affected (DMFT/100 teeth) for Experimental and Control Groups by Age.



80% of the total number of children. Research by Gates, R.E., (1964 [17]) showed that the upper and lower permanent canines, first and second premolars, and the first and second molars are present in the oral cavity after 9 years of age for the Australian children. Thus most of the permanent teeth were exposed fully to the influence of penicillin. In spite of the fact that children in the Control Group had received more dental care they would lose more teeth from caries eventually, they had higher scores for the dft, DMFT, and DMFS counts, and they had more teeth at risk decayed than children in the Experimental Group. Thus it appears that penicillin has an inhibitory effect on dental caries progress or is effective in the reduction of dental caries initiation. Results from this study confirm the findings of Littleton and White (1964 [46]) and Handelman, Mills, and Hawes (1966 [31]).

For the bacteriological study streptococci, lactobacilli, and monilia were chosen to be investigated. Streptococcus was chosen because it constitutes a major portion in the total oral flora (Gibbons et al 1963 [20], Gibbons et al 1964 [19], Handelman and Mills 1965 [30], McCarthy, Snyder, and Parker 1965 [51], and Gordon and Gibbons 1966 [22]).

Lactobacillus and monilia were chosen because of the ease of their identification and previous investigations of their relationship to penicillin therapy. A lack of facilities prevented a more

detailed study of the oral flora.

Before continuing with the discussion of the results obtained in this investigation a brief discussion on acid production by the streptococci and lactobacilli is appropriate. It has been found that lactic acid is produced by microorganisms as an end-product of anaerobic carbohydrate mechanism. The carbohydrate is utilized through the Meyerhof-Embden pathway for lactic fermentation. "Many lactobacilli and streptococci rely almost entirely upon this pathway" for the provision of their energy requirement (Burnett and Scherp 1962 [8]). This pathway is operated under anaerobic conditions. However, even in the presence of oxygen the streptococci and lactobacilli are able to make sole use of it. The homofermentative streptococci can only produce lactic acid as an end-product of their carbohydrate metabolism. According to Bissett and Davis (1960 [5]) it appears that all oral streptococci are homofermentative.

Microbial activity in similar samples of stimulated saliva from the two different groups of children was studied. The capacity of the microorganisms in any one sample to produce lactic acid must be related to the number of streptococci present as these are the chief acid producers. The streptococci have also been shown to produce the greatest proportion of acid from salivary organisms (Burnett and Scherp 1962 [8]). The role of a number of other

organisms as acid producers, notably lactobacilli, yeasts, and staphylococci, was also considered. However, there are approximately 1,000 times more streptococci present in the saliva than lactobacilli.

To study the acid producing characteristics of the bacteria in the stimulated saliva samples, a dilution equal to 1/100 c.c. of stimulated saliva was treated as outlined in the Method section. The time for each sample to produce a certain amount of acid in the test media was noted. It is considered that the briefer the time the greater would be the rate of acid production, and consequently the greater the number of streptococci present in the sample. Of further interest is the fact that the terminal pH of the various salivary samples was reached by an uninterrupted pH-time relationship, with a range from pH 4.5 to pH 4.2. These terminal pH values are comparable with the limiting pH values listed in Bergey's Manual[6] for a variety of streptococcus species.

From the review of the literature it was found that the effect of penicillin on lactobacilli, streptococci, yeast or on the bacterial population as a whole in the oral cavity was varied and contradictory for different studies. Animal study by McClure and Hewitt (1964 [52]) showed that penicillin reduced lactobacilli. Stephan, Harris, and Fitzgerald (1952 [71]) and Rosen et al (1956 [57]) found that penicillin suppressed both lactobacilli and streptococci in rats.

Topical application of penicillin was effective in reducing lactobacilli in the studies with human subjects by Hill and Kniesner (1949 [32]), White, Kniesner, and Hill (1949 [76]), and Slanetz and Reynolds (1952 [67]). Results from studies by Fitzgerald, Zander, and Jordan (1950 [16]), and Hills, Sims, and Newman (1953 [34]), showed that topical penicillin had no effect on the lactobacilli.

Slanetz and Reynolds (1952 [67]) and Williams (1963 [77]) observed a reduction in streptococci and an increase in yeast with topical penicillin. However, Hill, Rasch, and Wollpert (1953 [33]) reported an increase of Streptococcus viridans. Topical penicillin had no effect on monilia in a study by Brudevold and Hawes (1952 [7]). There was no change in the oral flora with topical penicillin according to Lunin and Mandel (1955 [50]).

Long (1947 [47]), Smith, Skinner, and Erickson (1952 [68]), Carter, White, and Bass (1953 [9]), and Handelman and Hawes (1965 [28]) found that systemic administration of penicillin to human subjects caused a reduction of streptococci in the oral cavity. There was also an increase in yeast in the study by Carter, White, and Bass (1953 [9]). Systemic penicillin had no effect on Lactobacillus acidophilus according to the results of Ludwick, Bass, and Jay (1953 [48]).

There was no shift in the oral bacterial flora in the studies by Bender, Pressman, and Tashman (1953 [4]) and Handelman, Hawes, and Yap (1961 [29]).

Results from the present study showed that penicillin suppressed streptococci but had no effect on the lactobacilli. There was an increase in the yeast population with the systemic administration of penicillin. These confirm the findings by Long (1947 [47]), Fitzgerald, Zander, and Jordan (1950 [16]), Slanetz and Reynolds (1952 [67]), Smith, Skinner, and Erickson (1952 [68]), Carter, White, and Bass (1953 [9]), Hill, Sims, and Newman (1953 [34]), Ludwick, Bass, and Jay (1953 [48]), Williams (1963 [77]), and Handelman and Hawes (1965 [28]).

## SUMMARY

1. Controversy in the literature regarding the effect of antibiotics, particularly penicillin, on dental caries, calculus formation, periodontal disease, and on oral flora was briefly reviewed.

2. The present study was set up to test the findings of some of the previous investigators.

3. Ninety children who had a history of rheumatic fever and had been taking penicillin for the prevention of subacute bacterial endocarditis (the Experimental Group) and 113 children who did not receive any antibiotics (the Control Group) were examined. The groups were out-patients at a Childrens' Hospital and a Dental Hospital.

4. After being matched carefully according to age, sex, and the number of teeth present, 83 children were selected for each group. Socio-economic factors were in general comparable in both groups.

5. The ages of the children examined ranged from 7 to 19 years. The mean age for the Experimental Group was 13 years (male 13 years 1 month and female 12 years 11 months), and for the Control Group 12 years 9 months (male 13 years and female 12 years 6 months).

6. Children in the Experimental Group had been receiving twice-daily 200,000 units of oral Penicillin V (Potassium phenoxmethyl penicillin, LPV tablets 125 mg., Commonwealth Serum Laboratory) for a minimum period of 12 months. Duration of therapy varied from one year to 12 years. The average duration was five years.

7. Dental caries experience was expressed using the dft, dmft, dfs, DMFT, and DMFS indices.

8. The Periodontal Index of Russell was used to record the clinical condition of the periodontal tissues.

9. The Oral Hygiene Index of Greene and Vermillion was used to score the presence and extent of oral debris and calculus deposits.

10. Paraffin-stimulated saliva samples were taken from 18 children randomly selected in the Experimental Group and from 20 children approximately matched by age and sex in the Control Group for bacteriological study.

11. Periodontal disease in both groups was limited to gingivitis. Long-term penicillin appeared to be effective in suppressing progress of periodontal disease as measured by the Russell Index.

12. Penicillin appeared to have no inhibitory effect on the formation of calculus and there was more calculus in the Experimental Group.

13. The unmet needs for restorative dental care were similar in both groups but children in the Control Group had received more dental care.

14. The number of deciduous and permanent teeth erupted in both groups was similar.

15. Long-term systemic penicillin appeared to be effective in the reduction of dental caries in the deciduous and permanent dentitions.

16. Penicillin suppressed oral streptococci but it had no effect on the oral lactobacilli.

17. There was an increase in the monilia population associated with long-term systemic administration of penicillin.

# CONCLUSION

There is evidence suggesting that bacteria play an important role in the development and progress of periodontal disease and dental caries. Any direct or indirect proof of the bacterial association with periodontal disease or dental caries should contribute to the understanding of these complicated processes.

Individuals taking long-term penicillin for the prevention of subacute bacterial endocarditis offer good opportunity to study the effect of penicillin on dental caries, calculus formation, periodontal disease, and on the oral flora.

In the present study it appeared that penicillin was effective in suppressing the progress of periodontal disease and in the reduction of dental caries, but there was no inhibitory effect on calculus formation. Penicillin suppressed streptococci, which constitute a major portion of the oral flora and they are the chief acid producers, but no effect on lactobacilli was shown. There was an increase in the monilia population associated with long-term systemic administration of penicillin.

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