BIOENERGETICS IN CLINICAL MEDICINE.
XIII Progress in the United States and in Japan on the Study of the Use of Coenzyme Q in Periodontal Disease

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臨床医学の生体力学

XIII 米国および日本における歯周疾患治療に際するコエンザイム Q の使用成績

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米国においては青年期の 60% が，又中年期の 80% もの大部分の人々が歯周疾患に罹患している。多数日本においても同じことがえられるであろう。現在歯周疾患の治療効果をより一層たかめることが要求されているが，しかし口腔内療法はあまり効果があがっていないと思われる。

近年，歯周組織の健康保持に全身の栄養状態が考慮されるようになってきた。又，歯牙，歯根膜，歯槽骨等におけるビタミン類の生化学的研究も行われてきた。コエンザイム Q10（以下 CoQ10 と略）は歯肉のミトコンドリアに存在し，歯肉におけるエネルギー獲得には必要欠くべからざるものである。歯周疾患歯肉では CoQ10 が欠乏していることが（p<0.001）たびたび報告されている。

現在，臨床で使用されている CoQ は CoQ10，CoQ9，ヘキサハイドロ CoQ10 の三種類であり，それらを用いた歯周病患者への投与が歯科医，歯周病専門医によって行われている。その結果，このビタミン様物質に治療効果があることが証明された。又，二重盲検法によるこれら三種の CoQ の薬効がすでに 6 例報告されている。CoQ はヒト組織においては CoQ10 の型で存在している。そこで歯周病患者を 8 人の CoQ10 投与群と 10 人の placebo 投与群とに分けて二重盲検法による実験が行われた。CoQ10 投与群の人中 8 人に，又 placebo 投与群では 10 人中 3 人に歯周疾患症状の改善が認められ，統計的に CoQ10 の治療効果が確認された（p<0.01）。

一方，29 人の歯周病患者について行われた実験では歯肉における CoQ10 deficiency が 100%，又血球における deficiency が 86% の頻度で出現した。血液の CoQ10 deficiency は栄養のアンバランスを意味する。特に口腔清掃状態が悪い場合には歯肉における CoQ10 の欠乏が歯肉炎，歯周炎の増悪に関与すると考えられる。又，その逆に歯周炎が歯肉の CoQ10 deficiency を惹起しているとも考えられる。

CoQ は生体のエネルギー獲得を促進するから，CoQ 投与により効果的な治療が期待できる。又，歯周疾患の基本的な治療と併行して CoQ を投与すれば治癒を促進するであろうし，予防にも使用しうるとと思われる。
Summary

Statistics show that about 60% of young adults and 80% of middle-aged people in the United States have periodontal disease, and presumably about the same incidence occurs in Japan. More effective treatment of this affliction is needed. Oral physiotherapy can be ineffective.

There is increasing awareness that good nutrition is related to good periodontal health, and the many known vitamins influence the biochemistry of teeth, periodontium, and related bone. Coenzyme Q₁₀ (CoQ₁₀) naturally exists in the mitochondria of gingival tissue and has indispensable functions in the bioenergetics of the gingiva. A significant deficiency (P<0.001) of CoQ₁₀ in diseased gingival tissues has been repeatedly found.

The clinical administration of three forms of CoQ, CoQ₁₀, CoQ₇, and hexahydro CoQ₄, has been conducted by general dentists and periodontists with a common conclusion that the administration of this vitamin-like substance was therapeutically beneficial. Six double-blind administrations involving all three forms of CoQ have also been conducted with significant results. The double-blind administration of CoQ₁₀, the form in human tissue, was significant (P<0.01). Before decoding, all eight patients receiving CoQ₁₀ and 7/10 patients receiving placebo were correctly assigned.

A study of 29 periodontal patients showed that 100% had a gingival deficiency, and 86% also had a leucocytic deficiency of CoQ₁₀. The blood deficiency appears to result from nutritional imbalance. A preexisting deficiency of CoQ₁₀ in the gingiva may predispose this tissue to periodontitis, particularly during neglected oral hygiene. Periodontitis could enhance and also cause a gingival deficiency.

Therapy with CoQ to improve bioenergetics can be effective treatment, and may be used prophylactically or adjunctively for extraordinary healing during routine periodontal therapy.

INTRODUCTION

As recently as 1969, Loe (1) made the following two statements at the International Conference of Periodontal Research in Rochester, New York: (1) "Bacterial plaque on teeth and gingiva is the only direct cause of marginal periodontal disease", and (2) "Provided plaque formation can be controlled, it is possible to maintain a qualitatively and quantitatively normal periodontium throughout old age". Also, "...it seems justified to conclude that general malnutrition and lack of specific dietary compounds...do not cause periodontal disease, but may, in a modest way, influence the progress of already lesions".

Loe added that his statements "...may not be entirely correct." However, in these mid-70's, his statements do seem to represent the general thinking of the dental profession. The important fallacy in this general thinking is the knowledge that some periodontal patients do not satisfactorily respond to the treatment of the periodontists. The role of genetics, systemic conditions, and immunology are now receiving more interest by the periodontal profession. The advent of coenzyme Q and its potential importance for adjunctive use with oral therapy in the treatment of periodontal disease is a departure from the older thinking, and represents and advanced investigation on a modern treatment of periodontal disease which is based on fundamental knowledge of biochemistry and bioenergetics.

The dental health needs of the United States was appraised by Greene (2) in 1972 who cited statistical evidence showing the 60% of the children in the United States have orthodontic conditions which warrant corrective treatment. These conditions are crippling or deforming in 20% of these children. Also, 60% of young adults, 80% of the middle-aged, and 90% of people over 65 years have periodontal disease. In contrast to the common belief the periodontitis is an adult disease, Greene pointed out the the number of adolescents suffering from periodontal disease is "astounding." The statistics have not taken into account the cumulative effects, year after year, of this disease, but is is known that dentures, complete or partial, are the major end results.

Enlightened general dentists and periodontists are increasingly recognizing the importance of nutrition in oral health. McBean and Speckmann (3) reviewed
the involvement of nutrition for the teeth, supporting structures, dental plaque, and the oral environment, all of which influence dental caries and particularly periodontal disease. Nutrition is being recognized today as an important component of preventive dentistry. It is known that deficiencies of vitamin A and some of the B vitamins affect the epithelium. Vitamin C and certain B vitamins affect the mesodermal structures, connective tissue of the periodontal ligament, gingiva, bone and cementum. Vitamin D, calcium, phosphate, and other inorganic essentials influence the composition of alveolar bone, cementum, and dentin according to Peterson, (4), 1972.

It was in 1957 that Crane et al. (5) chemically discovered coenzyme Q₁₀ and revealed its functionality and role in certain mitochondrial enzyme systems. The pioneer and early researches on coenzyme Q or ubiquinone were reviewed at a Ciba Symposium in (6) in 1960.

Coenzyme Q exists as a group of compounds in nature, and some of these compounds have been synthesized. Certain analogs have also been synthesized but which do not exist in nature. Those forms of coenzyme Q which have been relevant to the biomedical and clinical research on periodontal disease are depicted by structures I and II. In I, n=10 for that member of the group which exists in human tissue. In I, n=7 for a member of the group which is commonly found in some microorganisms. In I, n=3 for a member of the group which is extremely rare in nature, but which was made synthetically and is used in enzyme assays to detect and measure human deficiencies of coenzyme Q₁₀. II is hexahydrocoenzyme Q₁₀, which has not been found in nature, but which has been synthesized, and has been used in nutritional animal studies and in clinical studies.

Folkers (7) extensively reviewed in 1969 the vitamin aspects of coenzyme Q. If the 65-year old definition of a vitamin were updated to take into account modern knowledge of vitamins, particularly on biosynthesis, then coenzyme Q could be defined as a vitamin.

The vitamin nature of coenzyme Q₁₀ in human tissue provides the basis for studies on the role of coenzyme Q₁₀ in human nutrition and disease, which could be followed by the clinical use of coenzyme Q₁₀ in treating human disease just as many of the well-known vitamins have established clinical importance.

Certain studies have appeared since 1971 which have revealed a significant role of coenzyme Q₁₀ in periodontal disease. It is the purpose of this review of underscore the importance of those studies which have led to the recommendation on the adjunctive use of coenzyme Q₁₀ with periodontal therapy for effective treatment of periodontal disease. Also, it is anticipated that the time may not be far off when general dentists and periodontists whose primary area of interest is prevention could soon be showing meaningful interest in coenzyme Q.

DETECTION AND MEASUREMENT OF HUMAN DEFICIENCIES OF COENZYME Q₁₀

Human deficiencies of coenzyme Q₁₀ may be detected and measured by a relatively new enzyme assay by Nakamura (8) et al. and Iwamoto et al. (9). The principle of the enzyme assay is based on the finding

I  
\[ \text{n}=10 \text{ (in human tissue)} \]
\[ \text{n}=7 \]
\[ \text{n}=3 \]

II  
\[ \text{hexahydrocoenzyme Q₁₀} \]
that the specific activities of the coenzyme Q\textsubscript{10}-enzyme system from normal or healthy tissues are not significantly increased by exogenous coenzyme Q\textsubscript{10}. In contrast, the specific activities of a coenzyme Q\textsubscript{10}-enzyme system from diseased tissues can show substantial increases in activities on addition of exogenous coenzyme Q\textsubscript{10}. An enzyme system in the presence of exogenous coenzyme Q\textsubscript{10} are apparently correlated with deficiencies of coenzyme Q\textsubscript{10} in the tissue. An enzyme system requiring the coenzyme form of a vitamin when saturated with the coenzyme does not show an increase in activity in the presence of supplementary coenzyme, because more is not needed. In contrast, a deficiency of the coenzyme form at the multitudinous sites of the complex with the apoenzyme will be revealed by an increase in the activity when the enzyme system is supplemented with exogenous coenzyme.

It is known that coenzyme Q is a component of the respiratory assembly of enzyme complexes in the mitochondria, and that there are many thousands of these assemblies in each mitochondrion. Consequently, there are many thousands of enzyme sites for coenzyme Q\textsubscript{10} in the mitochondrion, and it may be presumed that saturation of these sites with coenzyme Q\textsubscript{10} is related to health and the unsaturation is related to ill health.

The principle of the enzyme assay to detect and measure a vitamin deficiency is not new. In 1960, Brin et al. (10) reported on the effects of a thiamine deficiency on the enzyme activity of a transketolase in hemolysates from erythrocytes. Erythrocytes served as the biopsy tissue to detect and measure a deficiency of thiamine. The principle of this differential enzyme assay to measure vitamin deficiencies has also been used in research on human deficiencies of riboflavin by Glazle et al. (11) in 1970 and of vitamin B\textsubscript{6} by Krishnaswamy et al.(12) in 1971 and by Raika et al. (13) in 1964.

Folkers in 1974 defined this principle as follows (14):

The specific activity of a coenzyme-apoenzyme system is differentially assayed in the absence and in the presence of added coenzyme. A significant increase in the specific activity of the enzyme system in the presence of added coenzyme measures a deficiency of the coenzyme at the site or of the vitamin in the tissue. The expression "CAS Principle" has been used to define this assay wherein CAS is derived from Coenzyme Apoenzyme System.

The assay for a deficiency of coenzyme Q\textsubscript{10} is conducted on a leucocyte preparation from 10 ml of blood which is generally drawn from the cubital vein into a vacutainer containing EDTA. A mitochondrial preparation is obtained from the leucocytes, and an assay is first conducted to measure the specific activity of the succinate dehydrogenase-coenzyme Q\textsubscript{10} reductase. The assay is repeated in the presence of added coenzyme Q\textsubscript{10}. A significant increase in the specific activity (S. A.) of this enzyme indicates a deficiency of coenzyme Q\textsubscript{10} not only at this enzyme site, but in the leucocytes. The percentage of deficiency of the enzyme activity is determined by dividing (S. A. with CoQ\textsubscript{10} minus S. A.) by (S.A.with CoQ\textsubscript{10}) x100.

RECOGNITION OF BIOENERGETICS IN CLINICAL MEDICINE

Expressions including bioenergetics or biochemical energetics have been used by many investigators to designate the energy transformations of critical chemical substances in human tissue. The biochemistry of the respiratory chain, which is the basis of bioenergetics, has been depicted by Lehninger in his "Biochemistry" (15) of 1975 by Scheme I. The electron transport of respiration and the coupled reactions of oxidative phosphorylation with concomitant formation of ATP provide the energy for the biochemical processes of tissue healing and repair and other vital body processes. Tissue healing after surgery, such as for destructive periodontal disease, is dependent upon the mechanisms of bioenergetics, which includes the functions of coenzyme Q\textsubscript{10}.

Coenzyme Q\textsubscript{10} is positioned in Scheme I between flavoprotein (EP\textsubscript{1}) and cytochrome b. Coenzyme Q\textsubscript{10} is indispensable to those mitochondrial enzymes in which it functions, including succinoxidase, NADH-oxidase, and \(\alpha\)-glycerophosphate dehydrogenase. These mitochondrial enzymes require coenzyme Q\textsubscript{10} for their activities and these enzymes participate in the bioener-
getics which yield the all-important ATP, which is basic to the healing of tissue in periodontitis after debridement of the teeth and effective oral physiotherapy, or after periodontal surgery, or general surgery.

Coenzyme Q₁₀ is indispensable to the bioenergetics of human tissue. Deficiencies of coenzyme Q₁₀ can exist in human tissue, because of nutritional imbalances and inadequate intake of the B-vitamins and essential minerals which are required for the biosynthesis of coenzyme Q₁₀ in tissue. Deficiencies of coenzyme Q₁₀ can also exist, because of molecular destruction through peroxidation, and also probably as a secondary result of disease processes. Periodontitis is a chronic and inflammatory disease process (Glickman (16), 1972), and there are now five years of data showing that diseased gingival tissue is very frequently associated with a deficiency of coenzyme Q₁₀. The correction of this deficiency would be biochemically expected to improve tissue healing, and presumably aid in the recovery process of the tissues as influenced by oral physiotherapy and/or periodontal therapy.

PINGIVAL DEFICIENCY OF COENZYME Q₁₀ IN PATIENTS WITH PERIODONTAL DISEASE

The specific activities of the succinate dehydrogenase-coenzyme Q₁₀ reductase in gingival tissues from patients with periodontal disease have been compared with the corresponding specific activities of this enzyme from normal human periodontal tissue. The gingival biopsies from patients having diseased periodontal tissue showed a deficiency of coenzyme Q₁₀ in contrast to those of the normal periodontal tissue which showed no deficiency of coenzyme Q₁₀ according to Littarru et al., (1971).

The increases in activity, in this dual enzyme assay, by the CAS Principle, ranged from 38-120% and averaged 81% for the individuals with periodontal disease, and were significant (P<0.001). There were 13 patients whose periodontal involvement ranged from 18 to 62 years, and one patient had diabetes. These patients were considered as typical and representative of the people who visit a periodontist or general dentist for treatment.

During this initial recognition (Littarru et al., (17) (1971) of the CoQ₁₀ deficiency in gingival tissue, a 43-year old male with periodontal disease came under the care of William C. Kuzell, M. D. (Littarru et al., 1971). This patient had gums which were edematous, red, and there was gingival bleeding. The right-lower-central incisor was loose.

Dosage Schedule (Littarru, 1971)-A decision
was made to treat this patient with a dose level of hexahydrocoenzyme Q₁₀, which was regarded as probably excessive but without side effects. The dosage was 1 g, formulated in corn oil, on a daily basis for one month, and then the dosage was reduced to 500 mg/ml corn oil and continued. After the first month, the gums were less red, and after two months on the reduced dosage, the incisor was not as loose, X-ray examination revealed no evidence of special abscess or devitalized teeth. Alveolar recession was present in the lower anterior mandible. Bilaterally impacted third molars were present, and on the left they were approaching a horizontal axis. After a total dosage period of four months, the general dentist stated that the gums were tighter and showed more pinkness. After about one year of total dosage, a general dentist reported, "tremendous improvement in the gingival tissue, which was appropriately pink with normal stippling and no edema." He concluded that "there has been a tremendous improvement."

Nakamura, Littarru, and Folkers, in cooperation with Wilkinson (18) (1974) extended the initial study on the deficiency of CoQ₁₀ in gingiva and particularly to assess the difference between the diseased and the normal tissues. They assayed a group of gingival biopsies from fifteen individuals who showed no visible periodontal disease, and a group of biopsies from twenty-two patients with obvious periodontal disease. The mean percent increase in specific activities of the succinate dehydrogenase coenzyme Q₁₀ reductase and the NADH-cytochrome c reductase were determined in mitochondria from 40 diseased gingival biopsies from patients with periodontal disease, and from 24 control biopsies from non-diseased areas (clinically evaluated gingival tissues from the same mouths of the patients from whom the diseased gingival tissues were taken). These control tissues were taken during normal surgical procedures as for gingival recontouring and removal of redundant tissue from maxillary tuberosities. The diseased gingival biopsies showed a mean specific activity for the succinate dehydrogenase-coenzyme Q₁₀ reductase which were higher (P<0.02) than that of the control biopsies, and which increased (P<0.01) when the assays were conducted in the presence of exogenous coenzyme Q₁₀, and corresponded to a mean value for the deficiency of coenzyme Q₁₀-enzyme activity of 35%. Also, 60% of the 40 diseased gingival tissues showed a deficiency of coenzyme Q₁₀ at its site in this CoQ₁₀-enzyme. Of the 24 control tissues, there was an incidence of 20% deficiency of coenzyme Q₁₀, which doubtless reflects aspects of nutritional imbalances. By group analysis, the control tissues showed no deficiency of coenzyme Q₁₀.

These investigators (Nakamura et al., 18) (1974) found no deficiency of coenzyme Q₁₀ at its site in NADH-cytochrome c reductase for either the control of diseased gingival tissues, as groups or individuals.
STUDY OF ADMINISTRATION OF COENZYM E Q TO PATIENTS WITH PERIODONTAL DISEASE

Tsunemitsu and Matsumura (1967) (19) have described the clinical administration of coenzyme Q7 to patients with severe destructive periodontal disease and who had hypercitricemia. In their study, the hypercitricemia was normalized by the oral administration of coenzyme Q7.

Dosage Schedule (Tsunemitsu et al., 1967)-
The hypercitricemia in twenty-five patients with severe destructive disease was remarkably improved. The dosage of coenzyme Q7 was 30 mg daily for 10 days by the oral route.

Imai (20) (1972) administered 30 mg of coenzyme Q7 daily for 20 days to humans with periodontal disease, and reported a decrease in the high blood levels of citrate.

Iwamoto, Nakamura, and Folkers, in cooperation with Morrison (21) (1975) treated with hexahydrocoenzyme Q4 a 25-year old Caucasian with uniquely severe and chronic periodontal disease requiring extraction of all teeth. During the fourth and fifth examinations after the seventh and eighth weeks of treatment, three dentists separately and independently scored clinical improvements of five symptoms by a significance of P<0.01 to P<0.001. It was particularly observed that the rate of healing of the tissue after extraction of the teeth was unusually rapid, and could have been due to the administration of the hexahydrocoenzyme Q4.

Dosage Schedule (Iwamoto et al., 1975).- Hexahydrocoenzyme Q4 was formulated in corn oil at a concentration of 500 mg of H6CoQ4 per ml. Such dosage was considered on the high side, but a positive therapeutic response was sought on the basis that minimal effective dosage could be determined in the future. The patient took 1 ml of the formulation before lunch and 1 ml before dinner. The period of therapy was limited to eight weeks.

Wilkinson and Arnold, in cooperation with Folkers, Hansen, and Kishi (22) (1975), reported upon eight patients under routine care for periodontitis who were provided with an oral treatment of either coenzyme Q10 or hexahydrocoenzyme Q4. The unchanged plaque score showed that these patients cooperated and were under plaque control. On treatment with coenzyme Q, the periodontal score decreased (P<0.01). Unexpectedly, the periodontal pocket depth was observed to decrease significantly (P<0.01) on CoQ treatment, since all of these patients were considered conditions for surgical intervention. The healing was so excellent in 5-7 days post-biopsy that the biopsy sites were difficult to locate. This healing was viewed as extraordinarily effective. The mean value of the specific activities of the succinate dehydrogenase-coenzyme Q10 reductase of the gingival biopsies were observed to increase (P<0.05) during the treatment, and which could correlate with the extraordinary healing. Such treatment of periodontitis with a form of coenzyme Q was considered as adjunctive treatment with current dental practice.

Dosage Schedule (Wilkinson et al., 1975).- Seven patients were treated with coenzyme Q10 and one with hexahydrocoenzyme Q4. The coenzyme Q10 was taken by mouth in capsule form (25 mg/capsule) at a dosage of 50 mg/day/21 days. One patient was given a dragee form of hexahydrocoenzyme Q4 containing 200 mg of H6CoQ4/dragee, which was allowed to dissolve slowly in the mouth. The dosage was 5 dragees taken throughout the day. This dosage of hexahydrocoenzyme Q4 was deliberately selected on the high side and also because this dosage had been used to treat the 25-year old Caucasian as described by Iwamoto et al., 1975.

SIX DOUBLE BLIND TRIALS OF ADMINISTRATION OF THREE FORMS OF COENZYME Q TO PATIENTS WITH PERIODONTAL DISEASE

Tsunemitsu et al., (23) (1970) reported on the double-blind administration of coenzyme Q7 to 19 patients and a placebo to 17 patients with alveolar pyorrhea. The treatment was effective in improving both subjective and objective symptoms of the disease including the gingival involvements.

Dosage Schedule (Tsunemitsu et al., 1970).-
The dosage of coenzyme Q was 30 mg daily, as 10 mg t. i. d. after meals, for 21 days.

Matsumura and Saji, in cooperation with Nakamura and Folkers (24) (1973) conducted a double-blind study of the administration of hexahydrocoenzyme Q, and placebo formulations to patients who had clinical and radiographic signs of destructive periodontal disease, and who had not satisfactorily benefited by oral therapy. Thirteen patients received a synthetic form of coenzyme Q, Hexahydrocoenzyme Q, and 11 patients received the placebo. Three of eleven patients on placebo showed a "weak false-response" by statistics, and only one of these three patients showed a false response by judgement, and none of these eleven patients revealed complete disappearance of the periodontal symptoms. Nine of the thirteen patients treated with hexahydrocoenzyme Q, were improved as evaluated by statistics. These results clearly showed that patients with severe destructive periodontal disease were significantly benefited by the oral administration of hexahydrocoenzyme Q.

Dosage Schedule (Matsumura et al., 1973).- Pure synthetic hexahydrocoenzyme Q, was formulated in corn oil at a concentration of 200 mg of H6CoQ4 per 1 ml. The placebo formulation consisted of the same corn oil which was tinted with a medically-acceptable pigment so that the appearances of the formulations of coenzyme Q and placebo were visually indistinguishable. Each patient took 2 ml of the appropriate formulation in the morning, 2 ml in the afternoon, and 1 ml in the evening. The sequential assignment of the patients to the coenzyme Q- and placebo-formulations were by a procedure for statistical significance in double-blind methodology. The code on each bottle was maintained at the Institute for Biomedical Research at The University of Texas at Austin, and the bottles of formulation were shipped to the Department of Preventive Dentistry, Dental School, Osaka University, Japan, where the double-blind study was conducted. The coenzyme Q, and placebo-formulations were administered for eight weeks.

These investigators (Matsumaru et al., 1973) concluded that oral therapy alone can correct the bacterial component of periodontal disease, but cannot correct a gingival deficiency of coenzyme Qm, which can be largely due to causes other than the inflammation. It was also stated that the administration of coenzyme Qm can correct a systematic and/or gingival deficiency of coenzyme Qm, but cannot replace oral physiotherapy. If a deficiency of coenzyme Qm were to exist for any cause in the gingival tissue of patients with periodontal disease, then the therapeutic administration of coenzyme Q and effective oral physiotherapy could lead to an improved treatment.

Kusunoki et al. (25) reported a double blind study in 1975 on the clinical effects of the administration of coenzyme Q, to patients having marginal periodontitis.

Dosage Schedule (Kusunoki et al., 1975).- The coenzyme Q, was administered at a daily dosage of 30 mg for four weeks. The coenzyme Q, and placebo were administered by a double blind method.

There were 77 patients in the study who had a marginal periodontitis. The mandibular anterior teeth were selected for specific examination. The criteria which were used consisted of redness, swelling of gingiva, pus discharge, bleeding from the periodontal pocket, pocket depth, and mobility of teeth.

There was a significant difference (P<0.05) as judged by the improvement of the discharge of pus between the coenzyme Q-treated group and the placebo group.

Hashimoto et al., (26) also reported in 1975 their results by a doubleblind method from the clinical administration of coenzyme Q, to patients having marginal periodontitis.

Dosage Schedule (Hashimoto et al., 1975).- The patients received, on a double-blind basis, 30 mg of coenzyme Q, a day for 4 weeks after a period of local treatment. During the administration of coenzyme Q, and the placebo, these patients did not receive any other treatment.

Eighty-nine patients with marginal periodontitis were selected for the double-blind study. There were significant differences between the two groups receiving coenzyme Q, and the placebo, as based on improvement of objective symptoms. Gingival redness decreased (P<0.03), swelling decreased (P<0.04), bleeding decreased (P<0.02), and pocket depth decrea-
This double-blind study failed to confirm a correlation between the reduction of the levels of citrate in the blood and the improvement of clinical symptoms.

These clinical results of Hishimoto et al., (26) led to the suggestion that it was better for periodontal patients to receive coenzyme Q₁₀ concomitantly with local treatment.

A double-blind administration of coenzyme Q₁₀, which is that form of coenzyme Q in human tissue, was administered on a double-blind basis to patients having periodontal disease by Wilkinson, Arnold and Folkers (27) (1971).

Dosage Schedule (Wilkinson, et al., 1976). Ten bottles of capsules of CoQ₁₀ and ten bottles of matching placebo were randomly coded by consecutive numbers, 1-20. Each capsule of CoQ₁₀ contained 25 mg of the substance. The code was known only to Karl Folkers at The University of Texas at Austin, who filled the bottles. The double-blind administration was conducted at the Travis Air Force Base in California. The dosage was two capsules/day for three weeks, so the dosage of CoQ₁₀ was 25 mg twice daily. At the conclusion of the study, Edward G. Wilkinson, D. D. S., and Ralph M. Arnold, D. D. S. interpreted their data assigned each patient to a treatment or placebo group. After this commitment of assignments, the code was broken and the result of the double-blind trial was evaluated.

Eighteen patients with periodontal disease and measurable pockets were treated on a double-blind basis with coenzyme Q₁₀ and a matching placebo. The treatment was significant ($P<0.01$). Before decoding, all of the eight patients receiving the formulation of coenzyme Q₁₀, and 7/10 patients receiving a matching placebo formulation were correctly assigned. The status of one of the remaining 3 placebo patients was so borderline that this patient could have been assigned to either group. The remaining three placebo patients had extremely inadequate oral hygiene and had visited the dentist infrequently. It is commonly observed that such patients will attempt to improve their oral hygiene when they have frequent dental appointments, and the improved periodontal health of two of these three patients caused the erroneous assignment to the CoQ₁₀ group.

Crevicular fluid flow as a measure of inflammation was monitored, as it has been shown to be a measure of gingival inflammation (Brill, 1958: (31) Mann, 1963) (32). The measuring of gingival temperature as an indicator of health versus diseases was explored, and appears to offer interesting observations and a degree of assistance in final evaluation. However, the measuring of gingival temperature as a criterion is still an unproven technique.

Pocket depth evaluation periodontal health, calculus, and plaque scores offered the most valuable data for evaluation. Decreased pocket depth with plaque score remaining constantly high, coupled with photographic evidence of improved health, was considered as strong evidence of improved periodontal health due to the administration of coenzyme Q₁₀.

The double-blind administration of coenzyme Q₁₀ to six patients with moderate to advanced periodontitis and who had at least 24 natural teeth was studied by Wilkinson, Arnold, and Folkers in 1976 (28).

Dosage Schedule (Wilkinson et al., 1976). Three bottles of capsules of coenzyme Q₁₀ and three bottles or matching placebo were randomly coded by numbers. Each capsule of coenzyme Q₁₀ contained 25 mg of the substance and the vehicle was soybean oil. The code was known only to Karl Folkers at The University of Texas at Austin, and the double-blind administration was conducted at the Travis Air Force Base in California. The dosage was 2 capsules before each of the three daily meals and at bedtime so that the dosage of coenzyme Q₁₀ was 200mg per day, and for three weeks. After the interpretation of all data, the six patients were assigned to the treatment or to the group. After this commitment, the code was revealed and the result of the trial was evaluated.

Six consenting patients with moderate to advanced periodontitis and who had at least 24 natural teeth were selected for this study. After selecting the patients, they had three appointments for evaluation. As usual, no side effects were observed and there was little change after seven days of treatment. Consequently, the appointments for evaluations after 14 and 21 days
provided the clinical results.

After the third date collection, pocket-depths were evaluated by (1) average total pocket-depth: (2) average significant pocket-depth, where pockets were 4 mm or more in depth: and (3) average significant pocket-depth divided by a constant which was a number of significant pockets found at the first appointment. The number of significant pockets were also recorded. No periodontal or dental treatment was started on any patient until after the 21 days of treatment with coenzyme Q₁₀ or placebo. Even discussion of oral hygiene was avoided until all patients were started on a full course of periodontal therapy.

The criteria of evaluation were: a) average pocket-depth by combined pocket analysis, b) periodontal health score; c) crevicular fluid flow; d) number of significant pockets (>4mm) when the calculus score and plaque score remain the same or had increased.

The statistical analysis of the data was based on comparison of the % improvements of average pocket-depth and the number of pockets for the two groups. The % improvements in the average pocket-depth was significant for both the 14- and 21day measurements ranging from 0.01<P<0.01. The % improvement was significant by 0.02<P<0.05 for the number of pockets at both periods. The % improvement in periodontal health score was also significant, 0.01<P<0.02, after 21 days for those on CoQ₁₀ in comparison with placebo.

Clearly, improvements were evident by pocket criteria and by the periodontal health score for those patients treated with coenzyme Q₁₀ but not for those who were given the placebo. Measurements of crevicular fluid flow and gingival temperatures were helpful in assigning patients to the CoQ₁₀ or the placebo groups, but the significance of these two measurements requires further study.

A total of two periodontists, one general dentist, and two paraprofessionals participated in the final assignments and correctly identified the three patients who received the coenzyme Q₁₀ and the three who received the placebo before the code was revealed.

These clinical results on coenzyme Q₁₀ were interpreted on the basis of improved bioenergetics since coenzyme Q is indispensible to the biochemistry of electron transfer and coupled oxidative phosphorylations of respiration.

OENZYME Q AND CLINICAL APPLICATIONS INCLUDING PERIODONTAL DISEASE

Iwamoto and Nakamura (29) in 1975 reviewed certain literature on the clinical application of coenzyme Q in periodontal disease when there was and was not a related study on the activity of coenzyme Q₁₀-enzymes and data on deficiencies of coenzyme Q₁₀, information on systemic factors in periodontal disease, and particularly in formation on data on citric acid and coenzyme Q. They also reviewed certain clinical studies on the administration of coenzyme Q to systemic diseases including cardiac disease, muscular dystrophy, and hypertension.

GINGIVAL AND LEUCOCYTIC DEFICIENCIES OF COENZYME Q₁₀ IN PATIENTS WITH PERIODONTAL DISEASE

A study has been made on whether the deficiency of coenzyme Q₁₀ in gingival tissues from patients with periodontal disease is largely localized in this tissue, or whether there is a concomitant gingival tissues from patients with periodontal disease is largely localized in this tissue, or whether there is concomitant deficiency of coenzyme Q in other tissues of the same patient, particularly in the blood. This study was conducted by Folkers et al. (30) in cooperation with Lynn E. Thompson, D. D. S. in 1976.

The specific activities of the succinate dehydrogenase-coenzyme Q₁₀ reductase in mitochondria were determined for patients from a periodontal practice. The criteria for selection were patients having a bone score of 1.0-4.0 and a pocket depth of 2.5-5.2 mm. All 29 patients showed a deficiency of coenzyme Q₁₀-enzyme activity in their gingival biopsies which ranged from 20-63%. The mean value was elevated (P<0.001) over that of controls. For corresponding blood samples, 24/28 (86%) showed deficiencies which ranged from 20-66%, and a higher (P<0.001) mean value than that of
controls.

This study and related previous investigations were interpreted as follows.

Since all 29 periodontal patients had a gingival deficiency of coenzyme Q₁₀, and 86% of these patients also had a significant leucocytic deficiency of coenzyme Q₁₀, it did not seem plausible that neglected oral hygiene could be the cause of a blood deficiency involving coenzyme Q₁₀ in bioenergetics. It seemed likely that the blood deficiency was the result of a nutritional imbalance and was essentially independent of the periodontitis.

Periodontitis could enhance a pre-existing gingival deficiency of coenzyme Q₁₀, or cause such a deficiency. Four of the 29 periodontal patients had gingival deficiencies of 36-61%, but leucocytic deficiencies of less than 20% (9-19%).

It was considered that a pre-existing deficiency of coenzyme Q₁₀ in the gingiva could pre-dispose this tissue to periodontitis, particularly during periods of neglected oral hygiene.

Blood samples are generally more feasible to obtain than gingival biopsies, and the leucocytic coenzyme Q₁₀ analysis can be readily performed. If a significant leucocytic deficiency is present, adjunctive treatment with coenzyme Q₁₀ may be even more strongly justified since the patient has a deficiency in addition to that of the gingival tissue.

It was concluded that these data on gingival and leucocytic deficiencies of coenzyme Q₁₀ supported the previous conclusion by Wilkinson (1976) that therapy with coenzyme Q can be adjunctive with periodontal therapy resulting in extraordinary healing and enhancing treatment of periodontal disease. The indispensability of the intrinsic coenzyme Q₁₀ in bioenergetics was emphasized as the basis for the extraordinary healing and benefit resulting from the administration of coenzyme Q₁₀ to periodontal patients.

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