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ANTIHYPERTENSIVE MEDICATIONS AND SALIVATION

by

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of Loyola University of Chicago

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DEDICATION

This thesis is dedicated to my husband, Carlos Andrés, and my son, Carlos Felipe, whose love, patience and support are my inspiration. I also wish to dedicate it to my parents, Hélder and Nuhr, whose love, guidance and innumerable personal sacrifices, I will never forget.

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INTRODUCTION

Hypertension is a major health problem in the USA and is the single most important contributing factor to cardiovascular disease. Nearly 60 million Americans have elevated blood pressure and many of these persons warrant treatment with medication (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 1984). A stepped-care approach has been widely recommended for more than ten years as an empiric treatment of hypertension (Gerber and Nies, 1990). This approach is relatively simple to implement, effective in most patients, and permits individualization of therapy. However, its general use is decreasing because of the development of medications more specific for each patient (Chobanian, 1986). The stepped-care approach for the treatment of hypertension is:

Step 1:   Diuretic or B-Blocker.

Step 2:   Adrenergic Inhibitor, Calcium-Channel Blocker, Angiotensin-Converting Enzyme Inhibitor.

Step 3:   Vasodilator.

Step 4:   Guanethidine.

If a Step 1 medication is not effective, then other agents are added in order to bring hypertension under control (Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, 1984).

Because of the marked prevalence of hypertension, many dental patients are taking one or more medications for the treatment of this disease. Dry mouth, for example, is a frequent side effect produced by some of these medications and it can be very bothersome to patients. The health-care provider must be aware of this complication in order to improve patient discomfort and to treat the several problems xerostomia may give rise to, such as, root caries, mucositis, alteration of taste, candida overgrowth, and increased plaque accumulation (Mandel and Katz, 1971; Mandel et al, 1975; Mandel, 1972; 1974; 1976; 1977; 1989; Ferguson, M.M., 1989; Fox, 1989; Sreebny, 1989).

It is the aim of this thesis to study the effects of diuretics used as antihypertensive agents, alone or in combination, on salivary flow rate, osmolarity, and sodium, potassium and calcium composition, and also determine if the subjective complaints of the patients can correlate with specific changes in saliva. This information could then serve as a basis for the possible modification of medical therapy in dental patients for whom normal salivary flow and/or composition are especially important.

SALIVARY GLANDS

All salivary glands are complex, compound tubulo-alveolar glands. Each gland is composed of a series of secretory units, which consist of an acinus, intercalated duct, striated duct, and excretory duct (Tandler, 1972; Izutsu, K.T., 1989).

Each acinus gives rise to an intercalated duct. An acinus consists of a spherical group of cells, classified histologically into two types according to their appearance after staining with hematoxylin and eosin (Ferguson, D.B., 1975):

(1)   Pink-staining cells with large granules or vacuoles are found in the acini of the sublingual gland and the submandibular gland but rarely in the parotid. They have been referred to as mucous cells.

(2)   Pale blue-staining cells with much smaller granules than those in the mucous cells make up most of the acini of the parotid gland and the glands of von Ebner, also known as serous cells; and their characteristic product is the starch-splitting enzyme, amylase.

The cells of the intercalated duct are small, cuboidal cells with large nuclei and few organelles. The duct is relatively short and the small cells give way to larger cuboidal cells with centrally placed nuclei and striated basal thirds.

The appearance of these cells gives this next part of the duct its name of striated duct (Ferguson, D.B., 1975). From the striated duct there is an abrupt transition to the excretory ducts which have two-layered epithelia.

In addition to these cells of the acini and duct system, another cell type is found in the major salivary glands, the myoepithelial cell. These cells have a regular orientation of fibers like those of smooth muscle cells, and are usually described as stellate. Their contraction is believed to cause the expulsion of formed saliva (Tandler, 1972; Ferguson, D.B., 1975).

PAROTID GLANDS --- The parotid glands are the largest salivary glands. They are located immediately beneath the skin over the ascending ramus of the mandible and extend into the groove between the ramus of the mandible and the sternomastoid muscle to reach the styloid process and the styloid muscles. They are pyramidal in shape, the base of the pyramid being rhomboidal. Each gland weighs around 25 grams. A dense fibrous capsule separates the gland from other structures. The main duct of these glands, Stensen's duct, leaves at the mesial angle, passes forward over the masseter muscle and then turns sharply inward to pierce the buccinator muscle. It runs for a short distance between the buccinator and the oral mucosa to terminate in a small papilla close to the buccal surface of the upper first molar tooth. The duct is about 5 cm. long, with an internal diameter of 3 mm. Its walls contain fibrous tissue and smooth muscle fibers. Blood supply is via the external carotid artery and return is through the retromandibular vein. They are entirely serous glands (Ferguson, D.B., 1975; Mason and Chisholm, 1975).

SUBMANDIBULAR GLANDS --- The submandibular glands are next in size; they are usually described as being about the size of walnuts and weigh 10-15 grams. They are irregular in shape and are located in the floor of the oral cavity. Each has a larger, superficial portion in contact inferiorly with the skin and platysma muscle, laterally with the body of the mandible, and medially with the extrinsic muscles of the tongue and the mylohyoid muscle. The smaller, deep part lies between the mylohyoid muscle and the hyoglossus and styloglossus muscles. This part also extends forward and inward above the duct coming from the superficial part, to reach the posterior edge of the sublingual gland. The main duct, Wharton's duct, is about 5 cm long; after leaving the superficial part of the gland it runs beneath the deep part, passes between the mylohyoid and hyoglossus muscles, then between the sublingual gland and the genioglossus muscle to end at the summit of the sublingual papilla (sublingual caruncle) at the side of the frenulum of the tongue. The blood supply is via branches of the facial and lingual arteries. They are mixed glands, mainly serous (Ferguson, D.B., 1975; Mason and Chisholm, 1975).

SUBLINGUAL GLANDS --- The sublingual glands are the smallest of the major glands. Each is of

the size and shape of an almond and weighs 3-4 grams. Each lies immediately beneath the oral mucous membrane in a fold beside the tongue. Below the gland is the mylohyoid muscle, laterally is the mandible, and medially is the genioglossus muscle. Anteriorly, each reaches its fellow; posteriorly, each reaches the deep part of the submandibular gland. Usually a number of small ducts from the glands open independently on the surface of the sublingual folds on either side of the tongue. Bartholin's duct is the main excretory duct, and the minor ducts are known as the ducts of Rivinus. Blood is supplied by the lingual artery and branches of the submental artery. They are mixed glands but mucous acini predominate (Ferguson, D.B., 1975; Mason and Chisholm, 1975).

ACCESSORY GLANDS --- The minor, or accessory, glands are located beneath the epithelium in almost every part of the oral cavity, except in the gingiva and anterior regions of the palate. Apart from the dorsal lingual glands which are entirely serous (von Ebner glands), all these minor glands are mucous or predominantly mucous, with few serous acini.

(1)   Anterior Lingual Glands: The two anterior lingual glands lie on either side of the frenulum on the under surface of the tip of the tongue. They are 12-20 mm long and 8 mm broad with several small ducts piercing the mucous membrane which covers them.

(2)   Serous Glands of von Ebner: These are small glands whose ducts open into the sulci of the vallate papillae.

(3)   Lingual, Buccal, Labial and Palatal Glands: These small glands have short ducts and produce a secretion rich in mucoproteins. They are found scattered over the surface of the tongue, the inside of the lips and cheeks, and in the mucosa covering the hard and soft palates (Ferguson, D.B., 1975; Mason and Chisholm, 1975).

NERVE SUPPLY --- Secretion of saliva is entirely under nervous control. Control is exerted mainly by parasympathetic, but also by sympathetic, nerves. Parasympathetic, secretomotor nerve fibers

to the parotid gland are present in a branch of the glossopharyngeal nerve; synapses occur in the otic ganglion and from there fibers pass in the auriculotemporal nerve to the gland. Both the submandibular and sublingual glands are innervated by parasympathetic secretomotor fibers originating in the facial nerve, which continue in the chorda tympani and reach the glands via fibers of the lingual nerve. Afferent fibers for the sensation of pain are also contained in these various parasympathetic pathways.

Four possible effects in the glands can occur as a result of stimulation by nerves as summarized by D. B. Ferguson (1975):

1)   Secretory Activity --- May be stimulated by parasympathetic or sympathetic activity. Variations in secretion may occur as a result of stimulation of different receptor sites on the cell membrane and thus different secretory pathways being activated. The effect of parasympathetic and sympathetic stimulation seems to be synergistic when both are active.

2)   Increase in Blood-Flow to Maintain Secretion --- Parasympathetic fibers are vasodilator and the sympathetics are vasoconstrictor, but once secretion is initiated bradykinin is produced and this polypeptide causes a vasodilation, which overrides nervous control of the blood vessels.

3)   Changes in Activity of the Ductal Cells --- No evidence exists on the question of whether autonomic stimuli affect the functioning of the salivary gland ducts, although cholinesterase activity in or near ductal cells suggests at least some parasympathetic control.

4)   Contraction of the Myoepithelial Cells --- It is still not clear whether the myoepithelial cells of human salivary glands respond to either sympathetic or parasympathetic stimulation. Laboratory experiments have shown that they respond to bradykinin (Emmelin, 1970).

FUNCTIONS AND COMPOSITION OF SALIVA

FUNCTIONS --- Saliva is the fluid secreted by the three, paired major salivary glands and the various minor glands; it plays important roles in such activities as communication and digestion. Overall its functions may be classified as protective, digestive, excretory, and solvent. The specific functions of saliva depend on the wide variety of its components. Saliva prevents drying of the cells of the oral mucosa. It acts as a mechanical cleansing medium, washing away particles or solutions remaining on and around the teeth and other oral tissues. The salivary glycoproteins and mucoproteins coat the oral tissues, shielding them from the air movement of breathing and talking, and from ingested liquids and chemicals. These proteins are also mixed with food and act as lubricants to aid in swallowing. Saliva's antibacterial properties are due to its content of lysozyme, antibodies and peroxidases. Salivary amylase is the only important digestive enzyme present in saliva, and it is responsible for digesting up to half of ingested starch before the enzyme becomes inactivated by gastric juice. Saliva aids in the maturation of newly erupted teeth by making them less susceptible to dissolution in acid. Also secreted Ca^{++} ions can function in recalcification if decalcification of the tooth surface has occurred. Several other blood components are also secreted in the saliva and their local effects in the oral cavity may be important. Urea, uric acid, and ammonia pass into saliva and their breakdown may occur in the mouth and/or later in the gastrointestinal tract. Heavy metals, such as, lead, mercury and bismuth, pass into the saliva and may be deposited in the oral tissues if blood levels are high. Saliva dissolves sapid substances and spreads them over the surface of the taste papillae to bring them into contact with the taste buds (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Jenkins, 1978; Fox, 1989; Tenovuo, 1989).

VOLUME --- The total volume of saliva produced in 24 hours is between 1 and 1.5 liters. Of this volume approximately half is thought to be basal, unstimulated flow, and the other half is produced in response to the various stimuli associated with eating. The production of saliva is related to

activity patterns, and the sleeping subject produces very little. Observations reported on sleeping subjects indicate that only 10 ml of saliva are produced by the major glands during eight hours of sleep; this slow flow rate is probably due entirely to the lack of stimulation, since subjects roused from sleep in the early hours of the morning may show a maximum flow of parotid saliva in response to stimulation (Mason and Chisholm, 1975; Jenkins, 1978).

The relative proportions of the secretions in mixed saliva vary with the amount of stimulation and also with the nature of the stimulus. During sleep, there is no flow from the parotid glands and the submandibular glands contribute 80% and the sublingual glands 20% of the saliva produced. These proportions ignore the contribution of the accessory glands. If these contribute a similar proportion to the flow in sleeping subjects as they do to unstimulated saliva from subjects who are awake, the above proportions will be reduced to 75% and 18% respectively. Another possibility is that the flow from the accessory glands remains effectively unchanged during sleep. If this were the case, saliva from accessory glands might be the major component of saliva in the sleeping subject and estimates of saliva production during sleep would have to be raised to around 20 ml/hour. Unstimulated, resting flow in subjects who are awake amounts to 200-300 ml over 12-14 hours, which is also about 20 ml/ hour. Of this, the contributions of the major glands are about 70% from the submandibular glands, 20% from the parotid glands and 1-2% from the sublingual glands. When the glands are stimulated, the rate of flow increases. As stimulation increases, the contributions of submandibular and parotid salivas to mixed saliva become more nearly equal (Ferguson, D.B., 1975). Gingival fluid may be only 10-100 microliters/hour, but near the gingival margin it may represent a significant proportion of the oral fluid. Gingival fluid may make an important contribution to the environment of the tooth (Ferguson, D.B., 1975; Jenkins, 1978; Tenovuo, 1989).

Of the mixed saliva produced in response to a mechanical stimulus, such as the chewing of paraffin wax, some 5-10% can be centrifuged out as solid material. Saliva produced this way, contains many mucosa cells and plaque bacteria dislodged by the physical action of chewing

(Ferguson, D.B., 1975).

Overall, water accounts for 99% of saliva. Several organic and inorganic substances can be subdivided into proteins, enzymes, low-molecular-weight organic compounds, vitamins and electrolytes.

ORGANIC COMPONENTS ---

1)   Proteins: The proteins present in oral fluid are derived mainly from secretions of the parotid, submandibular, sublingual, and minor salivary glands. Small amounts originate, however, from oral microorganisms, crevicular fluid, epithelial cells, polymorphonuclear leukocytes, and dietary constituents. The total protein content of stimulated saliva is around 2.2 g/liter, but at low flow rates it drops to about 0.2 g/liter. Protein concentration is thus very dependent on flow rate (Ferguson, D.B., 1975; Dawes, 1978). Saliva contains 7 or 8 proteins which show antigenic properties similar to those of blood proteins. Their percentage of total serum proteins may be as much as 20% (Jenkins, 1978).

(a)   Enzymes --- The number of enzymes present in oral fluid is much higher than that of pure salivary gland secretions. Additional sources of enzymes are crevicular fluid, polymorphonuclear leukocytes, epithelial cells, dietary constituents and oral microorganisms (Jenkins, 1978; Tenouvo, 1989).

(1)   Amylase: This is the most important organic constituent of saliva in relation to digestion because it is capable of splitting cooked starch down to maltose. The parotid gland is the primary source of salivary amylase. It has an optimum pH of 6.8 and requires chloride for full activity. Approximately 30% of the protein in parotid saliva is amylase. Amylase secretion increases as flow rate increases (Ferguson, D.B. 1975; Tenouvo, 1989).

(2)   Lysozyme: This enzyme splits the carbohydrate of cell walls of certain bacteria. It is present in most body secretions and its

concentration is especially high in submaxillary saliva (Ferguson, D.B. 1975; Tenouvo, 1989).

(3)   Acid Phosphatase, Cholinesterase and Ribonuclease: These are present in similar concentrations in parotid and submaxillary salivas (Ferguson, D.B. 1975).

(4)   Kallikrein: During activity it is produced by the glandular tissue, diffuses into local blood vessels and causes the functional dilatation necessary to supply increased blood flow to the active gland (Ferguson, D.B. 1975).

(5)   Peroxidase: This enzyme gives saliva its antibacterial property (Ferguson, D.B., 1975; Tenouvo, 1989).

(6)   Other Enzymes: In oral fluid there is a diverse group of enzymes derived from living, dying and dead leukocytes and bacteria. Some of these enzymes are capable of splitting carbohydrates, fats and proteins (Ferguson, D.B., 1975; Jenkins, 1978; Tenouvo, 1989).

(b)   Glycoproteins --- These are complexes of carbohydrates and proteins and give saliva its characteristic slimness. They are important as lubricants and aid in the chewing and swallowing of food and in articulation (Ferguson, D.B., 1975; Tenouvo, 1989).

(c)   Blood-Group Substances --- These are carbohydrate-protein complexes present in the cell walls of red blood cells. They are present in submandibular and sublingual salivas, but not in parotid saliva (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978).

(d)   Hormones --- Parotin is a protein that has been isolated from saliva which may act as a hormone to regulate serum calcium level and promote calcification. Corticosteroids, mainly cortisone, are present in parotid saliva in a concentration

of 30-40 mg/liter (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978; Jenkins, 1978).

(e)   Nerve Growth Factor --- This substance stimulates the growth and development of sympathetic nerves (Ferguson, D.B., 1975; Mason and Chisholm, 1975;).

2)   Carbohydrates: Parotid saliva contains approximately 5 mg/liter of free carbohydrate; most of this is glucose and its concentration is related to its blood concentration. Submandibular saliva contains about 30 mg/liter, 25 mg of which is glucose and fucose; hexosamine and silica acid account for the remaining 5 mg. This high concentration of carbohydrate is due to the presence of the enzyme system capable of breaking down mucoproteins. The concentrations are higher in oral fluid because of even more enzymatic activity (Ferguson, D.B., 1975; Jenkins, 1978).

3)   Lipids: The lipid content of saliva is very low, 20 mg/liter. Cell wall components raise the concentration in oral fluid (Ferguson, D.B., 1975; Dawes, 1978).

4)   Vitamins: Most of the water-soluble vitamins have been found in whole saliva. Part of them is synthesized by oral bacteria, and another part may be present from food debris. Vitamin C, ascorbic acid, is present in resting mixed saliva at 2.4 mg/liter. Stimulation of salivary flow causes the concentration to fall because of dilution. The B-complex vitamins and vitamin K are present at very low levels (Ferguson, D.B., 1975; Dawes, 1978; Jenkins, 1978).

5)   Low-Molecular-Weight Organic Compounds: Oral fluid contains approximately 50 mg/liter of amino acids. The major amino acid present is glycine. The concentration of urea in saliva depends on the flow rate. Unstimulated saliva contains between 60-200 mg/liter (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Jenkins, 1978).

INORGANIC COMPONENTS --- The total inorganic content of saliva is about 2.5 g/liter. All the usual ions found in physiological fluids are present but their concentrations depend on the rate of

salivary flow .

1)   Sodium: Sodium, the most abundant ion in extracellular fluids, is present in primary salivary secretion, produced by acinar cells, at 140-150 Mm/liter, a concentration similar to that found in extracellular fluids. Its concentration in whole saliva is directly related to salivary flow. It is as low as 1-5 mEq/liter at low flow rates and 100 mEq/liter at maximum rates of secretion. The site of entry of sodium into the saliva is through the acinar cells, and as the sodium is reabsorbed by the tubular cells, potassium moves in the opposite direction. At high flow rates there is less time for reabsorption of the sodium and thus its concentration is higher than at low flow rates. This exchange is driven by an energy- dependent, Na-K, pump in the duct cells (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978; Tenovuo, 1989).

2)   Potassium: At flow rates above 0.2 ml/min, the potassium concentration in saliva stays constant at around 20 mM/liter. At lower flow rates, potassium concentrations increase to as much as 80 mM/liter. These values are related to the length of time the saliva spends in the ductal system, and thus the time available for the Na-K exchange (Mason and Chisholm, 1975; Dawes, 1978; Tenovuo, 1989).

3)   Chloride: Chloride is the major anion of extracellular fluids and its concentration is around 100 mEq/liter. This is also its approximate concentration in the primary secretion of the acinar cells. As the flow rate increases, bicarbonate is actively transported into saliva. In order to maintain electrical neutrality more Cl⁻ is reabsorbed. The concentration of Cl⁻ therefore falls both because of dilution and increased reabsorption (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Tenovuo, 1989).

4)   Bicarbonate: The concentration of this ion is very low in resting saliva. The concentration increases with the flow rate to reach as high as 60 mEq/liter. Bicarbonate is the principal buffer in saliva. Loss of carbon dioxide results in an effective loss of carbonic acid and so is associated with a more alkaline saliva. Since the bicarbonate and

carbon dioxide levels in saliva are high, exposure of saliva to air leads to loss of carbon dioxide and hence an upward shift in pH. If the pH of saliva is to be measured, it is necessary to prevent loss of carbon dioxide. Further the solubility of calcium in saliva is affected by pH, and thus the loss of carbon dioxide can result in the precipitation of calcium salts (Ferguson, D.B., 1975; Dawes, 1978; Tenovuo, 1989).

5)   Hydrogen Ion: The pH of saliva is below 7.0 in resting secretions but rises to as high as 8.0 in fast-flowing saliva. This is largely due to the bicarbonate content of saliva (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Tenovuo, 1989).

6)   Iodide: Salivary glands actively secrete iodide, so its concentration is higher in saliva than in plasma. The concentration increases with flow rate (Ferguson, D.B., 1975; Dawes, 1978).

7)   Fluoride: Saliva contains 0.1 ppm fluoride, a concentration of the same order as that in plasma. Very small variations in total fluoride are found in relation to fluoride intake (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978; Jenkins, 1978;).

8)   Thiocyanate: This ion is present in a higher concentration in saliva than in serum, especially in the saliva of cigarette smokers. The ion in conjunction with a salivary globulin, has a bacteriostatic function in saliva (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978; Jenkins, 1978).

9)   Calcium: The calcium content of submandibular saliva is approximately twice that of parotid saliva. As flow rates rise above resting rates, the concentration at first falls but from 0.25 ml/min upwards the concentration increases again. In whole or mixed saliva, the pattern is one of decreasing calcium concentration as flow rate increases (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978; Jenkins, 1978).

10)   Phosphate: Almost all the phosphate present in saliva is inorganic. A small amount of pyrophosphate has been found in saliva in some subjects (Ferguson, D.B., 1975; Mason and Chisholm, 1975; Dawes, 1978; Jenkins, 1978).

LEUCOCYTES --- The leucocytes present in oral fluid are mainly polymorphonuclear neutrophils with a few lymphocytes and basophils. They are found in the oral fluid of subjects with natural teeth but not in that from edentulous infants or adults. Access to the oral cavity is gained by diapedesis through the walls of the gingival vessels, which in most subjects with mildly inflamed tissues are dilated, enhancing permeability (Ferguson, D.B., 1985).

REVIEW OF THE LITERATURE

ON THE EFFECTS OF ANTIHYPERTENSIVE MEDICATIONS

ON THE FLOW AND COMPOSITION OF SALIVA

Most of the studies on antihypertensive medications refer to just one or two drugs and to their effects primarily on blood pressure. Many of them mention the inhibition of salivary flow as a side effect, based on patients' complaints (Parvinen et al, 1984; Materson, 1986; Laurikainen et al, 1988).

Clonidine, a centrally-acting, antihypertensive drug, produces a decrease in salivary flow and may cause severe dryness of the mouth (Rand et al, 1969; Green et al, 1979). In a study by Conolly et al (1972), 12 out of 13 patients taking clonidine and 8 out of 13 patients taking methyldopa, a somewhat similar drug, developed dry mouth. Not only was dry mouth more commonly observed with clonidine but, in general, it was also more severe. Other trials in which clonidine was used alone or in which it was compared with an established drug, such as, guanethidine or methyldopa, have yielded similar results (Amer et al, 1970; Mroczek et al, 1972; Putzeys and Hoobler, 1972; Dollery and Reid, 1982). In some cases, dryness of the mouth was severe enough to interfere with normal talking and eating. The inhibition centrally of salivation is due to an action on alpha-adrenoreceptors. Clonidine apparently exerts a dual effect on salivary secretion: at high doses it can actually increase salivation through activation of alpha-1 adrenoreceptors, whereas at lower doses activation of alpha-2 adrenoreceptors inhibits secretion (Dollery et al, 1976; Kaniucki et al, 1984; Kaniucki et al, 1986).

Dryness of the mouth produced by methyldopa is more common than is generally realized. By analogy with clonidine this is also believed to be central in origin. It is a more persistent side effect than sedation (Conolly et al, 1972). Two other centrally-acting antihypertensives, guanabenz and guanfacine, markedly inhibit the secretory responses induced by epinephrine.

The peripherally-acting antihypertensive, reserpine, also inhibits salivary flow and the dryness of the oral mucosa produced by reserpine is most likely due to a central inhibition of cholinergic secretory tone (Rand and Juverics, 1977). In the study of Bogdanski et al (1961), however, reserpine elicited salivation until six hours after administration to dogs, after which there was complete dryness of the mouth. This was found not to be due to exhaustion of the glands ability to secrete saliva because pilocarpine was able to stimulate production of saliva. Guanethidine, another peripherally-acting hypotensive, was also found to reduce salivary secretion (Eccher et al, 1977).

The diuretic furosemide produced significant reductions in Na^+, K^+ and Cl^- concentrations and a marked increase in Ca^{++} concentration. These effects on salivary concentrations were attributed to direct effects of furosemide on salivary acinar cells. Wright et al (1986), however, observed that furosemide did not affect salivary secretion rate and composition at a concentration of $10^{-3}M$ in the blood. They also studied ouabain, amiloride, monensin and methazolamide, in sodium-depleted sheep and found that only amiloride affected salivary composition and only it gained access to luminal epithelium at concentrations within one-tenth of parotid arterial concentration.

MATERIALS AND METHODS

Subjects were obtained from the patient pool of Loyola University School of Dentistry Clinic. Patient charts were reviewed and subjects selected based upon the patients' histories in regard to a diagnosis of hypertension, and other considerations; namely, age 20-77 years, male or female and no other major disease. Subjects were categorized according to their medications, and the following groups were chosen for the study in order to determine whether or not diuretics alone or in combination with other medications modify salivary flow and composition:

Group 1:   Control (healthy individuals not taking any medications).

Group 2:   Diuretics.

Group 3:   Diuretics in addition to Beta Blockers, Calcium-Channel Blockers and/or Vasodilators.

Group 4:   Beta Blockers in addition to Calcium-Channel Blockers and/or Vasodilators.

The screened patients that fulfilled the above characteristics were asked to volunteer for the project. Between 13-16 subjects were obtained for each category. See Table I.

The patients were asked to chew vigorously on a stick of paraffin for 5 minutes. They were seated with their elbows resting on a table and with slight forward inclination of their heads. Saliva was collected by periodically spitting directly into a tube as often as needed. Collection time was either at 9 AM or at 1 PM.

The saliva was measured for determination of flow rate, and then samples were frozen and later analyzed for osmolarity, and Na^+, K^+ and Ca^{++} concentrations. Osmolarity was determined by the freezing-point depression method (Advanced Instruments Osmometer, Model 3W). The concentrations of the ions were determined by Loyola University Hospital Clinical Laboratories automatized equipment.

Analysis of variance was the statistical method used to compare the different groups in regard to volume, osmolarity, sodium, potassium and calcium. If any difference was found, the Student-Newman-Keuls test was used to assess the difference.

Table I: Experimental Groups				
Group	N	N'	Medications
1	13		None
2	16		Diuretic only
3	15	7	Diuretic + Beta-Blocker
		3	Diuretic + Ca-Channel Blocker
		5	Diuretic + Vasodilator
4	13	7	Beta-Blocker only
		5	Ca-Channel Blocker only
		1	Beta-Blocker + Ca-Channel Blocker

From the 1179 active charts from the dental school that were screened, 176 patients (102 females, 74 males) had a history of high blood pressure and were taking antihypertensive medications. According to their medications, the subjects were classified into 15 groups, 3 of which were selected for this study, as previously indicated. Fifty-seven patients agreed to participate in the study, 35 males and 22 females. Their ages ranged from 20 to 77 years, with a mean of 58 years. Thirteen were healthy individuals, taking no medications, and will be referred to as Group 1, or Controls; the remaining 44 were divided into the three experimental groups (Table I). Group 2 consisted of 16 patients on diuretics. Group 3 included 15 patients taking diuretics and other medications: 7 on diuretics and beta-blockers, 3 on diuretics and calcium-channel blockers, and 5 on diuretics and vasodilators. Group 4 included 13 patients on antihypertensive medications, but no diuretics: 7 on beta-blockers, 5 on calcium-channel blockers, and 1 on both a beta-blocker and a calcium-channel blocker.

All patients were asked if they felt their mouth was dry; none of the 57 patients and controls had a significant complaint of dryness.

The volume of saliva ranged in Group 1 from 0.30 to 3.12 ml/min, with a mean of 1.6 ml/min and a SD of 0.99. In Group 2 it ranged from 0.12 to 3.0 ml/min with a mean of 1.11 ml/min and a SD of 0.77. Group 3 patients produced between 0.34 and 2.4 ml/min with a mean of 1.06 ml/min and a SD of 0.72. The volume in Group 4 ranged from 0.26 to 2.7 ml/min with a mean of 0.97 ml/min and a SD of 0.70. Although there were no statistically significant differences, there was a tendency for the volumes to be decreased in the medicated hypertensive patients when compared to the controls.

The osmolarity values in Group 1 ranged between 62 and 113 mOsm/Kg with a mean of 86.33 mOsm/Kg and a SD of 17.91. In Group 2 it ranged from 56 to 127 mOsm/Kg with a mean

Table II: Volume Flow of Saliva, ml/min

Group	N	Minimum	Maximum	Mean	Standard Deviation	Significant Differences*
1	13	0.30	3.12	1.60	0.99	
2	16	0.12	3.00	1.11	0.77	
3	15	0.34	2.40	1.06	0.72	
4	13	0.26	2.70	0.97	0.70	

* Significant Differences were tested for by the least significant difference calculated with one-way analysis of variance, using 5% level.

Table III: Osmolarity of Saliva, mOs/Kg

Group	N	Minimum	Maximum	Mean	Standard Deviation	Significant Differences*
1	12	62	113	86.3	17.9	
2	14	56	127	86.2	22.0	
3	15	51	118	72.7	18.2	
4	12	58	110	79.6	13.6	

* Significant Differences were tested for by the least significant difference calculated with one-way analysis of variance, using 5% level.

Table IV: Sodium Concentration of Saliva, mM/L

Group	N	Minimum	Maximum	Mean	Standard Deviation	Significant Differences*
1	13	5.0	21.5	13.12	5.97	
2	16	4.0	31.0	14.25	8.80	From 3
3	15	4.0	16.0	6.60	3.02	From 1,2
4	13	5.0	20.0	9.31	4.28	

* Significant Differences were tested for by the least significant difference calculated with one-way analysis of variance, using 5% level.

Table V: Potassium Concentration of Saliva, mM/L

Group	N	Minimum	Maximum	Mean	Standard Deviation	Significant Differences*
1	13	9.1	32.0	20.75	5.87	
2	15	16.4	37.1	25.26	5.95	
3	14	18.4	37.0	24.76	5.64	
4	13	11.9	30.4	21.72	5.09	

* Significant Differences were tested for by the least significant difference calculated with one-way analysis of variance, using 5% level.

Table VI: Calcium Concentration of Saliva, mg/dL

Group	N	Minimum	Maximum	Mean	Standard Deviation	Significant Differences*
1	13	1.1	5.0	2.28	1.07	
2	15	0.9	2.3	1.61	0.42	From 1
3	15	0.7	2.1	1.44	0.35	From 1
4	13	1.1	3.5	2.07	0.76	

* Significant Differences were tested for by the least significant difference calculated with one-way analysis of variance, using 5% level.

of 86.21 mOsm/kg and a SD of 21.95. The minimum osmolarity in Group 3 was 51 and the maximum value was 118 mOsm/Kg, with a mean of 72.66 mOsm/kg and a SD of 18.21. Salivas from Group 4 patients had osmolarities that varied between 58 and 110 mOsm/Kg, with a mean of 79.58 mOsm/Kg and a SD of 13.61. During the analysis of these results 4 subjects were dropped as outliers: 1 in Group 1, 2 in Group 2, and 1 in Group 4. Their values were 3 SD's or more from the means of their group. No statistical differences were found between the groups when outliers were included or excluded. However, as a group, patients taking medications other than diuretics, had lower osmolarities than those taking only diuretics or the controls.

The results regarding the variable Na^+ were as follows: Group 1 patient's had a minimum value of 5 mM/L, a maximum of 21.5 mM/L, and a mean of 13.11 mM/L with a SD of 5.97. In Group 2, Na^+ varied between 4 and 31 mM/L, with a mean of 14.25 mM/L and a SD of 8.80. Group 3's salivas had a minimum value of 4 and a maximum of 16 mM/L, with a mean of 6.6 mM/L and a SD of 3.02. The minimum Na^+ in Group 4 was 5 mM/L, the maximum was 20 and the mean was 9.31 mM/L with a SD of 4.28. There were statistically significant differences between Groups 1 and 3 and Groups 2 and 3. These indicate differences between patients taking medications other than diuretics with or without diuretics, and those taking diuretics alone or the controls.

The K^+ variable in Group 1, had a minimum value of 9.10 mM/L and a maximum of 32.00 with a mean of 20.75 mM/L and a SD of 5.87. In Group 2 it varied from 16.40 to 37.10 mM/L, with a mean of 25.26 mM/L and a SD of 5.95. Group 3 had a minimum K^+ value of 18.40 mM/L, a maximum of 37.00 and a mean of 24.76 mM/L with a SD of 5.64. Potassium in Group 4 had a minimum value of 11.90 mM/L, a maximum of 30.40, and a mean of 21.72 mM/L with a SD of 5.09. There were no statistical differences for this variable between groups, but as with sodium, a slight increase in the concentration of K^+ was found in the patients taking diuretics when compared to the patients taking other medications or the controls. Two subjects were dropped as outliers: 1 in Group 2, and 1 in Group 3.

The results regarding the variable Ca^{++} were as follows: Group 1 had a minimum value of

1.10 mg/dL, a maximum value of 5.00, with a mean of 2.28 mg/dL and a SD of 1.07. Group 2 varied from 0.90 to 2.30 mg/dL, with a mean of 1.61 mg/dL and a SD of 0.42. The minimum value of Group 3 was 0.70 mg/dL, the maximum was 2.10, and the mean was 1.44 mg/dL with a SD of 0.35. In Group 4, Ca^{++} concentrations ranged from 1.10 to 3.50 mg/dL, with a mean of 2.07 mg/dL and a SD of 0.76. There were no significant differences between Groups 1 and 4, or between Groups 2, 3 or 4. Statistically significant differences were found though between Groups 1 and 2, and between Groups 1 and 3, indicating a difference between patients taking diuretics alone or in combination when compared with the controls. One subject, in Group 2 was dropped as an outlier.

DISCUSSION

Chronic use of medications that reduce salivary flow not only results in patient discomfort, but may alter taste perception and the ability to swallow a bolus as well. The latter effect can inhibit adequate food intake (Mandel and Wotman, 1976; Jenkins, 1978; Fox, 1989). In addition, the loss of the protective components of saliva can result in a rapid and marked increase in dental caries (Mandel, 1974; 1989). Such side effects are not to be taken lightly. Salivary flow rate should be monitored to objectively quantitate the degree of decrement. If the flow is decreased more than 50%, then alternate medication should be considered or a protective regimen prescribed for the patient (Ferguson, M.M., 1989). Although there is considerable literature dealing with the effect of pharmacologic agents on salivary composition in animals, there are relatively few studies in humans (Mandel and Katz, 1971; Mandel et al, 1975). These studies do indicate, however, that patients' complaints of thick, ropey, viscous saliva, for instance, may have a basis in fact and should not be dismissed as neurotic. High protein and high calcium concentrations may account for the complaint (Mason et al, 1963).

In this study we wanted to evaluate antihypertensive medications, especially diuretics, on their ability to decrease salivary flow and modify ion concentrations. Initially we thought that diuretics might alter salivary flow and ion concentration due to the similarity of physiologic mechanisms at the cellular level in both the kidneys and the salivary glands.

No significant changes in volume and electrolyte concentrations were expected in patients taking beta-blockers because the physiologic effect on the salivary glands by the beta-adrenergic system has been shown to be primarily on protein concentration (Emmelin, 1987; Baum, 1987).

Ca-channel blockers might produce a change, due to the possible modification in activation potentials of the salivary gland cells, but the presence of slow-calcium channels has not been demonstrated in salivary glands (Singh et al, 1980). If they are present, the expected change would

be decreases in volume and in sodium concentration, since the expected effect would be a decrease in the frequency of activation of the cell and therefore of the sodium/potassium pump activity.

The diuretics were expected to reduce salivary flow by their blocking effect in the Na-K pump at the acinar cells level and to increase the ion concentrations and osmolarity by blocking the Na-K pump at the canalicules where cells are impermeable to water (Wright et al, 1986). There were no significant differences in volume in any of the groups, although there was a tendency in the hypertensive patients to a decrease in volume. Sodium was significantly decreased from controls in those patients taking medications other than diuretics (Groups 3 and 4), but not in those taking diuretics only (Group 2). Increased concentrations of potassium were noted in patients taking diuretics. These findings are similar to those shown by several investigators that have reported differences in salivary flow and electrolytes when patients with essential hypertension were compared to normotensive subjects. Niedemeier et al (1956) noted a reduced sodium concentration in whole saliva of hypertensive patients. Wotman et al (1967) found a significantly reduced flow rate as well as a lower sodium concentration in the parotid and submandibular saliva of their hypertensive patients. These changes were reflected in the lower Na^+ to K^+ ratio in the paraffin-stimulated whole saliva of these hypertensive patients. They suggested that the lower sodium concentrations and Na^+ to K^+ ratios in the hypertensive patients were a reflection of the increased adrenal cortical activity of many of the people studied. An alternative possibility is a reduced flow rate due to reduced blood flow through the gland resulting from generalized vasoconstriction or an impairment of the glandular vasodilation mechanism (kallikrein-kinin system). These theories are difficult to support at present because there is no proof that hypertensive subjects have an increase in suprarenal activity, and studies of isolated salivary glands in animals have failed to demonstrate modifications in the secretion rate or composition by changing the perfusion pressure in the gland (Wright et al, 1986). At this time these findings cannot be clearly explained.

Our results, by showing some differences in ionic concentrations in saliva between patients taking different drugs, also suggest that medications may indeed modify the composition of saliva. The concentration of a particular ion in saliva is determined only partially by the mechanism(s) which causes that ion to appear in saliva. The concentration of the ion in plasma or in the interstitial fluid of the gland usually has little influence because of the separate nature of the mechanism for providing the water, and hence the volume flow of saliva. Thus any substance which is lipid-soluble or small enough to cross the epithelial cell membranes will diffuse across the glandular epithelium at a rate which depends upon its concentration gradient. This rate is affected by blood flow to the extent that blood flow maintains the concentration gradient. Such substances, therefore, usually decrease in concentration in the final saliva as flow rate of saliva increases. If an ion is actively reabsorbed in the ductal system, there will be less time for this to occur, as salivary flow rate increases, and the concentration in the final saliva will increase with an increasing flow rate. Examples of this phenomenon are provided by sodium and chloride. When an ion is actively pumped into saliva, particularly if that pumping takes place in the ducts, and the ion is not actively reabsorbed in subsequent parts of the duct, increasing salivary flow rate will lead to a decrease in concentration in the final saliva. Examples of this are calcium, iodide, thiocyanate, and nitrate (Tenovuo, 1989). Therefore, sodium and chloride concentration are directly related to flow. Potassium is independent of flow in the stimulated secretion, while calcium is flow-dependent only at high flow rates (Tenovuo, 1989).

Our findings showed a decrease in Na^+ concentration in those patients taking medications other than diuretics, when taken either alone or in combination with diuretics. Different medications with different mechanisms of action make these findings difficult to explain. There are two possible explanations. The first would be that the medications modified sodium secretion in the acinus and/or reabsorption in the canalicules. This is probable in the patients taking Ca-channel blockers, but not in those patients taking vasodilators or beta-blockers, which made up more than 50% of the patients in these groups. A second possibility would call for a decrease in Na^+ concentration in

saliva from hypertensive patients independent of medications, as suggested by Niedermeier (1956), that is modified by the diuretics. The diuretics may partially inhibit the sodium-potassium pump both at the acinar cells thereby decreasing the initial volume, and at the tubular cell thereby decreasing tubular reabsorption; overall the volume might be unchanged but the concentration of Na^+ would be increased. The last proposition could also explain the mild increases (not statistically significant) noted in the concentration of potassium, since an inhibition of the Na/K pump would increase the K^+ concentration in total saliva. The decrease in salivary sodium concentration in the patients of Group 3, on multiple medications including diuretics, goes against the latter theory. Perhaps the combination of medications somehow inhibits the direct effect of the diuretics in the salivary gland, or a totally different explanation must be considered.

As stated previously, a decrease in calcium concentration should correspond to an increase in volume flow. This is not the case in our findings, where the volume was slightly decreased in patients taking diuretics when compared with normals or maintained when compared with hypertensive patients not taking them. Such findings suggest a modification of the active excretion of calcium in the canalicules or an absorption of intact saliva in the distal aspects of the conducts in an otherwise stimulated gland. The fact that flow is similar in all groups of hypertensive patients suggest that the latter is not correct. Therefore, our findings suggest that hypertensive individuals may have modifications in their salivary physiology, with a possible decreased volume that was not statistically significant, and in ionic composition, and that medications actually have a role in the variation.

Diuretics appear to have a blocking effect in the Na/K pump at acinar and canalicular level as initially proposed. Effects of other medications cannot be evaluated at this time, but some of the changes observed suggest that they may affect the formation of saliva.

This study of salivary function in patients with hypertension taking different medications has many limitations. The use of whole saliva in diagnosis is limited by several factors. Whole saliva is a mixture of the parotid, submandibular, and minor gland secretions mixed with food debris,

bacteria, shed cells, leukocytes, and other particulate matter found in the oral cavity. Generally, the concentrations of ions and the volume should not be significantly altered by the presence of these non-salivary components, if their volume is insignificant. However, food debris and decaying cells may release sodium or potassium that could affect the concentrations of these ions. Patients rinsed their mouths before chewing in paraffin film to minimize this effect. Brushing might have decreased the load of bacteria and food particles better, but would have increased endogenous cellular debris. Catheterization of the major salivary glands' ducts would have avoided contamination, but would have markedly complicated the protocol. Canalization of one major salivary gland could give a better assessment of its flow, but would not consider minor salivary gland production, which form a significant part of whole saliva (Mandel, 1980). Further, the discomfort and risks due to cannulation would have deterred many patients from participation. The technique to measure volume might not have been adequate because, even though the patients were asked to spit before chewing the paraffin film, it was impossible to assure that they had adequately emptied their mouth (Mandel, 1980; Tenouvo, 1989).

Our idea was to measure stimulated salivary flow. There are many techniques to cause stimulation. Chewing provides an adequate stimulus, but we could not standardize its intensity. Further, it is impossible to assure that we were collecting all the saliva present in the mouth after chewing.

We measured Ca^{++}, Na^+ and K^+. Measurement of additional ions, like chloride and bicarbonate, would have given a more complete picture of glandular and tubular functioning.

The physiological relevance of ionic composition of saliva is unknown. Concentrations of other salivary components, such as, enzymes and sugars, may be more important from the clinical point of view since they modify the microbiologic milieu and alimentary function (Dawes, 1978). Changes in these components may also be caused by medications. A future study may be designed to address this point.

Although 176 patients on antihypertensive medications were identified, the number of

volunteers was too small to make homogeneous groups of adequate size for proper statistical evaluation. The formation of groups was artificial, including putting diuretics with slightly different mechanisms of action together, and medications like beta-blockers, Ca-channel-blockers and vasodilators in the same groups. The use of these groups make generalization of the results obtained difficult. A larger group of patients would be needed to confirm differences and evaluate possible causes.

SUMMARY

Antihypertensive medications are some of the most commonly prescribed drugs. There is minimal information available on the oral effects of medications other than alpha-adrenergic drugs. We enrolled hypertensive patients attending the dental clinic of Loyola University of Chicago in a study directed at evaluating the effects of diuretics alone and in combination with other medications on salivary flow and composition. Fifty-seven subjects were divided into four groups: one of normal healthy controls not taking antihypertensive medications, one of patients taking only diuretics, one of patients taking diuretics in combination with other medications and one of patients taking antihypertensive medications exclusive of diuretics. Patients taking centrally-acting, alpha-adrenergic medications were excluded. Our findings demonstrated no significant differences in salivary flow between the groups, but a tendency toward decreased flow was noted in hypertensive patients, in general. Potassium concentration was increased and calcium was decreased in the group of patients taking diuretics (Group 2), suggesting a direct effect of these medications in the salivary gland. The marked decrease in sodium in patients taking diuretics in combination (Group 3) is difficult to explain, and suggests other mechanisms of action. Our findings suggest that antihypertensive medications other than centrally-acting, alpha- adrenergic medications do not cause dry mouth but do cause some modifications in the ionic concentrations of saliva.

REFERENCES

Amer, A., M. Verstraete, H. Bossaert and K.G. Verstreken. Hypotensive action and side effects of clonidine chlorthalidone and methyldopa-chlorthalidone in treatment of hypertension. Brit. Med. J. 2:392-5, 1970.

Baum, B.J. Neurotransmitter control of secretion. J. Dent. Res. 66(Special Issue):628-32, 1987.

Bogdanski, D.F., F. Sulser and B.B. Brodie. Comparative action of reserpine, tetrabenazine, and chlorpromazine on central parasympathetic activity: Effects on pupillary size and lacrimation in rabbit and on salivation in dog. J. Pharmacol. Exp. Ther. 132:176-82, 1961.

Chobanian, A.V. Antihypertensive therapy in evolution. N. Engl. J. Med. 314:1701-2, 1986.

Conolly, M.E., R.H. Briant, C.F. George and C.T. Dollery. A crossover comparison of clonidine and methyldopa in hypertension. Eur. J. Clin. Pharmacol. 4:222-7, 1972.

Dawes, C. The chemistry and physiology of saliva. In: Textbook of Oral Biology. Shaw J.H., E.A. Sweeney, C.C. Cappuccino and S.M. Meller. Chapter 18:593-616. W.B. Saunders Company, 1978.

Dollery, C.T., D.S. Davies, G.H. Draffan, H.J. Dargie, C.R. Dean, D. Phil, J.L. Reid, R.A. Clare, and S. Murray. Clinical pharmacology and pharmacokinetics of clonidine. Clin. Pharmacol. Ther. 19(1):11-7, 1976.

Dollery, C.T. and J.L. Reid. Double-blind comparison of the hypotensive sedative and salivary flow effects of lofexidine and clonidine in normal subjects. Arzneimittelforschung 32(8A):984-7, 1982.

Eccher, S., C. Dodson, D.O. Quissell, and J.R. Martinez. Submaxillary secretion in rats treated with guanethidine. Eur. J. Pharmacol. 41(2):113-21, 1977.

Emmelin, N: Actions of kinins on salivary myoepithelial cells. J. Physiol. 207:539-41, 1970.

Emmelin, N. Nerve interactions in salivary glands. J. Dent. Res. 66(2):509-17, 1987.

Ferguson, D.B. Salivary glands and saliva. In: Applied Physiology of the Mouth. Chapter 7, pp. 145-79, John Wright & Sons Ltd. 1975.

Ferguson, M.M. Management of patients with xerostomia. Compen. Contin. Educ. Dent. Suppl. 13:470-75, 1989.

Fox, P.C. Saliva composition and its importance in dental health. Compend. Contin. Educ. Dent. Suppl. 13:457-60, 1989.

Gerber S.G. and A.S. Nies. Antihypertensive agents and the drug therapy of hypertension. In: Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 8th edition. Eds: A.G. Gilman, T.W. Rall, A.S. Nies, P. Taylor. pp.784-813, Pergamon Press, New York, 1990.

Green, G.J., H. Wilson and M.S. Yates. The effect of clonidine on centrally and peripherally evoked submaxillary salivation. European J. Pharmacol. 53:297-300, 1979.

Izutsu, K.T. Physiological aspects of salivary gland function. Compend. Contin. Educ. Dent. Suppl.13:450-56, 1989.

Jenkins, G.N. Saliva. In: The Physiology and Biochemistry of the Mouth. 4th edition. pp. 284-359. Blackwell Scientific Publications, 1978.

Joint National Committee: The 1984 Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Arch. Intern. Med. 144:1045-57, 1984.

Kaniucki, M.D., F.J.E. Stefano and C.J. Perec. Clonidine inhibits salivary secretion by activation of postsynaptic alpha 2 receptors. Naunyn Schmiedeberg's Archives of Pharmacology. 329(3);289-92, 1984.

Kaniucki, M.D., C.J. Perec and F.J.E. Stefano. Blockade of postsynaptic alpha 2 adrenoceptors enhances responses to mixed alpha 1, alpha 2 agonists in rat submaxillary gland. European J. Pharmacol. 121(2):245-9, 1986.

Laurikainen, K., E. Laurikainen, J. Tenovuo, T. Kaila, and P. Vilja. Effects of a B-Blocking agent, timolol maleate, on saliva in healthy volunteers. Scand. J. Dent. Res. 96:121-7, 1988.

Mandel, I.D. Saliva. In: Orban's Periodontics, Grant, D., Stern, I., and Everett, F. C.V. Mosby, 1972.

Mandel, I.D. Relation of saliva and plaque to caries. J.Dent. Res. 53:246-50, 1974.

Mandel, I.D. and Wotman. The salivary secretions in health and disease. Oral Sci. Rev. 8:25-27, 1976.

Mandel, I.D. Human submaxillary, sublingual, and parotid glycoproteins and enamel pellicle, In: The Glycoproteins, Horowitz M., Pigman, W. (eds.). Academic Press, New York, 1977.

Mandel, I.D. Sialochemistry in diseases and clinical situations affecting salivary glands. CRC Crit. Rev. Clin. Lab. Sci.. 12(4):321-66, 1980.

Mandel, I.D. Impact of saliva on dental caries. Compend. Contin. Educ. Dent. Suppl. 13:476-81, 1989.

Mandel, I.D. and R. Katz. Effect of pilocarpine and a beta adrenergic blocking agent on human saliva. Pharmacol. Ther. Dent. 1:71-6, 1971.

Mandel, I.D., A.N. Zengo, R. Katz and S. Wotman. Effect of adrenergic agents on salivary composition. J. Dent. Res. 54:B27-29, 1975.

Mason D.K. and D.M. Chisholm. Histology and histochemistry. In: Salivary Glands in Health and Disease. pp 18-36. W.B. Saunders Co., 1975.

Mason, D.K., R.McG Harden and W.D. Alexander. The salivary and thyroid glands. Br. Dent. J. 122:485-97, 1963.

Materson, B.J. Adverse effects of antihypertensive treatment. Cardiology Clinics. 4:105-15, 1986.

Mroczek, W.J., B.A. Leibel and F.A. Finnerty. Comparison of clonidine and methyldopa in hypertensive patients receiving a diuretic. Amer. J. Cardiol. 29:712-7, 1972.

Niedermeier, W., S. Dreizen, R.E. Stone and T.D. Spies. Sodium and potassium concentrations in the saliva of normotensive and hypertensive subjects. Oral Surg. Oral Med. Oral Pathol. 9:426-30, 1956.

Parvinen, T., I. Parvinen and M. Larmas. Stimulated salivary flow rate, pH and lactobacillus and yeast concentration in medicated persons. Scand. J. Dent. Res. 92:524-32, 1984.

Putzeys, M.R. and S.W. Hoobler. Comparison of clonidine and methyldopa on blood pressure and side effects in hypertensive patients. Amer. Heart. J. 83:464-8, 1972.

Rand, M.J. and H. Jurevics. Antihypertensive and peripheral side effects of reserpine. In: Gross, F. Handbook of Experimental Pharmacology: Antihypertensive Agents. pp. 110, 1977.

Rand, M.J., M. Rush and J. Wison. Some observations on the inhibition of salivation by St 155 [2-2,6-dichlorophenylamine)-2-imidazoline hydrochloride [Catapres, Catapresan]. Eur. J. Pharmacol. 5:168-72, 1969.

Singh, B.N., J.T. Collett and C.Y.C. Chew. New perspectives in the pharmacologic therapy of cardiac arrhythmias. Prog. Cardiovasc. Dis. 22:243-45, 1980.

Sreebny, L.M. Salivary flow in health and disease. Compen. Contin. Educ. Dent. Suppl. 13: 461-9, 1989.

Tandler, B. Microstructure of salivary glands. In: Rowe, N.H. (ed.). Salivary Glands and Their Secretion. Proceedings of Symposium. The University of Michigan. p. 8, 1972.

Tenovuo, J.O.: Human Saliva: Clinical, Chemistry and Microbiology. Vol I & II. CRC Press, Boca Raton, 1989.

Wotman, S., I.D. Mandel, R.H. Thompson, Jr. and J.H. Laragh. Salivary electrolytes, urea nitrogen, uric acid and salt taste thresholds in hypertension. J. Oral Ther. Pharmacol. 3:239-43, 1967.

Wright, R.D., J.R. Blair-West and J.F. Nelson. Effects of ouabain, amiloride, monensin and other agents on ovine parotid secretion. Am. J. Physiol. 250(3 pt 2):F503-10, 1986.

VITA

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APPROVAL SHEET

The thesis submitted by Ivette Martínez-Plata, DDS has been read and approved by the following committee:

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

The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Science in Oral Biology.

May 6, 1993
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