CONGENITAL XEROSTOMIA AND ASSOCIATED ANOMALIES: A PROPOSED MODE OF INHERITANCE

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ABSTRACT

Congenital xerostomia has been reported to occur as an isolated entity, in conjunction with lacrimal dysfunction, and in various ectodermal dysplasia syndromes. A child with congenital xerostomia, congenital epiphora and hypoplastic thumbs is presented in this report. Examination and family pedigree suggest that the etiology of his xerostomia may be due to atresia of his parotid and submandibular ducts, and that these duct abnormalities may be due to variable expression of an autosomal dominant gene which manifests primarily in lacrimal duct obstructions resulting in congenital epiphora. Lacrimal secretion deficiency may also be manifest. The pedigree intimates that other organ systems may be influenced by the trait.

INTRODUCTION

Local or systemic disorders affecting the salivary glands may produce a dryness of the mouth, termed xerostomia. In the adult, these disorders may include acute or chronic inflammatory processes due to obstructions or infections, atrophic changes due to radiation or aging, neoplasms, neurogenic factors or a disease, such as, diabetes mellitus. In the pediatric age group, the etiology may include vitamin and iron deficiencies, endocrine disorders and an agenesis or hypoplasia of the salivary glands.[36] Anomalous development suggests a dysfunction in morphogenesis induced by environmental or genetic factors and could produce congenital xerostomia.

Pediatric xerostomia has been reported to be both a sporadic and an inheritable condition, which has occurred as an isolated entity, in association with lacrimal dysfunctions, and in syndromes affecting primarily the ectodermally derived structures. It is the purpose of this report to present a case of congenital xerostomia due to apparent atresias of the parotid and submandibular ducts and to substantiate an autosomal dominant mode of inheritance for the atresias. Associated anomalies will be delineated, and an explanation of the embryonic origin of the defects will be advanced.

REVIEW OF THE LITERATURE

The following reports emphasize some of the associated physical features found in individuals with congenital xerostomia.

In one of the earliest reports, Bradbury[7] delineated the secondary signs of xerostomia. The twenty four year old male subject of his report had "broken down" teeth, labored speech, a reluctance to ingest solid foods and a fissuring of the dorsal aspect of the tongue.

Ramsey[43] depicted a father to daughter transmission of a condition he termed "congenital absence of the salivary glands". The girl, whose teeth were "discolored" and malposed, had no secretions whatsoever, and was the only sib of five affected.

While categorizing cases and causes of xerostomia, Faber[23,24] mentioned a thirteen year old male who had "congenital aplasia of the parotid glands". He assumed glandular absence as there were no openings of Stensen's ducts. The orifices of the submandibular gland were discernible by the author. Faber stated that the boy had extremely viscous saliva, which indicated functioning of the mucosal glands. Despite the involvement of only the parotid glands, the subject had rampant dental caries. The boy also had "hypoplastic" thumbs, one of which was completely non-functional. This case report described a digital anomaly with parotid duct atresias -- two unrelated defects for which no explanation was rendered.

Suher, et. al.[53] reported a case of a six year old girl who developed xerostomia after contacting bilateral parotitis at age two and one-

half years. She had "dark" primary teeth which decayed early. A sialogram demonstrated bilateral obstructions at the base of Stensen's ducts, and a presumptive diagnosis of "congenital aplasia of the serous salivary glands" was entertained; however, no consideration was given the status of the submandibular glands. An intramuscular injection of 1/8 gr. pilocarpine produced thick mucoid saliva of which only five c.c. were collected in forty-five minutes. Additional information procured through the Child Growth Clinic at the University of Oregon Dental School on this girl revealed that she had congenitally missing second pre-molars, a history of dizziness, sparse perspiration and "blacking-out" in warm weather. She eventually manifested allergic tendencies, and experienced "asthmatic" episodes. An axillary biopsy showed that the sweat glands were "less numerous than normal", but no definite association with ectodermal dysplasia could be made. A daughter inherited the salivary defect with the signs of xerostomia, including atypical demineralization, and black staining of her teeth.

Parotid and submandibular duct atresias were found in a fifteen year old male by Wood and Mitchell.[68] They noted that the scant saliva present in the oral cavity seemed to emanate from the accessory glands of the palate and buccal mucosa. Partial anodontia and unique tooth morphology were co-incidental abnormalities which prompted consideration of ectodermal dysplasia in the differential diagnoses. These authors suggested that surgical exploration would have been the most valid mechanism by which to secure an accurate diagnosis of the anatomic defect.

The preceding five reviews have shown that xerostomia can be inher-

ited, that it occurs in both males and females, and the atresia of the parotid ducts can cause xerostomia. The following reports indicate a relationship between xerostomia and a deficiency of lacrimal secretions.

A sixteen month old male child who had normal openings for Stensen's ducts, but scanty, thick mucoid oral secretions was reported by Cove-Smith.[18] The child had never teared upon crying and was the only one in his family so affected.

In contrast, Sharp[49] presented a case of an eight year old boy who also never teared, but whose orifices for the parotid ducts and one submandibular duct were atretic. Pilocarpine (1/2 gram) induced lacrimation, but not salivation even though the submandibular gland became "palpable". There was no family history of either the oral or ocular findings.

A deficiency of lacrimation was an associated finding in a male subject studied by Steggerda[52] while quantitating water intake in humans. This individual had a "complete absence of all salivary glands and ducts". No perceptable response was observed with pilocarpine except for an increase in mucoid secretions from the buccal and lingual accessory glands.

A female of short stature with a life-time deficiency of tears and saliva was reported by Mutch.[38] Despite her "dry eyes", she had no ocular pathology. The author estimated her saliva volume as 2 c.c. in three hours of chewing paraffin.

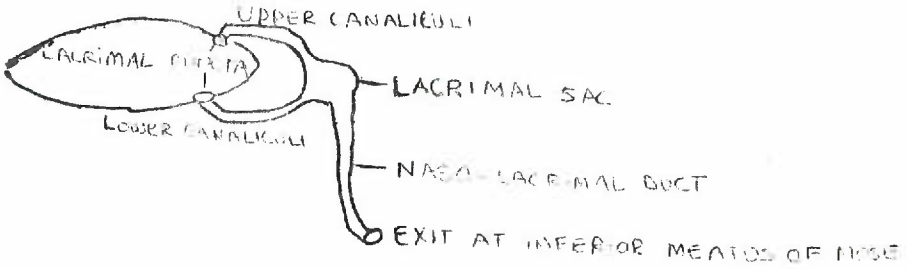
Hughes and Syrop[31] annotated a family with a trait of "dry mouth" in nine individuals over three generations. Seven individuals were examined, and found to be lacking the orifice of Stensen's duct. Two of the seven examined had an "absence or dysfunction" of the lacrimal glands.

Xerostomia has been reported to be a feature of Sjogren's (sicca) syndrome,[36,64] which is characterized by dry mucous membranes of the oral cavity, pharynx, larynx, nose and conjunctiva and chronic rheumatoid arthiritis. This syndrome affected primarily post-menopausal women in one study.[3] The etiology of the xerostomia is a glandular cell atrophy due to a chronic inflammatory process which can obstruct the excretory ducts of the glands. Coverdale[17] demonstrated that transmission of the syndrome from parent to child is possible, and that xerophthalmia can occur in infancy. An enlargement of the hands and feet upon manipulation and sparse perspiration were interesting findings in the patient with congenital dry eyes.

Chamberlain[13] documented a woman who experienced xerostomia at the age of twenty-five after an appendectomy, and over the next ten years, developed vision, hearing and sweating problems. She eventually became arthiritic. In this case, xerostomia preceded and forewarned of future glandular and inflammatory problems. Sjogren's syndrome may affect the sweat apparatus, the mucosal glands of the upper respiratory tract, serous salivary and lacrimal glands as well as joint capsules.

The preceding seven reports have implied that hypoplasia of lacrimal gland tissue may be assoicated with xerostomia. Alacrima is considered extremely rare,[20] because of the embryologic origin of the lacrimal glands from the conjunctival epithelium. Hence, decreased lacrimation entails either a hypoplasia of the glandular components, a decrease in number of ducts for the lacrimal secretions or a neurogenic disorder.

Atresias and stenoses of the lacrimal drainage passageways manifest by excessive tearing (epiphora), and convey the impression of hypersecretion of the lacrimal glands. The lacrimal drainage obstructions occur most frequently in the naso-lacrimal duct, and less frequently at the lacrimal puncta and/or in the canaliculi.



In a child with persistant epiphora the eyelids will tend to mat together, and infection can develop secondary to stasis.[14,15] The comments on the duct network which removes the lacrimal fluid are made to introduce the next series of reports, in which congenital xerostomia is found associated with a variety of obstructions of the lacrimal drainage system.

Blackmar[5] reported an eleven year old boy with congenital absence of his superior and inferior puncta bilaterally. There was no associated epiphora. He had parotid duct atresia, and discolored teeth, "almost destroyed by caries". His lungs were "emphysematous" secondary to asthma. This author claimed that the "low potential of the duct system" accounted for the failure of the ducts to canalize, or hollow out, at the appropriate morphological time.

Describing the effects of "hypofunction of the salivary glands" upon a young female's dentition, Losch and Weisberger[35] noted "constantly tearful" eyes due to an apparent agenesis of the tear ducts. They ruled out

ectodermal dysplasia and nutritional deficiencies, but offered no alternative explanation for the two abnormalities.

Congenital dysfunction of the salivary glands was attributed to embryologic failure in development by Zaus and Teuscher[70] in three cases of xerostomia for which they could find no therapeutic resolution. A lack of tear ducts was noted to be an associated defect in their cases.

An inheritance pattern of tear duct obstructions has been substantiated to be autosomal dominant with variable expression and penetrance.[21,25] Different anatomic locations of the obstructions might dictate clinical severity of the problem, and hence, be a variable expression of the trait. Woywitka[69] demonstrated an autosomal dominant mode of inheritance with one-hundred percent penetrance for atresia of the naso-lacrimal ducts for nine individuals over four generations. This problem had lead to dacryostenosis (inflammation of the tear sac), persistent tearing and periodic conjunctivitis. One affected child had a digit anomaly of his fifth finger.

Town[58] illustrated the variability of anatomic obstructions in a pedigree in which the affected father had absent upper puncta, one son had atretic lower puncta, and the other son had absence of the upper and lower puncta in just one eye. Xerostomia was not an apparent problem in the preceding two reports.

Xerostomia and lacrimal dysfunctions have been reported in several of the ectodermal dysplasia syndromes. Recent reviews by Witkop, C. et. al.[67] and Giansanti, J. et. al.[27] have summarized the variable expressions of the syndromes, which may involve organ systems developed from the mesoderm

and endoderm as well as the ectoderm. Atropic or hypoplastic changes in the salivary and lacrimal glands should be considered in children with ectodermal dysplasia.[11]

Decreased mucosal secretions from the glands of the respiratory tract has been reported with ectodermal dysplasia.[1,44,59] DeJager[19] documented a family pedigree of "congenital ectodermal dysplasia" in which two male sibs died of bronchial pneumonia at an early age. He emphasized two points. First, the endodermal derivation of the epithelium of the respiratory tract demonstrated that the defect is not confined to the "ectoderm". Second, the lack of secretions in these individuals may have predisposed the children to the pulmonary infections. An autopsy revealed "fatty tissue" in the area of the submandibular gland in one of the sibs, but the other salivary glands were not investigated.

An eight year old male with bronchial asthma of six years duration, anhidrotic ectodermal dysplasia and a deficiency of saliva with dry oral mucosa was reported by Everett, F. et. al.[22] Lacrimal secretions were "normal". The authors discussed the blurred border between anhidrotic and hidrotic ectodermal dysplasias claiming that over one hundred varieties of the syndrome existed. A complete absence of the esophogeal and mucoserous respiratory glands was reported in a male child who had ectodermal dysplasia and bronchial asthma by Reed, W. et. al.[45] They expressed the concern that an individual deficient in mucous secretions is prone to more frequent and severe infections. They also intimated that oral dryness with hoarseness and dysplasia could result from

a mucous deficiency; however, the mucous glands of the oral cavity contribute less than ten percent of the total salivary volume.[50] Xerostomia could not result from involvement of just the mucosal glands.

Parotid duct atresias were reported in two of seven children with ectodermal dysplasia by Vanselow.[61] These two were part of a study which proved an increased prevalence of allergic disorders in ectodermal dysplasia. He speculated that epithelial hypoplasia may increase the permeability of that layer of allergens, and facilitate contact with the plasma cells of the submucosal layer to stimulate antibody production. The speculation of epithelial hypoplasia was not related to the obliteration of Stensen's ducts.

The preceding reports illustrate that the serous and mucous glands of the oral cavity and respiratory tract can be affected. Taste bud atrophy with decreased salivation has also been reported with ectodermal dysplasia.[16] Respiratory, nasal and dermatologic allergies have predominated as complications of these "ectodermal" syndromes.

Ocular pathologic sequelae have also been reported with the ectodermal syndromes. A combination of xerostomia, asthma, epithora and photophobia characterized three cases of hypohidrotic ectodermal dysplasia offered by Bartlett, R. et. al.[1] A five year old male with the same diagnosis was reported by Summit and Hiatt[54] to have photophobia, corneal opacities, aplasia of the lower lacrimal puncta as well as severe dental decay, ear anomalies and clefting.

Corneal drying, photophobia and "hypoplastic" mucous membranes were the primary features in a thirteen year old girl with ectodermal

dysplasia documented by Wilson.[66] In contrast a teenage girl with atretic lacrimal puncta, epiphora and "dental enamel hypoplasia" was reported in the same journal a few months later.[2] This last report mentioned that lacrimal drainage anomalies could obscure the inherent dry eye by allowing enough secretions to collect for lubrication.

Levy[34] published a combination of physical features in a twelve year old male which he termed "mesoectodermal dysplasia", because of the skeletal involvement. The ulna and radius were estimated to be an inch short, and digit anomalies consisting of hypoplasia of the first digits, and inter-digit webbing were reported. His hands and feet were compared to the "lobser-claw" deformity. The ocular disorder was limited to congenital epiphora due to bilateral absence of the lower lacrimal puncta, which was resolved by the insertion of polyethylene tubes for drainage. The mouth in this boy was always dry, and he had "dysplastic" teeth, a high, narrow palate and congenitally missing teeth. He was unable to breathe through his nose due to "blocked" nares, and his ears were dysplastic. The author believed the fundamental morphogenic defect occurred in the third or fourth month in utero and was inherited as an "irregular" autosomal dominant trait.

Children with "ectodermal dysplasia" have exhibited a number of associated anomalies, such as, ocular and lacrimal problems, a dry mouth, clefting, digit aberrations, hearing loss,[37] and a propensity to allergic disorders. Two of these anomalies and ectodermal dysplasia have been incorporated into yet another syndrome. The E.E.C. syndrome (ectrodactyly or split hand and/or foot, ectodermal dysplasia and cleft lip and/or

palate) has been attributed to Rudiger, R. et. al.[46] who described these features in a three year old female. Variable expression was evident in this girl as she had absent lower puncta, bilateral keratoconjunctivitis and photophobic eyes along with rhinitis and hearing loss. Xerostomia can only be implied as she had "very carious" teeth at three years old. These authors claimed that the defect, whether genetic or environmental, would have occurred in the seventh to eigth week in utero -- a period of major morphodifferentiation.

Xerostomia, cheilitis and either rampant dental caries or enamel hypoplasia were evident in six children with the E.E.C. syndrome reported by Pries, C. et. al.[41] Two of the children had bilateral absence of the opening of Stensen's ducts, and in two other patients only two ml. of saliva could be collected in one hour by the Kirby cup method. This small volume suggests either hypoplastic glandular tissue, stenosed ducts, or a combination of the two. Ocular pathology consisted of conjunctivitis with decreased lacrimation. The conjunctivitis occurred in the three children with scarring of the lacrimal puncta.

Bystrom, E., et. al.[12] established a diagnosis of E.E.C. syndrome in two teenage girls after noting hypodontia. Both girls were reported to have extremely carious teeth. The parotid duct openings in the girl, who developed corneal ulcers and vision problems, were discerned only with difficulty. A deficiency of lacrimal secretions was an etiologic factor in the ocular pathology and both girls had obstructions of the lacrimal drainage canals.

An E.E.C. pedigree reported by Brill et. al.[10] illustrated trans-

mission of the trait from an affected female to three of her four children. Only two of the four subjects had clefting which implies a variable expression of the trait. Lacrimal duct stenosis was present in all four cases. The index case of this report developed bilateral hydronephrosis at the age of two years secondary to obstruction of the utero - vesical junction and a bladder neck contracture. Renal anomalies, including duplication of a kidney and ureter,[40] and agensis of a kidney,[33] have been reported to occur with the E.E.C. syndrome.

Variable expression has been characteristic of the E.E.C. syndrome. Bixler, D. et. al.[4] documented a "less severe" form of the E.E.C. syndrome in which the "lobster-claw" defect involved only the hands. These authors suggested an integration of the lacrimal duct obstructions into the criteria for the syndrome. These obstructions have been corrected with minimal probing and irrigation,[62] but Wiegmann and Walker[65] depicted persistent tearing despite surgical intervention. These authors claimed that the defect disturbed the "differential growth and death of certain cells which provide further division of limb buds into rays, for the invagination of the epithelial buds, and the final formation of the drainage system".

Xerostomia has not been reported as a consistent feature of the E.E.C. syndrome. The indirect evidence of parotid duct atresias,[41] discolored and/or hypoplastic enamel[40] and the early loss of teeth because of rampant dental caries[12,26] strongly suggest that a decrease in saliva occurs with this syndrome.

Atretic or stenotic obstructions may imply a congenital absence

of the glandular tissue. If the obstruction occurred subsequent to maturation of the secretory elements, a swelling of the gland would be observed. Degenerative changes have resulted from salivary duct atresias. Nayak[39] found the parotid space filled with fatty areolar tissue in an autopsy case in which there were no Stensen's ducts. The presence of fatty degeneration indicated that the gland was once present. The following two reviews will report the results of animal experiments in which exocrine ducts have been obstructed.

Wallenborm, W., et. al.[63] ligated Stensen's ducts in rabbits, and compared the histologic results with parotid gland tissue that had been irradiated. The degree of atrophy of the gland was greater in the irradiated group, as only nine of twenty five rabbits demonstrated moderate atrophy after twenty weeks of ligation. Anastomoses between the parotid and submandibular glands obscured the conclusions on the results of ligation.

Complete ligation of the pancreatic duct in a group of ten dogs was carried out by Hermann, R. and David, J.[30] Histologic examination showed edematous distention of the glandular architecture with various degrees of atrophy. In a second group, partial obstruction revealed acinar fibrosis and a chronic inflammatory condition. And in a third group, intermittent obstruction showed acute inflammatory changes in the glandular tissue. They concluded the partial obstruction permitted secretory flow, but that periodic stasis predisposed the tissue to infection and a varying degrees of inflammation. Intermittant obstruction yielded the histologic picture of acute pancreatitis. The authors con-

concluded that obstructions, either complete, partial or intermittant may be important factors in the etiology of pancreatitis.

Children with xerostomia have exhibited a number of physical features, such as, rampant dental caries, susceptibility to respiratory infections, digital abnormalities, ophthahmologic complications due to lacrimal deficiencies and obstructed lacrimal ducts, and those anomalies associated with "ectodermal" syndromes. The following case presentation and pedigree will demonstrate the occurrence of all these features in a single family unit.

CASE PRESENTATION

A two and one half year old male was referred to the Pedodontic Service for evaluation of his "brown" teeth and dry mouth. The child had been seen initially in the Pediatrics Out-Patient Clinic for his behavior of retaining food in his mouth for hours after eating. Emotional factors were considered contributory, since the child was in a foster home. An otolaryngological consult considered anemia and vitamin deficiencies in the differential diagnoses. Pediatric allergy and ophthalmology services were suggested for additional consultations because of the boy's history of food allergies and asthma, and the presence of bilateral tearing.

The initial intra-oral exam confirmed the dry mouth, and no appreciable saliva could be observed. Food debris and materia alba were retained on his teeth. Dental x-rays were taken, and the mother asked to return with the boy, and half sister and father.

A medical history was obtained from the mother and the medical record. The boy was born six weeks premature from a pregnancy complicated by naseau, bleeding and various medications. Delivery was breech. Birth weight was six pounds and two ounces. A "jaundice" episode kept the boy in the hospital for a week. His mother claimed that the boy was constantly fretful and "colicky", and a milk allergy necessitated several changes in the formula. At three months, a left hydrocele and right inguinal hernia were diagnosed, and a bilateral repair was accomplished without complication. At that admission, "tearing" and conjunctivitis were noted. Developmental milestones were mildly delayed. He crawled at one year and began walking at eighteen months.

The child had several episodes of "bronchiolitis" characterized by wheezing, rhinorrhea and coughing. Tedral® was prescribed for his "asthma" at age fifteen months. He was seen for a viral upper respiratory infection at age twenty months, and noted to have a dry throat, nasal discharge and crusty eyes. He is reported to be allergic to milk, fruits, dogs, cats and house dust. Difficulty in breathing and a nasal discharge have been present since infancy. The child has had episodes of chronic constipation and cries with bowel movements. Water and dietary intake is said to be sufficient.

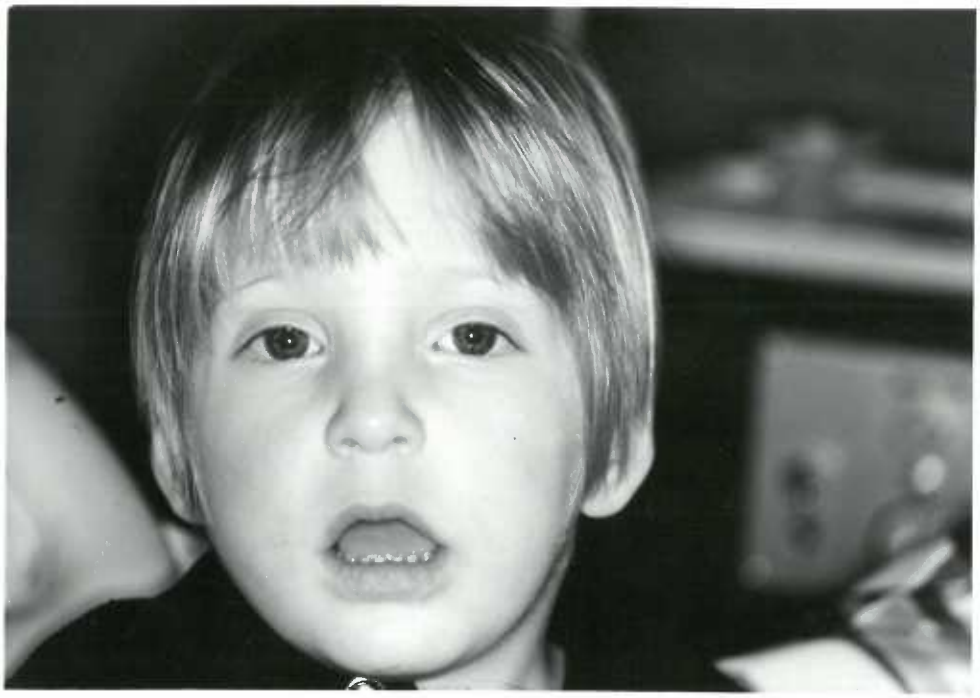
A physical examination revealed a reticent boy of normal stature for his age. No apparent musculo-skeletal, cardio vascular or neurologic abnormalities were observed, except for "small, finger like" thumbs. His hair is blond, fine in texture, but not thin. He has mild frontal bossing, sparse eyelashes, fair complexion and blue eyes. Ear shape and hearing

were within normal limits. The child breathes through his mouth. His eyes appeared watery, (see figure 1), but the mother reported that he had never teared when crying, and that she has never "teared". She also reported that his eyelids are matted together in the mornings, and have to be "bathed" apart. The crusty eyes are thought to be due to the absence of the lower lacrimal puncta bilaterally. (see figure 2). The boy's maternal uncle was reported to have no tear ducts.

An oral examination revealed dry crusty lips with cheilosis like changes at the corners of his mouth. The vestibule of the lower lip was dry with distinct, but sparse elevated mucosal glands. The buccal mucosa was dry, atrophic and rough in texture. The parotid duct orifices could not be discerned, and no secretions could be elicited upon massage. (see figure 3). The palatal mucosa seemed smooth, and somewhat hypertrophic in the glandular areas, where "beads" of mucous secretion were observed. The tongue was dry, but without fissures. The floor of the mouth was dry, and upon massage, no fluid could be expressed from the usual location of Wharton's duct opening. The scant saliva was frothy, thick and mucoid in nature.

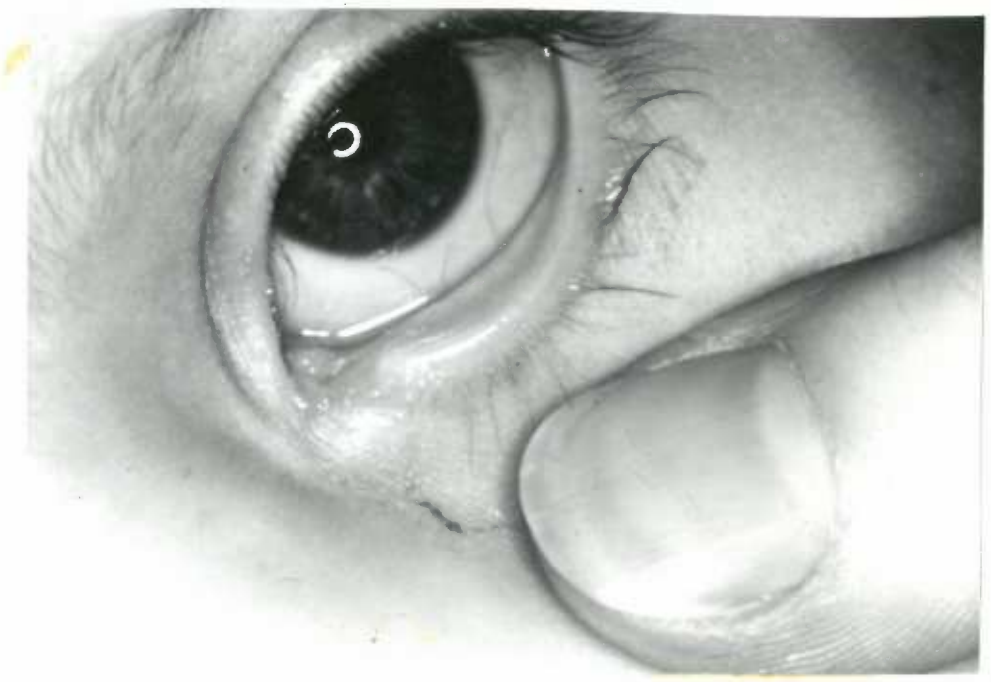
The patient had a full complement of primary teeth. Material alba was prominent on the upper molars and lower incisor teeth. A marginal gingivitis was noted about the maxillary and mandibular incisor teeth. A brown stain, observed on the buccal and facial aspects of all teeth, was most prominent on the lower lateral incisors and canines. (see figure 4). The location of the stain may be compatable with the early jaundice episode. Buccal surfaces of all first primary molars were decalcified.

FIGURE 1



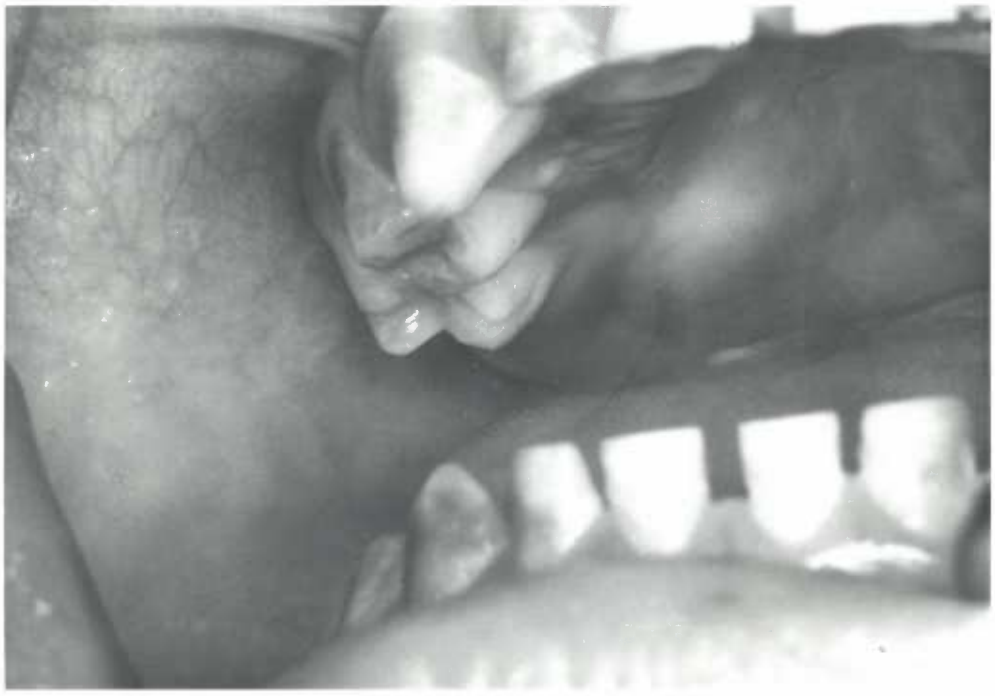
Proband breathes through his mouth. His eyes are "watery".

FIGURE 2



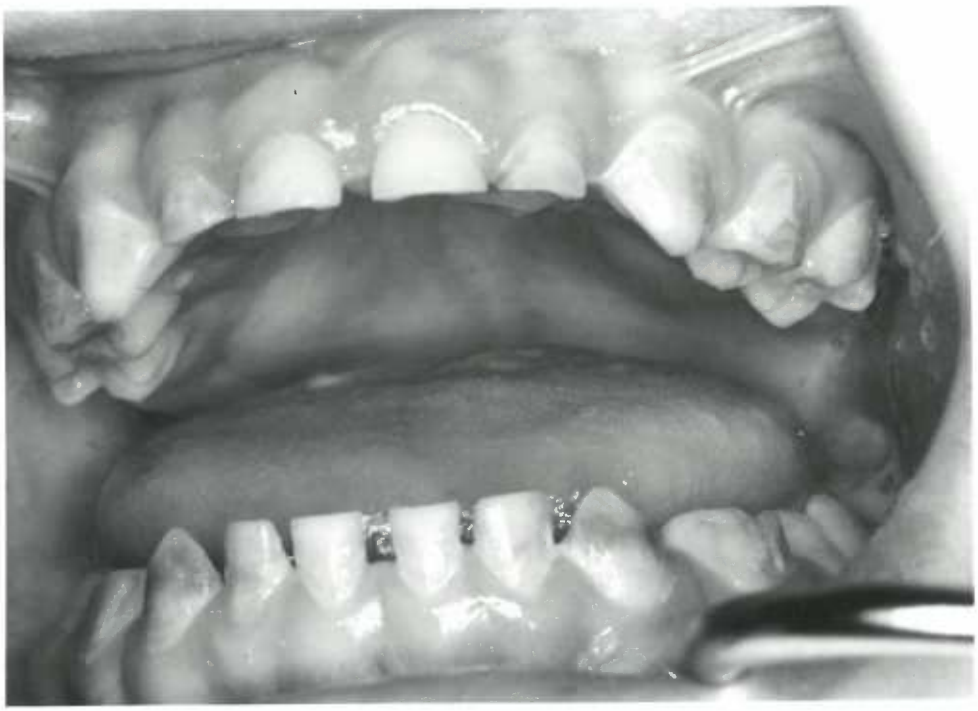
Proband's lower lacrimal puncta are absent.

FIGURE 3



Orifice of Stensen's duct could not be visualized,even after massaging the usual duct area. The absence is bilateral..

FIGURE 4



Proband has a full complement of primary teeth characterized by a brown stain and buccal decalcification of the first primary molars.

Pitting of variable severity characterized the primary canines and incisor teeth. Interproximal decay was confined to the lower anterior teeth. Radiographs demonstrated presence of permanent incisors, canines, and lower molars. Tooth and pulp canal morphology were deemed normal.

Sialographs and saliva quantification were not attempted due to the young age of the patient, and the marked anxiety expressed by the mother toward medical treatment for her son. The boy's half sister had an oral examination and was completely normal.

Dental treatment restored the first primary molars with stainless steel crowns, the occlusal surfaces of the second primary molars with silver amalgam and the lower anterior teeth with orthodontic bands. The parents were instructed in oral hygiene measures, and in the use of custom made fluoride trays. They were advised to use an acidulated fluoride phosphate gel (Kerr's Flura-gel, 0.5%) twice weekly for four minutes after cleaning the boy's teeth. Fluoride tablets (2.2 mg.) were prescribed for daily ingestion. The parents were informed that maintenance of the boy's dentition would depend on the preceding measures, and dental evaluation at monthly intervals.

METHODS AND MATERIALS

Part I

The findings of xerostomia and lacrimal duct obstructions in a young male child whose mother gave a history of dry eyes, and whose uncle had blocked tear ducts provided the stimuli for determining if, in fact,

the deficiency of saliva was related to the lacrimal deficiency and duct obstructions. The method used to establish the relationship was the family pedigree. If indeed a characteristic phenotype became manifest greater than expected by chance alone, a mode of inheritance could be proposed for the trait within the family.

The pedigree was established by interviewing relations of the proband. Those interviewed included the natural father and mother, the maternal grandfather and grandmother, a maternal aunt and two uncles, the maternal great grandmother's sister, the maternal grandfather's brother's wife and three of her children.

Medical records were available for the index case, his father, the grandfather's brother and two of the proband's second cousins. Basic physical examinations were performed on the proband, his half-sister, and two first cousins. The proband's mother deferred physical examination. Oral examinations were carried out on the proband, his half-sister, mother, two of the mother's first cousins and two of her second cousins. Hand x-rays were taken on the two second cousins to allow a comparison of a normal and a small hand within the same sibship.

The inherent drawbacks of constructing a family pedigree based on interviews became readily apparent. One set of problems was a denial by the maternal grandfather of all associated defects, even though his aunt stated that he did have the lacrimal duct obstruction as a young child. He also denied at least two marriages which had been attributed to him.

The interviews were conducted in person and initially sought information relative to the physical features of the proband; however, it proved

valuable to include all relevant medical problems as information increased. For example, the importance and pattern of heart disease was only realized late in the project. An example of the medical questionnaire is in the appendix A.

Part II

If the association of xerostomia with xerophthalmia and stenosed tear ducts, as variable expressions in a genetic disorder, is suggested in a review of the literature and in a family, a similar pattern of defects would be anticipated in children with any one of the disorders. Medical records at the University of Oregon Medical School were requested to supply records for the last twenty years for the clinical entities of: (1) congenital absence of salivary glands (xerostomia); (2) congenital absence of lacrimal secretions (xerophthalmia); and (3) congenital lacrimal duct obstructions. Xerostomia and xerophthalmia were related only in several elderly individuals. However, the diagnoses of "congenital atresia or stenosis of the lacrimal passages", "congenital absence of canaliculus or puncta" and "congenital atresia or stenosis of the lacrimonasal duct" yielded the records of thirty eight children for whom some surgical procedure was accomplished to resolve the excessive tearing. Associated medical problems such as allergic diseases, respiratory, cardio-vascular, gastro-intestinal, skeletal, genito-renal, CNS and ocular problems were noted. In addition, the oral status of the child was sought. Included in this review were the second cousins of the proband and several children

with congenital malformation, such as, rubella, craniofacial dyostosis of crouzon and the E.E.C. syndrome.

RESULTS

Part I

Four physical features are depicted in the family pedigree. The features are; lacrimal drainage obstructions which were resolved by surgical intervention or spontaneously, digital anomaly of "hypoplastic" thumbs, xerostomia of an early onset, and a decrease in lacrimation with a subjective dry and/or photophobic eyes. The pedigree demonstrates a transmission, through three generations and through two separate lineages, of lacrimal drainage duct obstructions.

The pedigree is displayed on the following page. The relevant medical and physical features of each individual are detailed also.

UNIVERSITY OF OREGON MEDICAL SCHOOL
HOSPITALS AND CLINICS

FAMILY HISTORY SHEET

Page No. _____ Race (Paternal): Caucasian

Family No. _____ (Maternal): Caucasian

Recorder _____ Religion: Pro —

Date _____ Referring Diagnosis: DRY mouth, epiphora

Informant II-1,5,7,9 II-3

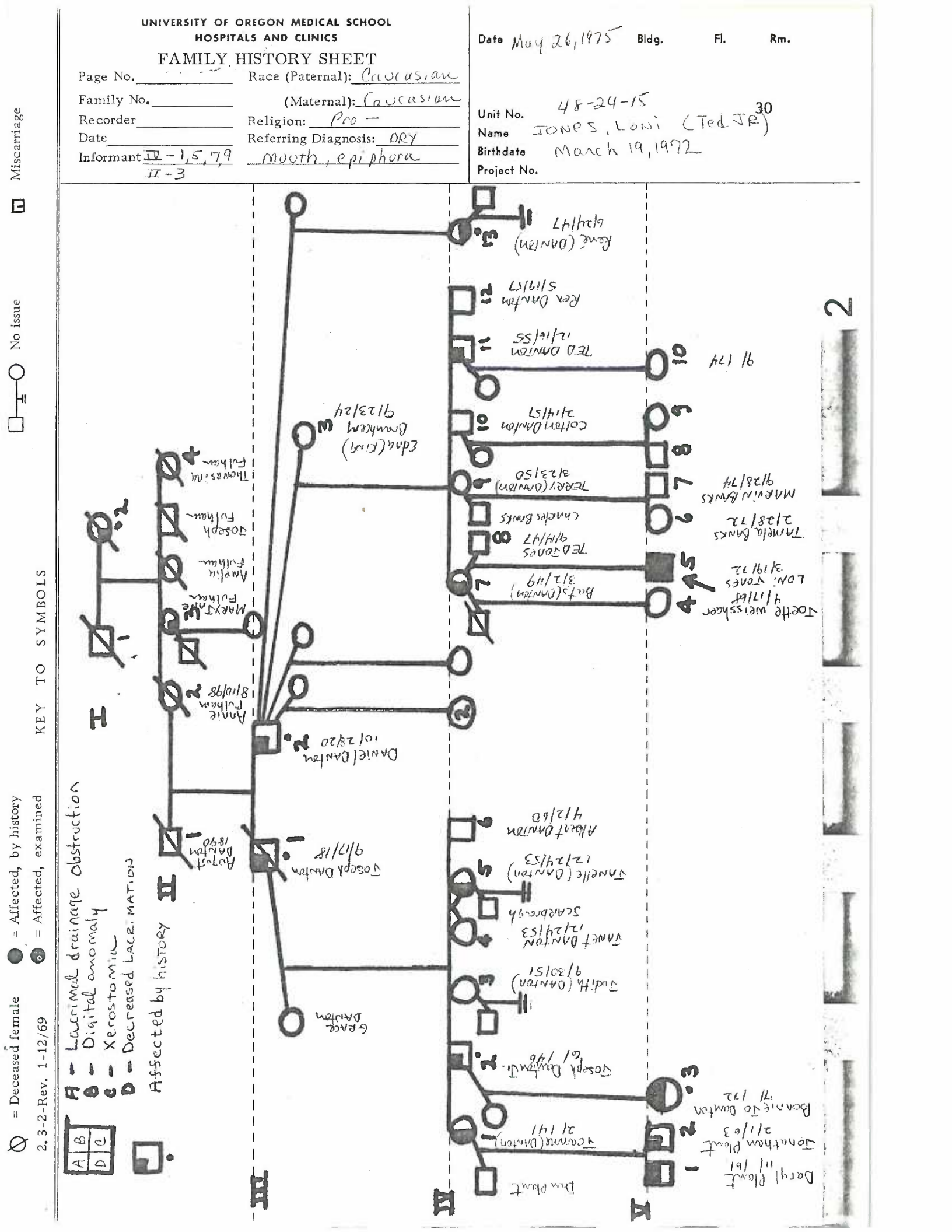
Date May 26, 1975 Bldg. Fl. Rm.

Unit No. 48-24-15

Name JONES, LONI (Ted JR) 30

Birthdate March 19, 1972

Project No.



Details of Pedigree

I-1 Heritage was Irish and English.

I-2 Heritage was Danish. She had diabetes mellitus, and preferred the ocean as her eyes were "more moist" there.

II-1 Heritage was French Canadian.

II-2 As a child she had "fainting" spells and seizures. She was claimed to have a second set of teeth. Her second marriage could not be followed up. She died in child birth at age thirty five.

II-3 She is afflicted with Sjogren's Syndrome and has kerato-conjunctivitis, a dry mouth and arthiritis. This disorder began ten years ago. As a child she seldom sweated, and was always "hot".

II-4 She lost her fingernails as a teenager but they did grow back. She had minor seizures.

III-1 He had a tear duct obstruction which was corrected by an eye doctor at 18 months of age. His eyes were crusty as a child. He sweated profusely. He expired at age fifty-two of coronary artery disease complicated with chronic pulmonary obstruction and cardiac arrythmias. He had a twenty year history of dyspnea, and developed a stomach ulcer at age forty nine.

III-2 By history he had crusty eyes with pus discharge much later than his brother. In an interview he asserted a war wound obstructed his tear ducts. He suffered a myocardial infection at age forty-seven which necessitated hospitalization. He has a "hiatal hernia", "emphysema" and takes nitroglycerine for angina.

III-3 The maternal grandmother of the proband claims she has an eighty

percent hearing loss, and has to wear hearing aids. There is a family history of mild mental retardation and hearing deficiency.

IV-1 An eye doctor has told her that she has bilateral absence of her upper puncta. She claims that her eyes are photophobic, and periodically become dry. She has a fifth digit which "cracks" and cannot bend. She had congenitally missing upper lateral incisors. By examination, she has adequate saliva.

IV-2 By history, this man has bilateral obstruction of his lacrimal passages, and one eye tears continuously. He has "heart problems", migraine headaches and periodic "swelling of his feet".

IV-3,4,6 Unaffected sibs in this family by history.

IV-5 This woman claimed that she had lacrimal ducts successfully probed and opened; however, she can not now tolerate contact lenses, and her eyes are photophobic. She had an episode of "pancreatitis" of undetermined etiology, and is now on a fat free diet. She had a "functional" heart murmur. Upon oral and x-ray examination, the upper right lateral incisor and upper left canine were missing, with the upper left primary canine still retained. The right Stensen's duct orifice could not be discerned, but the left one could. All oral mucous membranes seemed dry.

IV-7 The mother of the proband reports that she has photophobic, dry eyes. She claims to have had rheumatic fever, heart murmurs and asthma. She does not sweat, and gets dizzy in hot weather. She has sparse eyelashes, and is susceptible to sun blisters. She lost all her permanent teeth at an early age. She has a dry mouth, but an oral

examination showed the orifices of Stensen's ducts.

IV-8 Father of the proband had a congenital atrial septal defect, which has been asymptomatic. He has facial port-wine stains. He has a negative history for ocular and oral dryness.

IV-9 Maternal aunt of the proband has feet swelling upon manipulation and constantly congested nasal passages which she attributes to "hay fever". She gets tension headaches, watery eyes upon reading, and has a mild ulna deviation.

IV-10 Unaffected by history.

IV-11 Maternal uncle of proband had photophobic and watery eyes. He denies any other medical problem.

IV-12 Unaffected maternal uncle of the proband.

IV-13 Half sister of proband's mother has no tears and no saliva by history. All her teeth were removed at sixteen years of age.

V-1 This thirteen year old boy has a hypoplastic thumb and wrist bones in one hand confirmed by a radiograph. This abnormal thumb cannot approximate his palm or other fingers. He demonstrated an ulna deviation in that his elbow bends outward. He has congenital absence of the lower lacrimal puncta, and has had dacrocystorhinostomies (insertion of tubing from the inner canthus of the lower eyelid to the nose) to relieve his tearing, which has been moderately successful. He has an allergy to filbert pollen. An oral exam revealed absence of the orifice of Stensen's duct bilaterally with all mucosal surfaces appearing drier than normal. He had an intact dentition with evidence of moderate decay.

V-2 This boy exhibits bilateral parotid duct atresia and has congenitally missing upper lateral incisor teeth. He has bilateral absence of lower puncta with a polyethylene tube insert from the inner canthus to the nose unilaterally. He has mild frontal bossing and hypertelorism. All oral mucosa seemed dry. He claimed that he has a dry mouth only in the morning and when eating dry foods.

V-3 By history this cousin of V-1,2 has hypoplastic thumbs, and has crusty eyes in the morning. She is said to have no tear ducts.

V-4 Unaffected half sister of the proband.

V-5 Proband

V-6 This child is considered "hyperactive", but has none of the stigmata of the proband. There were no oral abnormalities upon examination.

V-7 There is a suspicion of a submucous cleft in this child. He exhibits lacrimal puncta but gets crusty eyes with colds. Saliva seemed adequate upon oral examination.

V-8,9 Unaffected sibs of unaffected parents.

V-10 This child of an affected father is described as "odd-looking", and by history has periodic body rashes, and difficulty in digesting foods.

Part II

A review of thirty-eight medical records of children that necessitated surgical intervention to resolve their excessive tearing revealed that nine children has no associated medical problems. Twenty-nine children with a persistent lacrimal drainage duct obstruction did have a range of associated physical problems, which are listed in Appendix B. Obstructions (atresia or stenosis) of the nasolacrimal duct predominated with twenty-three cases, while absence or atresia of the lacrimal puncta and/or canaliculi was the diagnosis in six cases. There was no appreciable difference between the sexes for the lacrimal obstructions.

Cardiac anomalies were among the more serious medical problems, and found in four children. Two of these four children had rampant dental caries in their primary dentition, but the status of the salivary glands was not noted. Skeletal aberrations were recorded in six children, including ectrodactly and supernumary digits. Susceptibility to respiratory infections and allergic manifestations were encountered in eight children. Ocular pathology was found in three children, as was clefting and seizure disorder.

Two children had histories similar to the proband of this report. One child (#3) was six weeks premature and had respiratory and nasal problems; and the other (#10) had inguinal hernias, difficulty in feeding due to allergies and had bronchitis.

Xerostomia was documented in only one child (#1) out of the thirty-eight. Rampant dental caries and early loss of teeth are the only indirect evidence of a saliva deficiency in two other children. Xerostomia is

either not a consistent finding with lacrimal duct obstructions or the entity is overlooked in examination. There does seem to be a tendency for obstructions of the lacrimal drainage ducts to occur with congenital heart defects, some skeletal anomalies and in conjunction with allergic manifestations.

DISCUSSION

The substaniation for an autosomal dominant inheritance pattern for the proband's xerostomia is predicated upon fulfilling specific criteria. The trait must appear in every generation; males and females are equally likely to have and transmit the trait; unaffected individuals do not transmit the trait; and, approximately one half of the children of an affected person will have the trait.[56] If the variety of lacrimal duct obstructions, the lacrimal deficiencies, as well as salivary duct atresias are assumed to be expressions of the same genetic defect, these criteria can be fulfilled. This discussion will emphasize the embryologic, anatomic and functional similarities between the salivary and lacrimal systems, in order to establish their mutual developmental predisposition to the influence of the same gene. Explanations for some of the more serious medical problems encountered in the pedigree, and for the possible embryologic-anatomic defects in the various phenotypes will be developed.

The essential functions of the salivary and lacrimal secretions are lubrication, cleaning and protection. The flushing and cleaning aspect of

the secretions is maintained by the watery component. The cornea is washed by the secretions of the major orbital and palpebral lacrimal glands located superiorly and laterally.[6] The oral cavity is cleansed by the secretions of the parotid and submandibular glands located laterally and inferiorly respectively. These glands contribute the bulk of the secretory volume.

The lubrication between approximating mucous membranes if provided for by the mucoid component of the secretions. The continuous secretion of the mucosal glands also is a deterrence to the deposition of bacterial or other organic accumulations on the epithelial surface. Hence, the mucous secretions can both lubricate and clean.

The protective mechanisms not only entail physical flushing and lubrication, but also a destruction of noxious bacteria by the secretory IgA, lysozmes and inorganic chemicals.[6,57] The development of the corneal pathologies in xerophthalmia may be attributable not only to dessication, but also to a deficiency of these anti-bacterial components.[66]

A number of reports have attempted to associate secretory IgA concentartion with the atopic tendencies of the patient with only moderate correlations.[8,9,47] Atopy is a propensity to form reagin antibodies to allergens, and this tendency has been associated with ectodermal dysplasia syndromes,[22,61] and is demonstrable in the hospital cases reviewed and in the family pedigree of this report. The cases in which there was a complete absence of mucoserous glands of the respiratory tract [19,45] though suggest that allergens, normally "flushed" away or destroyed, are allowed to "penetrate" and stimulate the plasma cells of

of the submucosal layer to elicit an IgE response. The expanded protective relationship of the concentrations of secretory IgA and the deficiency of serous and mucous gland secretion with an atopic tendency is still a matter of speculation.

The major parotid and submandibular salivary glands, and the major lacrimal glands contribute to the bulk of the secretions with a watery discharge.[48,29,6] The accessory lacrimal glands of the conjunctiva and eyelid dispense the mucoid and oily layers over the cornea, while the sublingual and minor salivary glands of the palate, labial and buccal mucosa and the glossopalatine areas contribute the mucoid secretions to the oral cavity. Thus, the homeostasis of the harsh oral and ocular environments is maintained by dual secretory systems which function to cleanse, lubricate and protect the tissues by means of their chemical and physical properties.

There is an anatomic disparity between the major salivary and lacrimal glands. The parotid and submandibular glands have one main excretory duct per gland, while the lacrimal glands have a number of excretory ducts. A deficiency in saliva could result from an obstruction in the main ducts; however, a deficiency of lacrimation would have to involve the majority, or all, of the ten to fifteen ducts for the lacrimal glands.

Both the lacrimal and salivary tissues are derived from the ectoderm,[20,50] although Provenza[42] contends that the submandibular and sublingual gland may originate from the endoderm. The ectodermal cells destined to become the glandular and ductal tissues proliferate and penetrate the

underlying mesenchyme at about the sixth week in utero. These solid cords of cells bud out to produce the network of branches, which is completed in the third month. The terminal cells of the branches differentiate into the specific secretory cells. Thus, any interference with the initial invagination, or branching of the cords of cells would result in aplasia or agenesis of the glands. A reduction in the number of network branches, and hence, a reduced number of potential secretory cells, could theoretically yield a hypoplasia of the glands.

The two autopsy reports[19,39] that revealed "fatty areolar" tissue in the anatomic locations of the parotid and submandibular glands with atresias and ectodermal dysplasia respectively suggest the glands did develop, but underwent atrophy and degeneration. There is a plausible explanation for these anatomic findings. The canalization or "hollowing out" of lacrimal and salivary ducts occurs in the last few months of fetal development. During this time glandular elements are undergoing maturation, which culminates in secretory activity post-natally.[20,32,50] In an early histologic study of the submaxillary and sublingual glands in seventeen embryoes, Thoma[55] reported not only the presence of patent ducts near the orifice, but also indications of secretions by the twelfth week. He explained canalization as an expansive response to the physical stimulation of early secretions. A failure of canalization, and a subsequent reflux of early secretions, could disturb the maturation of the glandular cells and induce an atrophic and degenerative process without glandular swelling. This process would also result in agenesis of the salivary glands.

Failures in canalization or failures in development account for the

persistent obstructions of the lacrimal drainage ducts. These ducts originate from ectoderm trapped in the mesoderm of the maxillary and lateral nasal processes. This buried ectoderm proliferates to form the lacrimal sac and its anatomic extensions -- the upper and lower canaliculi and the naso-lacrimal duct.[20] These ducts begin canalization in the third month, are are patent by the fourth month. Canalization proceeds without the stimulus of intra-ductal secretions, thus contradicting Thoma's explanation for the process. In those cases where irrigation and probing of the lacrimal passageway does not relieve the tearing problem, a developmental defect must be assumed. Examples of such defects were depicted in V 1,2 of the pedigree and in Levy's patient[34] -- all three of whom had polyethylene tubes placed from the inner canthus to the nose to allow lacrimal drainage. Insertion of these tubes has not been successful in all cases however.[33,65] The location of the tube in the eye of V-1 is shown in figure 5.

A successful probing and irrigation indicates that the obstruction may have been limited to epithelial membrane occlusion at the lacrimal puncta or the nasal end of the naso-lacrimal duct.

The embrologic and fetal development of the lacrimal and salivary secretory systems, as well as the lacrimal drainage system, are similar. They develop from ectodermal proliferation and canalize at the same stage of morphogenesis. If diminished oral and ocular secretions were the only anomalies encountered, glandular dysfunction could be proposed; however, the reports indicating absent[34] or rudimentary[65] lacrimal sacs and complete atresias of the naso-lacrimal duct[2] under surgical exploration support a

proposal that the fundamental defect is a dysfunction of either the development or canalization of the ducts with a subsequent failure or diminshment of secretions.

If the absent puncta of the index case are found to be manifestations of a failure elsewhere in the lacrimal drainage ducts, this discovery would support the assumption that his atretic parotid and submandibular ducts are indicative of failures in the salivary duct system, and not the secretory portion of the gland,which may have never developed. The failure in the duct systems may also be evident in the two brothers (V-1,2) with parotid duct atresias both of whom had anomalous development of the lacrimal drainage ducts that necessitated surgical correction. The embryologic similarities and the close association of developmental anomaies of the salivary and lacrimal system from this pedigree and the reports in the literature establishes that the fundamental defect is a failure in the morphogenesis of ductal systems - either in the initial penetration and branching stage or in the canalization stage. An acute pancreatic attack in a female (IV-5) of the pedigree indirectly suggests that the defect may extend to the excretory duct of the pancreas. This woman has the trait, as evidenced by her epiphora as a child, unilateral parotid duct atresia and photophobic eyes. She also has a congenitally missing upper lateral incisor. An obstruction in the main excretory duct of the pancreas would result in a reflux of the digestive enzymes and, upon rupture, auto digestion of the glandular apparatus.[28] This finding is the singular instance of pancreatic involvement in the pedigree.

A male (IV-2) by history and a female (IV-9) of the pedigree by

examination have swelling of the ankles and feet upon manipulation. The reason for this localized edema is not known, but this phenomenon was reported by Coverdale[17] to occur in a woman whom he diagnosed as inheriting "congenital Sjogren's Syndrome" from her mother. She had enlargement of both her hands and feet. Her xerostomia was accompanied by an enlargement of the parotid glands.

A review of the hospital medical records showed that of the thirty-eight children with lacrimal duct obstructions, four had documented congenital heart disease, and two were suspected of having congenital defects. The histories of heart disease and murmurs of affected individuals (III-1,2, IV-2,5,7, V-6) of the pedigree prompt some degree of speculation. Two males (III-1,2) had heart attacks in the middle forties, with one (III-1) having a twenty year history of dyspnea. Heart problems and dyspnea are now experienced by his son (IV-2). The important consideration is that histories of murmurs and heart disease have only been associated with individuals who have had lacrimal duct obstructions.

A defect which has also been associated with the salivary duct atresias and lacrimal duct obstructions in both lineages of the pedigree has been "hypoplastic" thumbs. The relative hypoplasia of the navicular bones,(1) and the metacarpal bone(2) and phalanges(3) of the first digit of V-1 of the pedigree is depicted in figure 6. A similar skeletal abnormality was reported by Faber in his male subject with congenital xerostomia.[23] More severe digital anomalies and xerostomia have been documented with meso-ectodermal dysplasia,[34] and the E.E.C. syndrome.[41] Digit anomalies have also been reported to occur with naso-lacrimal duct

obstructions [69] and ectodermal dysplasia.[37] The digit anomalies may be an expression of the pleiotropic effect of the gene, that is, a secondary effect of the gene's primary influence.[56] The explanation of the pleiotropic effect is obscure, unless localized obstructions occur during osseous development or mesodermal dysfunctions are considered.

The relationship of salivary duct atresias and lacrimal duct obstructions is depicted in generation V of the pedigree. Four children of affected individuals have, or have had, congenital epiphora, which did not correct with time. Three of the four children have salivary duct atresias, with the parotid duct atresias of V-1,2 having minimal effect upon their dentitions. These two boys did claim their mouths were dry upon awakening and with eating dry foods. Three of the four children also have hypoplastic thumbs, which strongly implies that the secretory and digital defects are related.

The inheritance of the trait can be traced back to the two brothers (III-1,2) who had, by history, congenital epiphora. A history of Sjogren's syndrome and sparse sweating in their maternal aunt (II-3) suggests that they inherited the trait from their mother. Lacrimal duct obstructions and lacrimal deficiences appear in both their lineages. A deficiency of saliva was reported in one individual (IV-13). Ankle swellings also were present in both family lines. This pattern of expressions of the trait demonstrates the persistence of the gene's capability for expression despite the introduction of a number of genotypes from the unaffected parent.

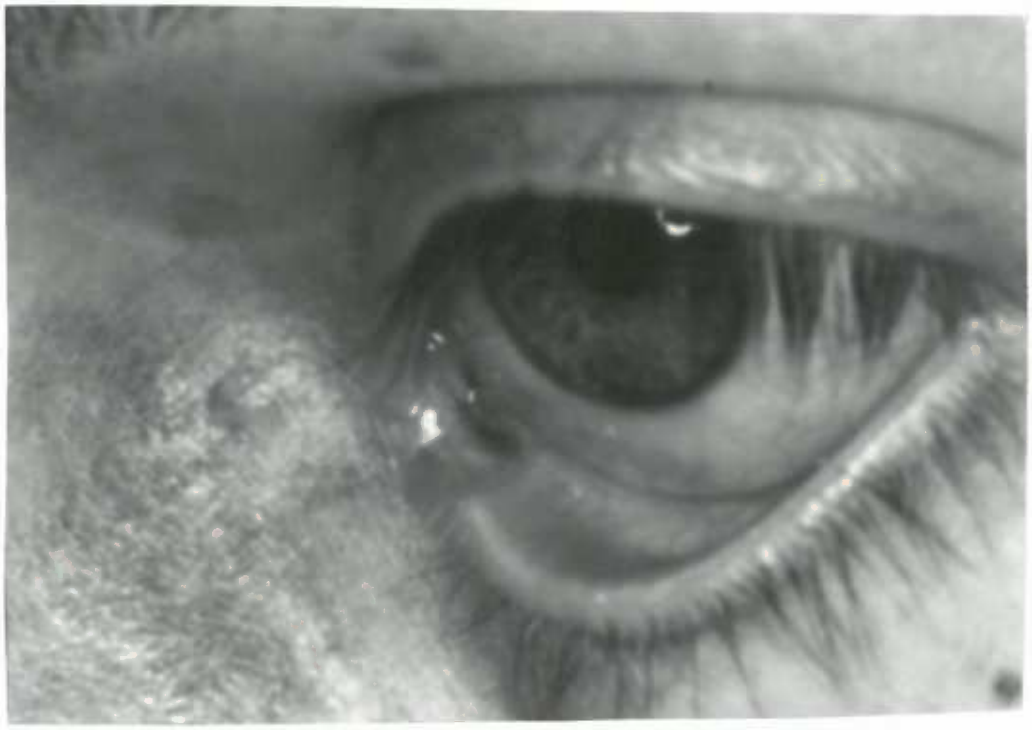
The expression of the trait varies. Lacrimal obstructions resolved

with time or by probing and irrigation may be mild expressions. Various moderate expressions may entail the salivary duct atresias, with or without xerostomia, lacrimal deficiencies, lacrimal duct defects which present with clinical complications, and the digital aberrations. There are a number of significant features, such as, the pancreatitis, allergic tendencies, and the onset of early heart disease, evident in the pedigree, but cannot be related to the fundamental defect.

The variable expression of a trait may be attributed to the influence of the unaffected parent's genetic contribution and to differences in environmental background.[51] The variability of the anatomic locations of the lacrimal drainage duct obstructions is exemplified in this family along with the variability of involvement of the salivary ducts. The extent of the anatomic severity dictates clinical severity.

The trait was transmitted to six of twelve children of III-1,2. Those six affected individuals have transmitted the trait to four of six children. An equal number of males and females have been affected in generation IV and V. The trait has not been transmitted by an unaffected individual, although many of them are not yet married. The similarity of the phenotypes of affected children in generation V demonstrates the passage of the gene from the two brothers in generation III through three generations. All of these facts support an autosomal dominant mode of inheritance for the clinical manifestation of xerostomia in the proband. The trait exhibits variable expression which primarily involves the eyes and the mouth.

FIGURE 5



The polyethylene tube insert extends from the inner canthus to the nose in V-1 of the pedigree.

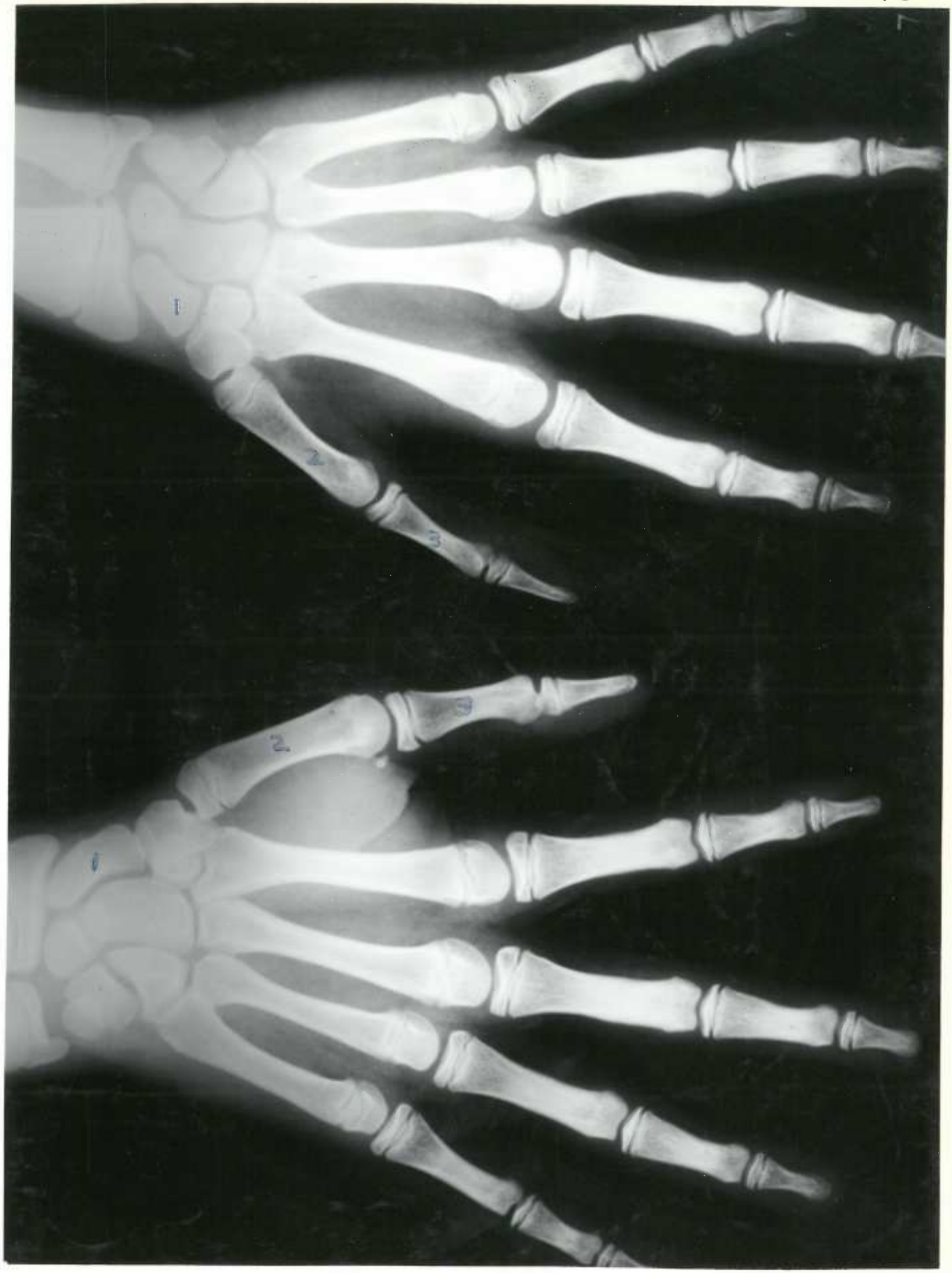


FIGURE 6

Hand and wrist radiograph of V-1 depicts the relative hypoplasia of the left navicular bone(1),metacarpal bone(2) and phalanges(3) of the first digit.

CONCLUSIONS

Lacrimal drainage duct obstructions in three successive generations in which affected individuals only transmit the trait, on the average, to one half of their children, with both males and females equally affected, substantiates an autosomal dominant mode of inheritance. The salivary duct atresias, decrease in lacrimation and skeletal defects suggest a variable expression of the trait with a pleiotropic effect.

The fundamental defect is a failure in duct morphogenesis in either the proliferative or canalization stage of development.

Involvement of both the parotid and submandibular ducts produces a xerostomia with mucoid compensatory saliva. In two individuals bilateral parotid duct atresia did not significantly effect the dentition or the mucous membranes.

A review of medical records of children who had surgical intervention for their lacrimal drainage duct obstructions revealed that seventy-five percent had associated physical anomalies. In the pedigree of this report those individuals with persistent lacrimal duct obstructions had a variety of associated physical anomalies, which included hypoplastic thumbs, periodic dry eyes, salivary duct atresias, congenitally missing upper lateral incisor teeth, allergic tendencies and a predisposition to early cardio-pulmonary disorders.

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APPENDIX A

Medical Questionnaire Form

The following questions were used in personal interviews:

Relationship to aberrations in duct canalization precesses or obstructions:

1. Have you ever had, or now have a "dry mouth"?
2. If you have lost your teeth, when and for what reasons?
3. Do your salivary glands ever become enlarged?
4. Do your eyes "crust up"? Do you have excessive tearing? Do you have dry eyes? Have you ever been told that you have a "tear duct" problem? Have you ever had any operations on your eyes? Are your eyes sensitive to light?
5. Have you ever had "pancreatitis"?
6. Is there any hearing problems in you, or your children?

Relationship to aberrations associated with ectodermal dysplasia:

7. Do you have any difficulty perspiring in warm weather? Have you ever had any unusual high fevers?
8. Do you have any unusually shaped teeth, or unusual dental conditions?
9. Are there any abnormalities of scalp or body hair in your family?
10. Do you have any fingernail abnormalities?

Relationship to other malformations with epiphora and xerostomia:

11. Is there a history of clefting in lips or palates in your family?
12. Are there any heart problems in you, or your children?
13. Are there any hand, finger or foot abnormalities in your family?
14. Have you ever been told you have kidney problems?
15. Were you premature? Were your children premature?

16. Is there a history of seizures or convulsions in your family?

17. Have there ever been any children who "failed to thrive"?

Relationship to allergic manifestations:

18. Have you or you children ever had any allergies to milk, eggs, nuts, berries or fruits, chocolate, wheat or any other food?

19. If so, what is the reaction?

20. Do you have eczema (skin dermatitis) or any other skin rashes?

21. Do you have difficulty breathing? Have you ever been told you have "asthma"? Do you have susceptibility to lung infections?

22. Do you have "hayfever" reactions? Do you ever get "runny noses"? Have you ever had a reaction to an immunization?

23. Are you allergic to any drugs?

24. Are you taking any medications at the present time?

Relationship to a general medical history:

25. Could you describe any unusual occurrence associated with your birth, or the birth of your children?

26. Do your children have any developmental problems?

27. How many times have you been hospitalized, and what for?

28. Have you ever had any serious illnesses, injuries or operations?

29. Do you have any of the following medical problems?

Rheumatic fever	Bleeding problems
Diabetes	High blood pressure
Jaundice	Foot swellings

30. Do you have any other medical problem or physical abnormalities which have not been previously asked about?

APPENDIX B

The twenty-nine children with additional medical or physical problems other than epiphora are listed below.

Child Number	Lacrimal Anomaly	Associated Anomalies
1	"Blocked tear duct"	Xerostomia, (absence of salivary gland).
2	Stenosis of nasolacrimal duct	"Suspected cardiac problems"; unilateral undescended testis
3	Absence of right puncta	Six week premature; Difficulty in breathing with congestion, wheezing and nasal obstruction.
4	Stenosis of puncta	Congenital glaucoma
5	Atresia of lacrimal passages	Petit mal seizures; difficulty breathing, and constant nasal discharge.
6	Stenosis of nasolacrimal puncta	Dry skin and chronic rhinorhea
7	Lacrimal obstruction	Patent ductus arteriosus; ventral septal defect; pyloric stenosis; cleft palate; rampant decay and alveolar bone loss. Congenitally missing upper lateral incisor teeth.
8	Stenosis and obstruction of lacrimal passages Absence of superior puncta	Craniostenosis, syndactyly of toes; bilateral cyptochism. Crouzon's face ; dry nasal mucosa; inguinal hernias.
9	Absence of lacrimal puncta	Chronic eczema
10.	Atresia of NL ducts	Inguinal hernias; vomiting and pain after feeding, allergic to milk, eggs & fruits. Bronchitis in infancy.

11	Obsturction of NL duct	Pericardial cyst; frontal bossing; very irritable child.
12	Stenosis of NL duct	Dextrocardia; congenital cataracts; supernumary digits; seizures; facial cleft; acute bronchitis.
13	Stenosis of NL duct	Chronic rhinitis
14	Stenosis of right lacrimal passages	Rash with fruits
15	Stenosis of NL duct	Hydrocephalus; cryptochism; Absence of corpus callosum
16	Stenosis of NL duct	Seizure disorder; kidney agenesis, bronchitis, (cystic fibrosis) congenital glaucoma.
17	Atresia of left NL duct	Atopic asthmatic child
18	Atresia of lacrimal canaliculi	Tomato allergy; suspected intraseptal defect; webbing of the second and third toes. All teeth removed at age 5.
19	Atreais of NL duct	Hydocele and inguinal hernia; atopic dermatitis.
20	Atresia of NL duct	Congenital cataracts
21	Atresia to lacrimal puncta	Congenital rubella; mitral valve deficiency; microcephaly
22	Obstruction of NL duct	Wheat allergy
23	Stenosis of NL duct	"Asthmatic"; fruit allergy
24	Obstruction of NL duct	Microcephaly
25	Stenosis of NL duct	Mental retardation, allergic to drugs, tomatoes and fruit

26	Absence of NL duct	Ectrodacyly of fingers and toes; short stature; sub-mucous cleft.
27	Absence of puncta	Bronchiolotis, "difficulty breathing" - wheezing and rales.
28	Stenosis of NL duct	Dry skin and pathologic jaundice due to prematurity
29	Unilateral obstruction of NL duct Absence of lower lacrimal puncta	Hypoplastic thumb; parotid duct atresia; Hayfever allergy.