Clinical Management of Salivary Gland Disorders

Louis Mandel, DDS
Oral and Maxillofacial Surgery
Columbia University /New York
Presbyterian Hospital
New York, NY, USA

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Dedication

The seeds for this book have been germinating within my mental field for many years. Its materialization was made possible only through the genes that I inherited from my Hungarian immigrant parents. Their nurturing, direction, work ethic, and sacrifices paved the way for me to achieve a professional education. Simultaneously, it facilitated my recognition of these indispensable qualities in the woman I courted and married, Mary Damiani. In turn, Mary and I endeavored to implant these values into our two children, Susan and Richard. The results have not been disappointing. They both have meaningful lives and successful careers. I have taken pride in their principles and accomplishments, and it is to Susan and Richard that I dedicate this book. It is one avenue made available to me, albeit insufficient, to express my love for them, something that I may not have always adequately demonstrated.

Although in truth the family always comes first, there are individuals whose interactions with me served as a continued inspiration and incentive for my writing, teaching and study, my students. Their thirst to learn galvanized my patient investigations. Standouts include, but are not limited to, Drs. David Alfi, Ashley Houle, Daria Vasilyeva, and Vicky Yau. In addition, I will be forever grateful for the opportunities afforded to me by my superior, Dr. Sidney Eisig, and for my friendships with Murray Slochover, Carl Nelson, Ian Hu, and George Minervini. They all contributed to making my life complete.

Preface

My interest in salivary gland disorders originated when I was a graduate student many years ago. Consequently, I have had ample opportunity to evaluate patients victimized by a wide variety of salivary gland diseases. Inevitably, I developed "smarts" or what is referred to as clinical expertise. In addition to my examinations of the more familiar salivary gland afflictions, my experiences have allowed me to become familiar with a group of salivary gland conditions that nowadays are seen infrequently. Surgical (acute) parotitis and HIV lymphoepithelial cysts represent examples of this cohort of salivary gland problems. Furthermore, the passage of time has allowed me to accumulate and evaluate a collection of false/positive patients. I have attempted to incorporate into this text the knowledge that I have acquired from my exposure to the full gamut of salivary gland disorders and to those entities (the false/positives) that mimic salivary gland pathology.

A huge step forward in my ability to evaluate salivary gland disorders occurred in 1988 with the establishment of the Columbia University Salivary Gland Center. The impetus for its establishment came from Dr. Irwin Mandel (no relation of mine, just a coincidence in names) who had a background in biochemistry and was interested in the biochemistry of saliva. I am a clinician and he thought that we would make a perfect team, we did. As you peruse this book, you will note that some chapters allude to salivary chemistry, a reflection of Dr. Irwin Mandel's influence upon me.

In addition, the continued value of sialography in the diagnosis of salivary gland disease has been recognized. Examples of its place in diagnosis have been sprinkled throughout the chapters. Sialography is a venerable diagnostic technique whose scope has gradually been impinged upon by other imaging (CT scan, MRI, etc.) approaches. Nevertheless, it has a significant place in the salivary gland diagnostic armamentarium. It is unrivaled in its ability to image normal/abnormal ductal patterns as they relate to glandular disorders. Mastering the technique will reward the clinician.

The reader should look upon this book's compendium of salivary gland disorders as only opening the door to the subject. The text should serve as a guide in attaining a diagnosis and in mastering pathophysiology. Digestion of this information should be followed by a pivot to current scientific journals for recent updates. The derived information should then be filed away in the reader's intellectual memory bank. Clinical expertise will now develop and can be added to the investigator's diagnostic abilities.

New York, NY, USA Louis Mandel, DDS

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Editor and Contributor

Editor

Louis Mandel, DDS Oral and Maxillofacial Surgery, Columbia University/New York Presbyterian Hospital, New York, NY, USA

Contributors

Kevin C. Lee, DDS, MD Department of Head, Neck/Plastic and Reconstructive Surgery, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Letty Moss-Salentijn, DDS, PhD Vice Dean for Curriculum Innovation and IPE, Columbia University, College of Dental Medicine, New York, USA

Chapter 1
Anatomical Considerations

Letty Moss-Salentijn

Abstract The general anatomy and histology of human major and minor salivary glands are described. The sublingual glands and all minor glands develop in the submucosa close to the sites of the oral mucosa where the openings of their excretory ducts are located. Particular attention is paid to the development of the submandibular and parotid glands. The final anatomical location and morphology of these glands, as well as the lengths of their excretory ducts, are influenced by the rapid facial growth and development, and the spatial restrictions imposed by the developing muscles, nerves, and organs that are present in this shared connective tissue space.

Introduction

Saliva is the product of a collection of major and minor salivary glands, which by their secretory activity contribute to the maintenance of a healthy oral environment.

Saliva plays a key role in maintaining oral health under normal conditions. If conditions change, for example, in sedated patients in intensive care, a rapid shift in oral flora may occur to Gram-negative species. This may subsequently spread into the respiratory tract, causing pulmonary afflictions.

While a detailed description of the composition and role of the salivary constituents is beyond the scope of this chapter, we note here the principal functions of these constituents (Fig. 1.1):

- Affecting the processing of food prior to swallowing.
- Protecting mineralized tissues against demineralization and stimulating remineralization.
- Providing innate and acquired immune protection against micro-organisms.

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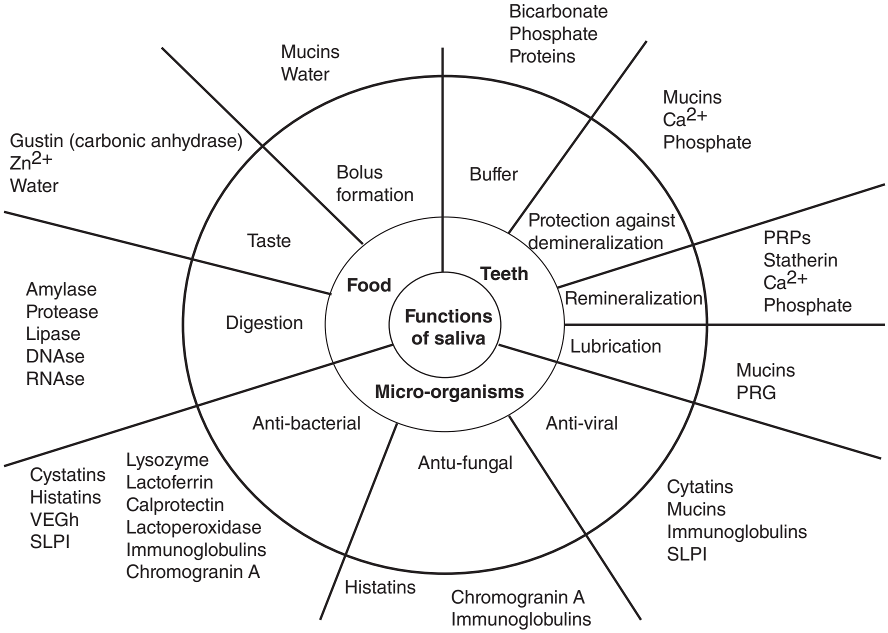

Fig. 1.1 Functions of saliva [1]

Traditionally, a distinction has been made between three pairs of *major* glands, the parotid, submandibular, and sublingual glands, and numerous *minor* salivary glands.

While these glands all have in common that they release their product into the oral cavity, the parotid and submandibular glands are not located directly below the oral mucosa, but at some distance, which necessitates the transport of saliva via lengthy excretory ducts: of the parotid (Stensen) with an opening on a papilla of the buccal mucosa near the second maxillary molar and of the submandibular gland (Wharton) which opens on the surface of the sublingual papilla. The smallest of the major salivary glands, the sublingual glands, are well developed in only about 65% of cases where a distinct anterior “major sublingual gland” is present [2]. The anterior major sublingual gland and a collection of minor sublingual glands that are located immediately below the sublingual oral mucosa have separate excretory ducts that open along the top of the sublingual fold (Rivinus). If an excretory duct of the major sublingual gland is well developed (Bartholin), it may join the submandibular duct (Wharton) and open on the sublingual papilla [3, 4].

Numerous minor salivary glands are found immediately below the oral mucosa in almost every location of the oral cavity. These glands are named according to their respective locations: **sublingual**: 8–20 in the floor of the mouth, **lingual**: directly below the ventral lining mucosa of the tongue and the dorsal specialized mucosa—particularly numerous near the lingual tonsil, **labial**: in the submucosa below the lining mucosa of the lips, **buccal**: directly below the lining mucosa of the cheeks, **palatine**: directly below the masticatory mucosa of the hard palate and the lining mucosa of soft palate, and **glossopalatine**: particularly rich near the tonsil. Finally, a rare developing gingival gland has been described [5].

In many of these locations, no submucosa is present. If a submucosa is present, the minor salivary glands are located in that layer.

General Structure

Salivary glands are organs that consist of epithelial and connective tissue components. The epithelial components are responsible for the production, modification, and transport of saliva, while the connective tissue components provide physical support and carry the neurovascular supply needed for the function of the glands.

Epithelial Component

The *epithelial component* resembles a tree in which the major branches and the "trunk" are the largest (excretory) ducts. The principal excretory duct opens into the oral cavity, while the "leaves" are the acini where the production of saliva begins. The intervening "branches" and "twigs" are part of the ductal system, through which the secretory product is moved and modified until it reaches the oral cavity as saliva [6] (Fig. 1.2). This epithelial structure is most visible during the fetal period when the salivary glands are still developing. When cytodifferentiation of the epithelial cells of the acini and the ductal system is completed, the epithelial components seem to dominate the histology of the lobules.

A well-known diagram that was published in 1924 by Braus [7] (Fig. 1.3) illustrates the principal cellular details of the epithelial components of a salivary gland (mixed seromucous):

- Acini—these may be serous or seromucous in nature.
- Intercalated ducts—long in serous glands and short or non-existent in seromucous glands.
- Striated ducts—longer in serous glands.
- Excretory ducts.

In the major salivary glands, the acini, intercalated ducts, and most of the striated ducts constitute the *parenchyma* of the lobules of the salivary gland and are therefore described as intralobular.

The remaining lengths of the striated ducts and the excretory duct system run in the connective tissue between the lobules and are therefore described as interlobular.

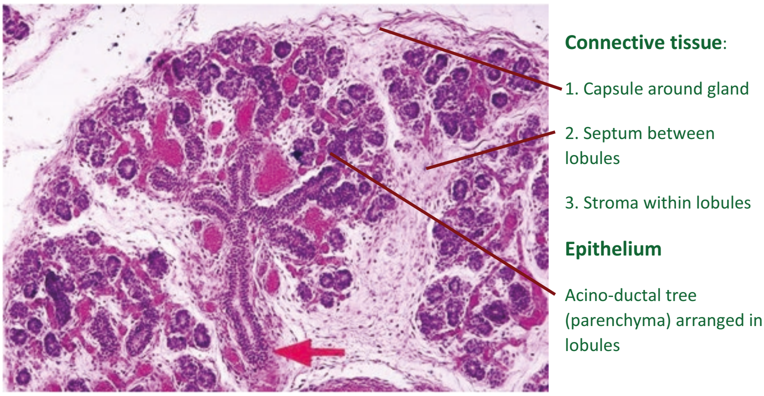

Fig. 1.2 Developing major salivary gland in a human fetus showing the distal epithelial components forming an acino-ductal tree intralobularly and one of the excretory ducts (red arrow) interlobular in a connective tissue septum. Original magnification 32 × [6]

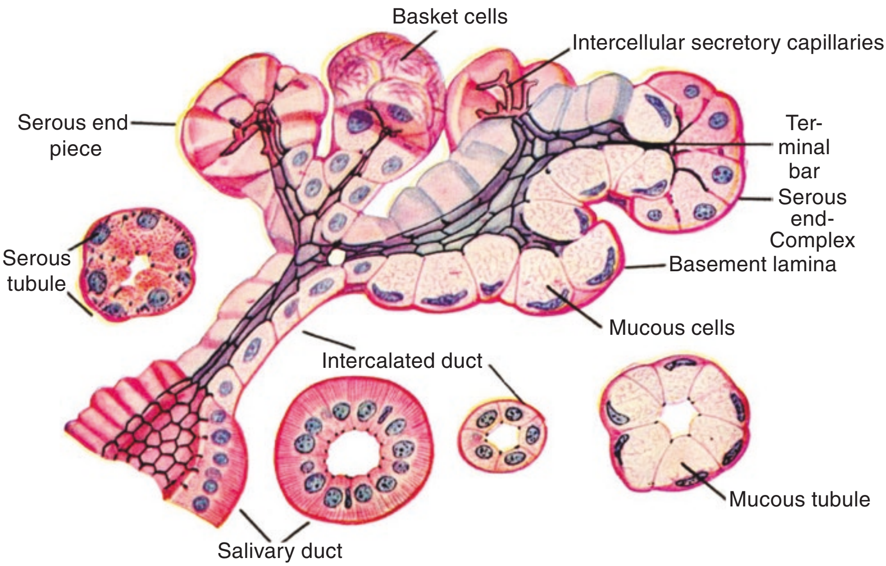

Fig. 1.3 Diagram. After a reconstruction by Vierling: Braus H (1924). Anatomie des Menschen. Berlin, Springer Verlag. Adjusted nomenclature: basket cells: myoepithelial cells: Mucous tubule: seromucous acinus (sectioned). Salivary duct: striated duct. Serous tubule: serous acinus (sectioned). Serous end piece: serous acinus (in 3D)

Connective Tissue Component

The *connective tissue component* forms a connective tissue *capsule* around the entire glandular mass. From this capsule, several *connective tissue septa* extend into the mass of the gland, between the lobules. These septa contain the interlobular ducts and the major neurovascular supply of the glands. A fine *connective tissue stroma* is present within the lobules and surrounds all the intralobular epithelial components. The stroma carries an abundant capillary supply and the afferent and autonomic nerves that supply the glandular tissue.

The epithelial components of the minor salivary glands generally are limited to seromucous acini and excretory ducts. A few cells resembling striated duct cells may be present in the excretory ducts. As will be discussed below, most minor salivary glands have seromucous acini, except for the purely serous von Ebner glands that are associated with the circumvallate and foliate papillae of the tongue.

The minor glands do not have distinct connective tissue capsules. In most cases, the connective tissue of these glands is limited to connective tissue stroma that surrounds the epithelial parenchyma and carries the vascular and neural elements needed for the epithelial functions.

Salivary Gland Development

The major glands start to develop during the embryonic period: the parotid glands (4–6 weeks) are first, and the sublingual glands are the last (8 weeks). The minor salivary glands begin their development slightly later, during the third prenatal month.

The salivary glands develop as the result of a series of epithelio-mesenchymal interactions that lead to an initial ingrowth of *solid epithelial strands* into the underlying mesenchyme, at the future site of the opening of the excretory duct into the oral cavity. The ductal system continues to expand by forming a series of successively smaller branches that will become striated ducts, intercalated ducts, and finally the terminal buds: the future acini. Thus, the pattern of development runs in a direction that is opposite to the production, flow, and secretion of saliva.

The pattern of development is characterized by several stages:

1. **Morphodifferentiation stages:** pre-bud, bud, and pseudoglandular: epithelial cord growth and successive rounds of branching of the solid cord [8–10].
2. **Canalicular stage**: During this stage, a hollowing or cavitation of the solid cord [11] leads to the formation of lumina in the developing glandular ducts.
3. **Terminal stage**: cytodifferentiation [12].

Eventually, *bulbous terminals (acini) are formed* at the ends of the strands during the third prenatal month. These terminals are the future acini.

The complexity of the growth and differentiation of the components of salivary glands has been studied by many investigators during recent decades. The selected references will provide some insight into the current literature on this topic. However, a full picture of the signaling cascades that are required in salivary gland development is still incomplete [13].

Finally, stabilizing effects of elements of the extracellular matrix: fibroblasts and collagen, and the basal lamina components: laminin and nidogen, are needed to support branching morphogenesis [13]. While the stages of morphogenesis have been well-studied, little is known about the factors that control cell differentiation in the terminal stage. Those factors differ from the ones that control the morphogenesis stages.

Salivary Gland Anatomical Relationships

Developmentally, a salivary gland starts proliferating from the future site of the oral opening of its excretory duct to become the tree-like structure that was described above. This process of growth and development occurs during the same period during which the surrounding tissues are proliferating and establishing their respective territories. So, the final "space" in which a fully developed gland is located is a compromise between the domains that are needed by the gland and its neighboring structures, tissues, and organs. Notably, it is subject to individual variation. The differences in thickness of the connective tissue fasciae which serve as packing structures between the salivary glands and the surrounding tissues and organs reflect these compromises in the establishment of such domains.

The patterns of vasculature and innervation of the salivary glands similarly need to be considered within the frame of the glandular development. Thus, while the function of the salivary glands usually is described from the distal-most acini to the oral openings of the excretory ducts, the arterial supply and venous drainage of the glands follow the pattern of the duct system in reverse, with the blood vessels entering the mass of the gland near the excretory ducts in a way that is somewhat like a hilum [4].

As noted before, there is no consensual agreement in the literature concerning some gross structural details that are potentially important in surgical procedures [3]. The descriptions that follow are general. Detailed studies based on extensive dissections may be found in [14, 15] and to a lesser extent in [2].

Parotid Gland

The parotid gland is the largest of the three major salivary glands. The shape of this gland is variable, and more than those of the other major glands, it is determined by the neighboring structures that define the space into which the gland has grown. The gland occupies the space between the posterior surface of the mandibular ramus and the sternocleidomastoid muscle. It extends vertically from a level below the external auditory meatus to a level below the angle of the mandible and extends anteriorly, covering the posterior part of the masseter muscle, where it is wedged between the skin and the muscle. The excretory duct (Stensen) of the gland runs in an anterior