THE MORPHOLOGY OF SALIVARY GLANDS

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Preface

This monograph arises as the outcome of the decision of one of us (J. A. Y.) to write a review article on the physiology of salivary glands with a short introduction on salivary gland morphology. Professor Karl Ullrich, Director of the Max Planck Institut für Biophysik in Frankfurt-am-Main, had suggested to him that he should write the review and, to this end, generously offered to provide funds and office space to enable him to work in scholarly seclusion in the Max Planck Institut for a period of 3 months. At the end of this period the first draft, covering only introductory material on morphology, had grown to a length of 30,000 words and was still far from complete.

It became apparent that the topic deserved to become the subject of a monograph in its own right. This seemed especially desirable in view of the fact that, although several short review articles on various aspects of histochemistry and ultrastructure had appeared in the last 20 years (Burgen and Emmelin, 1961; Fava-De-Moraes, 1965, 1969; Kurtz, 1964; Leeson, 1959, 1967; Radtke, 1972; Rutberg, 1961; Shackleford and Klapper, 1962; Shackleford and Wilborn, 1968; Young and van Lennep, 1977), no really comprehensive treatment of the topic of salivary gland morphology had been published since 1927, when Schaffer's (1927) and Zimmermann's (1927) fine articles in von Möllendorff's famous *Handbuch* appeared, and 1932, when Fahrenholz (1967) reviewed the comparative anatomy of salivary glands.

Accordingly, the idea of writing a review on salivary physiology was deferred and the authors of the present work decided to produce a monograph with the title, *The Morphology of Salivary Glands*, aimed at treating the subject of vertebrate salivary gland morphology comprehensively, giving considerable emphasis to functional implications. It is our intention to produce a second work of comparable length on the physiology and pharmacology of salivary secretion in mammals, in which will be included a section dealing with experimental morphology. Eventually, when both monographs have been published, we will review and expand them to produce a comprehensive *Handbuch* on *Salivary Gland Structure and Function*.

The bewildering variety of morphological and functional patterns that are to be observed among the different glands in various species is something that must be only too apparent to workers in the area. However, to others interested in secretion or transepithelial transport, the need for such an extensive morphological treatment may not be so apparent, and a few words of justification may not be inappropriate. First, it should be pointed out that the generic term, salivary gland, does not describe a single entity but embraces an entire family of glands, even perhaps several families. Parotid glands, for example, form an entity that has more in common with the pancreas than with the mandibular gland, and the use of the general term, salivary gland, may impede our understanding of the structure and function of the parotid at least as much as it may help to arrive at useful generalizations. Second, it should be stressed that, among various species, in contrast to what holds for other glands, such as the lacrimal, mammary, pancreatic and prostate glands, there is an incredible variation in the morphology and function of each of the major salivary glands, reflecting, in a general way, the diversity of dietary habits to be found among the vertebrates. A failure to appreciate that each major gland in a particular species must be regarded individually has been responsible for the development of innumerable apparent inconsistencies in the literature and resulted in increasing confusion as the number of publications has increased.

Accordingly, we have begun our review with some general remarks on the various functions ascribed to salivary glands and a discussion on the evolution and comparative morphology of the glands found in the various vertebrate orders. Except in these introductory sections, we have concentrated largely on mammalian salivary glands, since published studies on non-mammalian vertebrate glands are relatively few. As the gross anatomy of mammalian salivary glands is fairly uniform, we have been able to develop this topic briefly, taking the laboratory rat as our main example. Microscopic anatomy, however, is rather more complex, and an appreciation of it has been confused by the growth of a contradictory descriptive nomenclature. We have attempted to simplify this nomenclature but have resisted the temptation to coin new terms and have sought instead, to offer simple, consistent definitions of some existing terms while discarding others altogether. In the main part of the text we have attempted to describe the most commonly encountered histological features for each gland type, but in an appendix we have tried systematically to summarize all reliable information that is available for each individual mammalian species that has been the subject of investigation. We have included much, previously unpublished, original work of our own. To assist readers who are seeking information on gland structure in a particular species we have included a comprehensive animal index which should lead the reader to all pertinent information on any species for which information is available.

Since the use of modern histochemical procedures is responsible for a great deal of our knowledge about the synthetic and secretory properties of salivary glands, we have dwelt at length on those procedures most commonly employed and, in the text and the appendix, have indicated what results have been obtained from their use with salivary glands. Ultrastructural variation, among species and among glands, is developed mainly in the body of the text; special attention is given to the appearance of secretion granules and a detailed description of the process of secretion of organic compounds is provided that embraces results of studies both on salivary glands and on the pancreas (since much of our knowledge comes from studies on this gland). Special attention is given to the ultrastructure of myoepithelial cells and to a description of the neuroeffector junctions encountered in salivary tissue. Finally, a description of salivary embryology and developmental biology is provided.

Wherever possible, the text has been illustrated with original photomicrographs and diagrams, many of which have not previously been published; we have taken advantage of our antipodean domicile to study a number of marsupials and monotremes. Nevertheless, there are many gaps in the comparative table still waiting to be filled and the diversity so far uncovered among the mammalia should provide rich rewards for interested investigators.

We should like to acknowledge our indebtedness to many of our colleagues and students with whom we have discussed many parts of this monograph. Specific mention should be made of Professor K. J. Ullrich without whose enthusiastic encouragement the manuscript would never have been begun, let alone completed, and Professor John Garrett who gave us a critical appraisal of the work and made many helpful suggestions. We are also grateful to Mrs Eva Vasak for her expert section cutting and to Miss G. Hanzmann, Mr A. Kennerson, Mrs H. Melville and Miss K. Wilson for assistance with many phases in the preparation of the manuscript. The authors' experimental work has been supported at various times by the National Health and Medical Research Council of Australia, the Sydney University Research Fund, the *Max Planck Gesellschaft* and the *Deutsche Forschungsgemeinschaft*.

At the time of going to press we have taken the opportunity to bring the manuscript up to date by the addition of comments on work published in 1977. These additions comprise the addendum which has a separate bibliography. References to the numbered individual items in it are given in the text; page references in the addendum allow the reader to refer back to the original text.

Shortly before the manuscript was completed we were deeply saddened to learn of the untimely death of Professor Leon Schneyer who, during the last 20 years, has been a major contributor to the field of salivary biology. We would like to dedicate this volume to his memory.

John Atherton Young
Ernest Willem van Lennep

University of Sydney
December, 1977

Foreword

The most satisfying progress in biology can be achieved when a coincidence between structure and function is found. Consequently, morphology provides the basis for most biological research. The present monograph concerning the morphology of salivary glands by Professor J. A. Young and Dr E. W. van Lennep, which is intended to be followed by a second volume on *Physiology and Pharmacology of Salivary Secretion*, is therefore worthy of high appreciation. In recent years salivary glands have been used increasingly to investigate basic problems of biology such as transepithelial transport of solutes and water, protein synthesis and secretion, stimulus–secretion coupling, exocytosis and pinocytosis. The salivary glands in addition are easily accessible for perfusion, and for electrophysiological as well as biochemical studies. The experimenter, however, may be easily lost amongst the vast morphological diversities of the salivary glands within one individual as well as that of the same glands in different species. Thus, the present monograph, appearing half a century after the classic presentation of salivary gland morphology in von Möllendorff's *Handbuch*, fills a perceptible gap and should serve as a guideline for all investigators in this field.

Frankfurt-am-Main
April, 1977

K. J. Ullrich

Multa in physiologicis obscura sunt,
obscurius hac ipsa functione (sc. secretione) nihil.

Baron Albrecht von Haller (1760).
Elementa Physiologiae Corporis Humani,
Tomus II, Liber VII, p. 359.

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Introduction

In its broadest sense, a salivary gland should be defined as any cell or organ that discharges a secretion into the anterior (buccal) part of the alimentary canal. So defined, salivary glands can be said to occur, not only among most vertebrates, but also among many groups of invertebrates such as the Annelida, some Mollusca and some Arthropoda. Since the invertebrate salivary glands have a quite separate evolutionary origin to the vertebrate ones, and ought not therefore to be considered as homologous to them, no systematic coverage of invertebrate glands will be undertaken in this monograph. Readers interested in the general topic of invertebrate gland secretion are referred to review articles (Andrew, 1964; Berridge and Oschman, 1972; House, 1974; Oschman and Berridge, 1970, 1971; Wigglesworth, 1972).*

I. General Functions of Salivary Glands

In general terms, salivary glands can be considered as subserving four types of function. First, and perhaps most important, they evidently

* Of necessity our discussion will largely be confined to mammalian salivary glands since, with the exception of studies on reptilian venom (Odor, 1965; Kochva and Gans, 1966, 1970; see also p. 89) and salt glands (Young and van Lennep, 1978; see also p. 83), there are very few published studies describing the histology of salivary glands in reptiles and fewer still in birds, and, to our knowledge none describing their electron microscopic appearance.

provide lubrication to aid the swallowing of food. The lubricant may take the form of slimy mucus, as is usual in lower vertebrates, but more serous secretions, as are formed by the parotid glands of mammals, clearly achieve the same purpose when the ingested food is very dry (e.g. in ruminants). From an evolutionary point of view this is the oldest function of salivary glands and, in most vertebrates, it seems still to be the most important one. Included under the heading of lubrication is the further, obvious function of keeping the buccal cavity moist and clean with the implied effects that this must have on appetite; in man, moistening of the surfaces of the buccal mucosa seems also to be necessary for speech. Simple moistening is probably also one of the functions of von Ebner's glands, which are associated with the grooves of the circumvallate and foliate papillae of the tongue. Their secretory activity seems to be of importance for the proper working of the taste organs situated in the epithelium lining the grooves (see note 1, p. 232).

Second, salivary glands, by secreting enzymes, are able to play some role in digestion. Most animals have relatively high concentrations of amylase in their parotid saliva and somewhat lower concentrations in the mandibular secretions, although certain species of bat (*Desmodus rotundus rotundus* and *Anoura caudifera*) and the common laboratory white rat, *Rattus norvegicus* (but not *Rattus rattus* or the mouse, *Mus musculus*), have almost no amylase in their mandibular saliva, and, in both the parotid and mandibular saliva of the domestic cat and dog, the concentrations of this enzyme are rather low (Chauncey and Quintarelli, 1961; Ellison, 1967; Junqueira and Fava-De-Moraes, 1965). Although in most animals there is no doubt that, given time, salivary amylase can digest a substantial part of ingested starch, it is a matter of debate how big is the role that it normally plays, since, after swallowing, the low pH in gastric juice would be expected to reduce amylase activity and the enzyme would, of course, be subject to peptic digestion. Junqueira (see p. 102 in Sreebny and Meyer, 1964) has evidence that, in the rat, gastric mixing is slow enough to allow substantial digestive activity by salivary enzymes. Apart from amylase, proteases, including kallikrein (Bhoola *et al.*, 1973; Bhoola and Heap, 1970; Dorey and Bhoola, 1972b; Garrett and Kidd, 1975; Hirsch and Junqueira, 1965; Junqueira *et al.*, 1949; Junqueira and Fava-De-Moraes, 1965; Ørstavik *et al.*, 1975), as well as a variety of other enzymes (Ellison, 1967), seem also to be common constituents of many salivas but their biological roles are only a matter of speculation.

Recently, Hamosh and Scow (1973) found a high lipase activity in the stomach contents of suckling rats (i.e. at a time when very little pancreatic lipase is secreted) and investigated the source of this enzyme. It appears that von Ebner's glands secrete a large amount of lipase, both in the suckling rat and in the adult. In contrast to pancreatic lipase, this enzyme has a low pH optimum (about pH 5). The secretion produced by von Ebner's glands is presumably mixed with the milk during suckling, and, as there is little gastric secretion at this stage, partial digestion of milk fats can occur in the stomach.

A third role for salivary glands is the production of hormones and other pharmacologically active compounds. Although there is considerable doubt about the reality of the so-called hormone, parotin (Ellison, 1967; Ito, 1960), there seems to be general agreement that the mandibular glands of at least some species contain and secrete a protein hormone (Nerve Growth Factor) that stimulates sympathetic ganglion-cell growth (Goldstein and Burdman, 1965; Levi-Montalcini and Angeletti, 1961, 1964; Levi-Montalcini and Cohen, 1960; Schwab *et al.*, 1976), and another, called Epidermal Growth Factor, controlling epidermal keratinization and tooth eruption (Cohen, 1962; Cohen and Elliott, 1963) as well as others controlling thymic lymphocyte production (Naughton *et al.*, 1969) and two Mesodermal Growth Factors (Weimar and Haraguchi, 1975). In some animals at least, salivary glands appear to contain the hormone renin (Bhoola *et al.*, 1973; Bing *et al.*, 1967; Bing and Fårup, 1965; Cohen *et al.*, 1972; Gutman *et al.*, 1973). Since some salivary glands are known to be rich in serotonin the suggestion has also been advanced that the glands contain cells belonging to the Gastro-entero-pancreatic Endocrine System (Dietz, 1958; Feyrter, 1961; Müsebeck and Booz, 1966), although it must be said that the evidence supporting the hypothesis is rather slight. A recent study has demonstrated that the mandibular, but not the parotid or sublingual glands, in rat, mouse, rabbit and man, contain and secrete a glucagon-like protein (Lawrence *et al.*, 1977) (see note 2, p. 232).

A fourth role for salivary glands can be discerned in fur-bearing animals such as the cat and the rat, where the animals wet their fur with saliva in response to heat stress, thereby obtaining the same cooling possibility available to man by sweating (Hainsworth and Stricker, 1970). Another function, in some cases, is that of defence and of killing or paralysing prey. The only mammalian saliva known to be toxic is that of the American short-tailed shrew, *Blarina brevicauda* (Pearson, 1942, 1950). A possible defensive role of the saliva of the European hedgehog, *Erinaceus europaeus*, has been suggested by Tandler and MacCallum (1972), since this animal grooms its quills with saliva, although it is not known if the saliva is actually toxic. The venom glands of snakes are buccal glands specialized for the production of highly toxic substances for injection into victims. In one group of snakes (the sea snakes, Hydrophiidae), the large posterior sublingual gland is differentiated into a salt-excreting gland (Dunson *et al.*, 1971; Young and van Lennep, 1978) (see note 3, p. 232).

II. **Evolution and Comparative Morphology***

Among vertebrates, salivary glands show a progressive increase in complexity with progress along the evolutionary scale. With the exception of some of the Cyclostomata, salivary glands are usually completely absent in fishes and are poorly developed in Amphibia; they are well developed in reptiles, birds and mammals (Fahrenholz, 1967; Ihle *et al.*, 1927; Tucker, 1958). It is usually thought that the simplest salivary "glands" first began to develop with the appearance of secretion granules in otherwise unspecialized buccal epithelial cells; this development is then supposed to have led to the emergence of recognizable, specialized goblet cells scattered at random among unspecialized cells. Such is the picture usually seen among fishes and Cyclostomata with the exception of the lamprey, which has a large alveolar buccal gland (Gibbs, 1956). However, in some fishes the specialized cells are found gathered together into a uniform layer, folded upon itself, presumably to increase the available secretory area (crypt field).

Branched alveolar buccal glands have recently been described in the teleost fish, *Meiacanthus nigrolineatus* (Fishelson, 1974). These glands, which secrete a toxin, are used for defence. Secretion is holocrine and the PAS-positive secretory material is discharged into a groove of the fang. The structure (and mode of discharge) of this gland is similar to that of dermal poison glands of other fishes. The buccal glands of the feeding parasitic lamprey, *Petromyzon marinus*, secrete a saliva which contains anti-clotting and proteolytic substances (Lennon, 1954).

In Amphibia, crypt fields become quite extensive, particularly on the tongue. In addition, a gland develops from the epithelium of the roof of the mouth. This coiled, tubular gland, known as the intermaxillary gland, opens through a number of small ducts that pass through a hole in the vomero-palatine bone. This is the earliest instance in the evolution of

* See also pp. 114–123.