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## SALIVARY GLANDS AND SALIVA
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# Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion

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**Saliva has multiple essential functions in relation to the digestive process taking place in the upper parts of the gastrointestinal (GI) tract. This paper reviews the role of human saliva and its compositional elements in relation to the GI functions of taste, mastication, bolus formation, enzymatic digestion, and swallowing. The indirect function of saliva in the digestive process that includes maintenance of an intact dentition and mucosa is also reviewed. Finally, pathophysiological considerations of salivary dysfunction in relation to some GI functions are considered.**
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## Introduction

Control of gastrointestinal (GI) functions, in response to a stimulus such as a meal, is regulated by a number of neural reflexes. For example, the presence of food in the mouth initiates both mechanical and chemical stimuli via neural reflexes that results in an increased secretion of fluid (saliva) into the oral cavity. The major functions of the oral phase in response to a meal are the mechanical disruption of food into smaller particles by chewing and addition of saliva which aids in taste, bolus formation for swallowing (water and mucin), and initiates digestion of starch (amylase) and lipids (lipase) (Nauntofte and Jensen, 1999). In this review, we describe the role of human saliva in the upper parts of the GI tract in relation to ingestion of food, its transfer from the mouth to the esophagus, and transport of the bolus from pharynx to the stomach (Figure 1). Special attention will be paid to the multiple functions of saliva in taste, mastication, bolus formation, swallowing, enzymatic digestion, and maintenance of tooth and mucosal integrity. Moreover, we outline the impact of salivary dysfunctions on a number of GI functions and their mutual interactions.

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## Functions of saliva

The multiple functions of saliva relate both to its fluid characteristics and specific components (Table 1). Cleansing of the oral cavity, solubilization of food substances, bolus formation, facilitation of mastication and swallowing, food and bacterial clearance, dilution of detritus and lubrication of mucosa as well as facilitation of speech are examples of functions at least in part related to saliva's fluid characteristics. On the other hand, protection of the teeth by neutralization of acid by buffering actions, maintenance of supersaturated calcium phosphate concentrations with regard to hydroxyapatite, and participation in enamel pellicle formation are examples of functions related to specific components of saliva (see earlier article in this series by Nieuw Amerongen and Veerman). Furthermore, saliva components contribute to mucosal coating and provision of antimicrobial action and defense as well as digestive actions. Accordingly, saliva plays an important role in the maintenance of oral health and changes affecting salivary function may compromise the integrity of hard and soft tissues in the mouth as well as oral and GI functions.

## Saliva and the salivary glands

The mixed fluid (whole saliva) in the mouth, which is in contact with the teeth and oral mucosa, is derived predominantly from three paired major salivary glands, i.e. the parotid, submandibular and sublingual glands (together accounting for about 90% of the fluid production) as well as from the minor salivary glands in the oral mucosa. Whole saliva also contains gingival

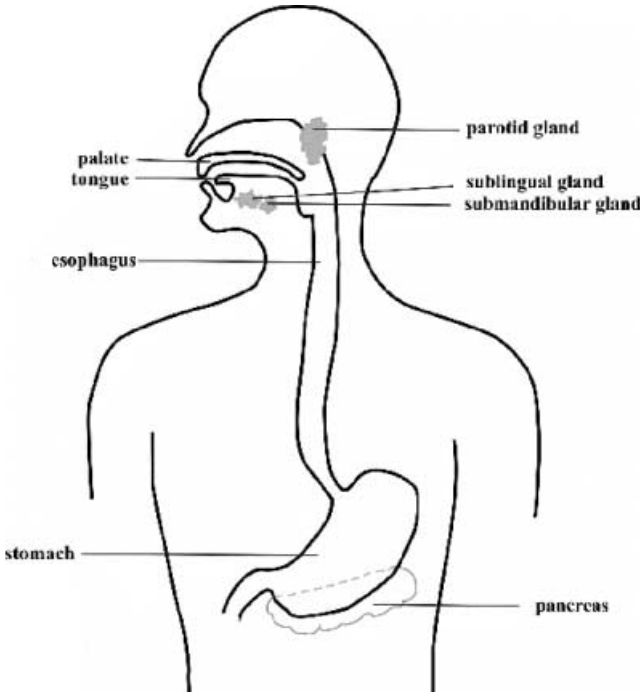


**Figure 1** Human saliva plays an important role in the first stage of the digestive process that takes place in the upper parts of the gastrointestinal (GI) tract. In the oral cavity ingested food is fragmented by mastication and mixed with saliva to form a food bolus that can easily be transferred from the mouth to the stomach by swallowing. Initial digestion of starches and lipids occurs as well

**Table 1** Multiple functions of saliva exerted in the upper part of the gastrointestinal tract and especially in the mouth

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|---|
| Mechanical cleansing of food and bacteria |
| Lubrication of oral surfaces |
| Protection of teeth and oro-esophageal mucosa |
| Oral acid neutralization and dilution of detritus |
| Antimicrobial activity |
| Dissolution of taste compounds |
| Facilitation of speech, mastication and swallowing |
| Formation of food bolus conducive for swallowing |
| Initial digestion of starches and lipids |
| Esophageal clearance and gastric acid buffering |

crevicular fluid, microorganisms from dental plaque and food debris. In healthy individuals the daily production and swallowing of saliva normally ranges from 0.5 to 1.5l and it is composed of more than 99% water and less than 1% solids, mostly proteins and salts. The serous parotid glands produce a thin, watery, and amylase-rich fluid on stimulation which accounts for up to half of the mouth volume of saliva under stimulated conditions, whereas it contributes much less to the unstimulated saliva secretion, which is produced predominantly by the submandibular glands comprising both serous and mucous acinar cell types. As compared with the parotid, the submandibular glands secrete a more viscous, mucin-rich saliva. The sublingual glands, which contribute with 1–2% of the unstimulated volume of whole saliva, mainly consist of mucous acinar cells and also produce a viscous mucin-rich saliva. The minor glands produce less than 10% of the total volume of saliva. Nevertheless, they play an important role in lubricating the mucosa, as even in the absence of local stimuli they produce saliva, thereby accounting for a large fraction of the total secretion of salivary proteins. The minor glands, which are distributed throughout the oral mucosa (labial, buccal, lingual, palatinal mucosa), are mixed glands largely comprising mucous acinar cells. However, the palatinal glands are strictly mucous, whereas the lingual von Ebner's glands are strictly serous (Young, Cook and van Lennep, 1987; Nauntofte and Jensen 1999).

## Formation of saliva and regulation of salivary secretion

Salivary secretion is regulated by a reflex arch comprising afferent receptors and nerves carrying impulses induced by actions on gustation and mastication, a central connection (salivation center), and an efferent part consisting of parasympathetic and sympathetic autonomic nerve bundles that separately innervate the glands (Figure 2). The secretory reflex arch is also under influence of higher centers in the brain (Garrett and Proctor, 1998). Saliva may be secreted in the absence of exogenous stimuli referred to as the resting or unstimulated salivary flow (Navazesh and Christensen, 1982).

Each salivary gland is composed of secretory end pieces (consisting of acinar cells) and a connecting duct system with varying lengths depending upon the gland type. It is generally believed that formation of saliva occurs in two steps (Thaysen, Thorn and Schwartz, 1954). For a complete discussion of this process see the earlier article in this series by Turner and Sugiya. Upon stimulation, the secretory end piece produces isotonic primary saliva, which has an ionic composition (NaCl) resembling that of plasma. When this fluid passes along through the duct system it is modified by selective reabsorption of sodium and chloride (without water) and some secretion of potassium and bicarbonate – the latter especially occurring under stimulated conditions. The final saliva secreted to the oral cavity becomes hypotonic with concentrations of sodium and chloride much below that of primary saliva. The final composition of saliva secreted to the oral cavity strongly depends on the flow rate. As flow rate increases, the concentrations of total protein, sodium, total calcium, chloride, and bicarbonate increase to varying extents, while the concentration of total phosphate decreases (Thaysen *et al*, 1954; Kreusser *et al*, 1972; Bardow, Madsen and Nauntofte, 2000b). The salivary flow rate, and consequently the composition of saliva, also may be influenced by the type and size of gland from which saliva is secreted (Ericson, 1971), state of hydration (Shannon, 1966), nutritional state (Johansson *et al*, 1992), the time of collection (Dawes, 1975), nature and duration of stimulus (Dawes, 1969), emotional state (Bolwig and Rafaelsen, 1972) and gender (Heintze, Birkhed and Bjørn, 1983). Reports concerning the relationship

between aging and salivary flow rates are conflicting. However, it is generally believed that age *per se* does not reduce the salivary function in healthy, non-medicated adults (Baum, 1989; Atkinson and Fox, 1992). In particular, the stimulated flow of whole saliva as well as the unstimulated and stimulated parotid flow appears to be stable with aging (Pedersen *et al*, 1999a; Sreebny, 2000). Salivary secretion follows a circadian rhythm in which the flow rate rises during the day to an afternoon peak and decreases almost to zero during sleep (Dawes, 1974). Thus, the salivary secretion increases at times of increased need of oropharyngeal and esophageal cleansing. Some saliva components show a considerable daytime variation that is independent of the variation in salivary flow rate (Atwood *et al*, 1991).

Evaluation of the salivary output can be determined by measurements of unstimulated and stimulated saliva flow rates. There are a number of different techniques

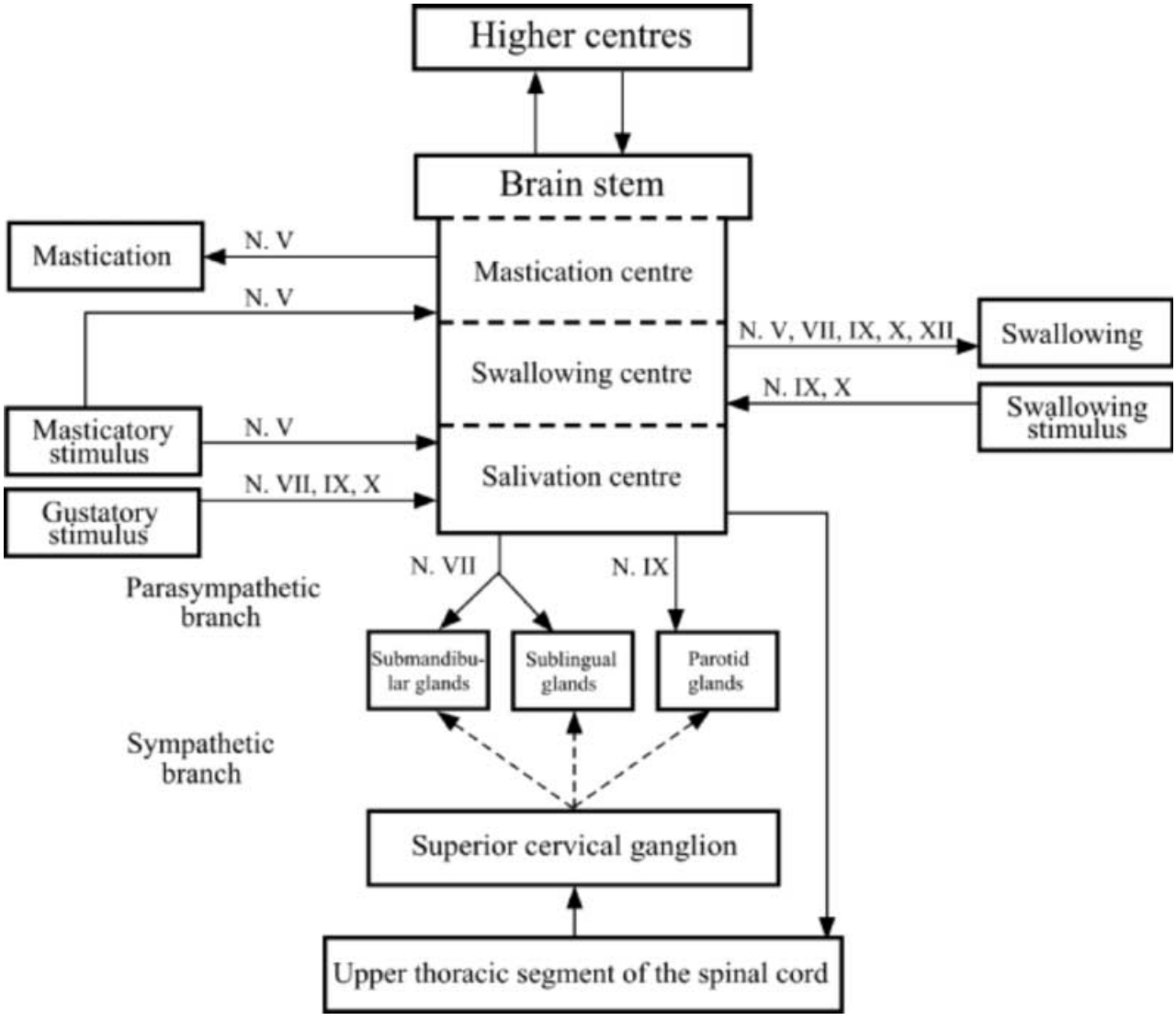


**Figure 2** The major components involved in the neural activation of the human salivary glands. *Initiation of salivation by an unconditioned reflex*: The afferent part is activated by stimulation of various sensory receptors including chemoreceptors in the taste buds and mechanoreceptors in the periodontal ligament. The afferent nerves carrying impulses to the salivary nuclei (salivation center) in the medulla oblongata are the facial, glossopharyngeal and vagal nerves (taste) and the trigeminal nerve (chewing). Olfaction and stretch of the stomach are other afferent inputs that can initiate formation of saliva. *Initiation of salivation by a conditioned reflex*: The sight and thought of food may lead to some formation of saliva. The salivary nuclei also receive impulses from other centers of the brain resulting in facilatory or inhibitory effects on salivation depending on, for example, the emotional state. *Efferents*: The salivary nuclei direct signals to the efferent part of the reflex consisting of parasympathetic (facial and glossopharyngeal nerves) and sympathetic autonomic nerves that separately innervate the glands. The sympathetic nerves, running from the sympathetic trunk, follow the blood vessels supplying the glands. Release of neurotransmitters from postganglionic neurons of both branches of the autonomic nervous system elicits secretion of saliva to the oral cavity. The facial nerve provides parasympathetic control of the submandibular, sublingual, and minor glands (except von Ebner's gland), whereas the glossopharyngeal nerves control the parotid glands (Garrett and Proctor 1998). Regarding the role of mastication and swallowing see specific sections in the text

for collection of whole saliva and of individual gland secretions. However, it is of crucial importance to select a technique, which is well defined and has demonstrated high reproducibility (Navazesh and Christensen, 1982). In healthy, non-medicated adults, the value for unstimulated and chewing-stimulated whole saliva flow rates are on average 0.3 and 1.5 ml $min^{-1}$, respectively (Bertram, 1967; Heintze *et al*, 1983; Sreebny, 2000). The salivary flow rates exhibit wide variation in range (Yeh, Johnson and Dodds, 1998), and the limits of normalcy for salivary flow in all age groups and both genders are considerable.

## Saliva and protection of teeth

Saliva exerts several important actions in the maintenance of tooth integrity (see earlier article in this series by Nieuw Amerongen and Veerman). First of all saliva dilutes and removes substances from the oral cavity which is referred to as salivary or oral clearance (Lagerlöf and Oliveby, 1994; Lenander-Lumikari and Loimaranta, 2000). Both the act of swallowing and the salivary flow rate are important to this process, and these are the principal ways by which oral bacteria and injurious, noxious agents are eliminated from the mouth. Accordingly, a high salivary flow rate results in a high clearance and vice versa (Miura *et al*, 1991). Most studies on oral clearance have concerned the rate of elimination of sugars from the oral cavity because of the cariogenic potential of this substance. In an experimental study, it was shown that oral sugar clearance becomes extensively prolonged when the whole unstimulated saliva flow rate is below 0.2 ml $min^{-1}$ (Dawes, 1983). Apart from clearing sugars, saliva also clears dietary acids and thereby protects the teeth against erosion. After a swallow, a small volume of saliva (on average 0.8 ml) will remain in the oral cavity referred to as the residual saliva (Dawes, 1983). It results in a thin film on the teeth surfaces and the mucous membranes containing mucins, enzymes, antibacterial proteins, and immunoglobulins that protects the oral cavity. The volume of this residual saliva is dependent on the maximum volume of saliva before swallowing and the unstimulated flow rate of whole saliva (Collins and Dawes, 1987). Furthermore, the residual saliva volume is negatively related to oral clearance (Dawes, 1983).

Another beneficial effect of saliva on the teeth is its ability to buffer acids. The saliva buffer capacity in relation to the development of caries has been extensively studied (Ericsson, 1959). In the physiological pH range (6.5–7.4) for saliva, a buffer capacity that originates from the content of bicarbonate, phosphate, and protein in saliva, is protective against caries, possibly by reducing the rate of tooth demineralization (Ericsson, 1959). The concentration of bicarbonate is highly dependent on the salivary flow rate in such a way that the concentration is very low in cases of severely reduced salivary flow (Grøn and Messer, 1965; Bardow, Nyvad and Nauntofte, 2001). Salivary pH and the salivary concentrations of calcium and phosphate are also important factors for maintaining saliva as saturated with respect to hydroxyapatite. As for bicarbonate, salivary pH and the concentration of calcium and phosphate are dependent on the salivary flow rate (Schmidt-Nielsen, 1946; Bardow *et al*, 2000a,b). Specific salivary proteins, statherin and proline-rich proteins, inhibit precipitation of calcium phosphate salts, and thereby protect the teeth against demineralization (Moreno, Varughese and Hay, 1979; Hay, Carlson and Schluckebier, 1987; Schupbach *et al*, 2001). In the stimulated state the bicarbonate buffer system is responsible for approximately 90% of the buffer capacity, whereas in unstimulated salivary flow rates the phosphate concentration is nearly equal to the bicarbonate concentration and they contribute almost equivalently to the buffering capacity. At low flow rates and low salivary pH below 5, proteins constitute the major buffering capacity (Lilienthal, 1955; Bardow *et al*, 2000a).

An additional protective action of saliva is the agglutination, promotion or inhibition of bacterial adhesion mediated by several salivary proteins. A number of studies have found an inverse relationship between the salivary activity of agglutination and colonization of *Streptococcus mutans*, as well as a positive correlation between the salivary activity of adhesion and dental caries (Scannapieco, 1994; Lenander-Lumikari and Loimaranta, 2000). It seems that the salivary antimicrobial proteins act in both additive and synergistic interactions; examples are the positive interactions between secretory IgA and peroxidase, lactoferrin and peroxidase, lactoferrin and lysozyme, and lysozyme and histatins. Mucins (see below) also interact with dental hard tissues and may mediate specific bacterial adhesion to the tooth surface (Scannapieco, 1994; Lenander-Lumikari and Loimaranta, 2000).

## Saliva and protection of oro-esophageal mucosa

Saliva contributes to the maintenance of oro-esophageal mucosal integrity by lubrication, clearance, buffering as well as repair (Helm *et al*, 1983; Sarosiek and McCallum, 2000). Lubrication of the oral, oropharyngeal and esophageal mucosa is to a large extent mediated by the high-molecular-weight glycoproteins, i.e. mucins, secreted from the submandibular, sublingual and minor salivary glands. The major mucins comprise a family with at least two members referred to as MG1 and MG2. The low-molecular-weight form, MG2, is more efficient in bacterial agglutination and clearance than MG1 (Tabak, 1995). Mucins are hydrophilic and retain much water, and thereby resist mucosal dehydration. Mucins also have the potential for binding to bacterial surfaces, inhibiting direct epithelial–bacterial binding, and thereby limiting bacterial colonization of oral surfaces (Tabak, 1995). Given their extensive glycosylation, mucins are able to cross-link several bacteria and therefore to aggregate bacteria, which subsequently are eliminated from the oral cavity by the act of swallowing and eventually destroyed by the gastric juice. The combination of bacterial aggregation by mucins and

mechanical salivary washing action is considered to be an important factor in limiting the microbial colonization of the oral cavity and preventing primary infection of the oral mucosa (Tabak, 1995; Lenander-Lumikari and Loimaranta, 2000). As with histatins, well-known salivary proteins with potent antifungal activities, mucins also play a role in the colonization of *Candida albicans* (Pollock *et al*, 1984; Oppenheim *et al*, 1988; Hoffman and Haidaris, 1993).

The protective function of saliva is further highligthed by the fact that it clears the esophageal acid because of normal reflux activity (Helm *et al*, 1983, 1984). Esophageal acid clearance is considered to be a two-stage process of esophageal emptying and acid neutralization (Helm *et al*, 1984). The first phase is initiated by swallowing by which one or two peristaltic waves clears about 95% of the refluxed acid volume from the esophagus. In the second phase the residual acid is diluted and buffered by subsequent swallows of stimulated saliva and then cleared from the esophagus by secondary peristaltic waves (Helm *et al*, 1984). By sweeping the gastric reflux back into the stomach, the time of contact between the esophageal mucosa and acidic reflux is significantly reduced. Increasing salivary flow results in increased bicarbonate concentration and therefore increased acid neutralization (Helm *et al*, 1984). It has been reported that stimulation of salivary secretion by the muscarinic cholinergic agonist, bethanechol, and by chewing gum enhances the esophageal acid clearance (von Schonfeld *et al*, 1997).

Epidermal growth factor (EGF) is a low-molecular-weight polypeptide first purified from the mouse submandibular gland (Cohen, 1962), but since then found in many human tissues including submandibular gland, parotid gland, kidney, pancreas and Brunner's glands of the duodenum. Salivary EGF plays an important physiological role in the maintenance of oro-esophageal and gastric tissue integrity. The biological effects of salivary EGF, and also esophageal derived EGF, include healing of ulcers, inhibition of gastric acid secretion, stimulation of DNA synthesis as well as mucosal protection from intraluminal injurious factors such as gastric acid, bile acids, pepsin, and trypsin and to physical, chemical and bacterial agents (Barnard *et al*, 1995; Marcinkiewicz, Grabowska and Czyzewska, 1998). Mastication as well as esophageal exposure to acid/pepsin result in an increased salivary EGF output (Konturek *et al*, 1989; Marcinkiewicz *et al*, 1998). Salivary EGF contributes to maintain an appropriate preepithelial esophageal defense barrier by its interaction with other salivary components such as mucins, transforming growth factor alpha and salivary prostaglandin E2 (Rourk *et al*, 1994; Sarosiek *et al*, 1994; Marcinkiewicz *et al*, 1998; Sarosiek and McCallum, 2000). In a recent animal study, the removal of rat submandibular and sublingual glands resulted in the loss of fungiform taste buds and normal fungiform taste bud maintenance. These effects were reversed by EGF supplementation, indicating a role for EGF in fungiform taste bud maintenance (Morris-Wiman *et al*, 2000).

## Saliva and taste

The sense of taste is activated during the initial stage of ingestion of food particles allowing for identification of essential nutrients and of harmful and potentially toxic compounds. Taste is a main stimulant for formation of saliva. On the other hand, presence of saliva in the oral cavity is also essential for taste perception, first of all because food particles need to be in solution in order to stimulate taste receptor cells in the taste buds within the lingual papillae (fungiform, foliate, and vallate papillae). Furthermore, taste sensitivity is related to saliva composition as each receptor cells upper surface is bathed by the oral fluids. For example, salty taste is perceived above the background salt concentrations in unstimulated saliva to which the taste receptors are adapted.

Taste impulses are carried to the brain by parasympathetic nerves, many of which travel with branches of the trigeminal nerve (Figure 2). The sensory nerves, which carry signals in response to stimulation of taste receptors are, with regards to the tongue, the facial nerve (in particular sweet, salty and acid stimuli), whereas the glossopharyngeal nerve innervates the circumvallate papillae, the back of the tongue and also the palate. Fibers of the vagal nerve innervate taste buds in the tonsillar region, the epiglottis, the pharyngeal wall and esophagus (Gilbertson, 1998).

Taste sensation is traditionally divided into the four classical basic taste modalities: sweet, salty, sour, and bitter. Each modality is based on distinct transductional systems in the single receptor cell leading to depolarization of the receptor potential and generation of action potentials. This facilitates the release of neurotransmitters, stimulating gustatory afferent nerve fibers that then carry the taste signal onto the higher-order systems. Each taste receptor cell responds, however, in varying degrees to substances that fall into more than one taste category (Spielman, 1998). Among additional taste modalities that have been identified is umami, which is elicited by monosodium glutamate and certain ribonucleotides (Gilbertson *et al*, 1997). Moreover, perception of taste is affected by general sensory impulses arising from pain ('hot spices'), food temperature and texture through the trigeminal nerve (Gilbertson, 1998).

The taste pathway activated by inputs from the facial, glossospharyngeal and vagal nerves have ipsilateral reflex connections to the salivatory center in the brain stem (Figure 2). The first neurons synapse in the tractus solitarius and its nucleus, where the secondary neurons cross the midline and travel to the thalamus. Also in this region, the third neurons communicate with the postcentral gyrus-facial area and there are also projections to the olfactory cortex (Rolls, 1998).

Increased salivary secretion in response to taste stimulation is, like chewing, induced reflexly (Lashley, 1916). The highest saliva stimulation is obtained with sour taste, which can easily result in salivary flow rates between 5 and 10 ml $min^{-1}$, followed by salt (NaCl),

sweet, and bitter (Kerr, 1961; Dawes and Watanabe, 1987). There is no additive effect on salivary flow by giving a mixture of different taste stimuli. In fact, it elicits a lower flow rate than the sum of the separate stimuli (Speirs, 1971). Furthermore, salivary flow increases with increasing concentration and amount of a separate taste stimulus (Froehlich, Pangborn and Whitake, 1987; Watanabe and Dawes, 1988; Bardow *et al*, 2001). Continuous taste stimulation usually leads to varying degrees of adaptation, which is highest for sweet taste, but lowest for sour taste (Shannon, 1958; Bornstein, Wiet and Pombo, 1993).

## Saliva and mastication

Mastication, or chewing, serves several functions including breakdown of large food particles into small pieces upon which the digestive enzymes can act, lubricating and softening of food particles into a bolus conducive to swallow, thereby facilitating GI absorption of food particles.

Mastication is controlled by a central pattern generator located in the formatio reticularis of the pons (Goldberg and Chandler, 1990) in close interaction with inputs from peripheral sense organs that have a modifying effect upon the pattern generator (Hiiemae *et al*, 1996) (Figure 2). The physical part of chewing involves the action of the teeth, masticatory muscles, temporomandibular joint, and tongue (Orchardson and Cadden, 1998). The quality of chewing can be evaluated as the masticatory performance, which is determined as the capacity to reduce the size of food particles, for example almonds, by chewing for a standardized period of time (Dahlberg, 1942; Mowlana *et al*, 1994). Masticatory performance has also been determined as the number of chews necessary to render food ready for swallowing (Chauncey *et al*, 1984). The masticatory performance is dependent on the number of teeth in functional occlusion (Akeel, Nilner and Nilner, 1992), probably the maximal biting force (Julien *et al*, 1996), and deteriorates with tooth loss (Manly and Braley, 1950). The biting force is, among other factors, positively correlated to the periodontal supporting area (Watt *et al*, 1958; Bates, Stafford and Harrison, 1976). Consequently, partial or full denture wearers have a low biting force and also a lower masticatory performance than do fully dentate age- and gender-matched individuals (Michael *et al*, 1990). The salivary flow rate also influences the masticatory performance and declines in relation to a reduction in salivary secretion (Liedberg and Öwall, 1991; Dusek *et al*, 1996). Furthermore, during pharmacologically induced hyposalivation, the number of chewing cycles before initiating a swallow increases (Liedberg and Öwall, 1991). As seen in Figure 2, increased salivary secretion in response to chewing is the result of a masticatory-salivary reflex (Lashley, 1916), which has been found to be primarily unilateral and dependent on the applied stimulus intensity (Mackie and Pangborn, 1990; Dong, Puckett and Dawes, 1995; Bardow *et al*, 2000b). The variation in the frequency of chewing between 40 and 80 strokes $min^{-1}$ does not seem to influence the salivary flow rate (Kerr, 1961).

In the oral cavity chewing activates mechanoreceptors in the periodontal membrane (Anderson and Hector, 1987; Hector and Linden, 1987). Chewing compresses the teeth into the periodontal membrane, which activates the mechanoreceptors, followed by transmission of impulses through the trigeminal nerve to the salivation center (Figure 2). The threshold for the activation of these mechanoreceptors is relatively low (Linden and Millar, 1988), i.e. less than 5% of the comfortable chewing force (Anderson, Hector and Linden, 1996). The response to chewing paraffin is normally a three- or fivefold increase in the salivary flow rate compared with the unstimulated level, and activation of mechanoreceptors is positively correlated to the salivary flow. Salivary secretion increases with the hardness and the size of the object being chewed as well as the chewing force by the chewing muscles (Kerr, 1961; Anderson and Hector, 1987; Hector and Linden, 1987; Rosenhek, MacPherson and Dawes, 1993).

Generally, there is little evidence that differences in diet can exert systemic effects on salivary flow rate and composition. However, a regular diet that requires considerable mastication or a rigid chewing gum regimen in addition to a normal diet has been shown to increase parotid salivary flow rate (Johnson and Sreebny, 1982; DeMuniz *et al*, 1983; Dodds and Johnson, 1993). The masticatory process seems to be crucial for GI absorption of a number of essential foods like meat and vegetables, but not to others such as bread, cheese, rice, fish, and egg (Farrell, 1956).

## Saliva and bolus formation

During mastication the food mixes with the saliva to form a bolus, which is a rounded, smooth, and lubricated portion of mechanically broken down food (Prinz and Lucas, 1997). The water in saliva moistens the food particles, whereas the salivary mucins bind masticated food into a coherent and slippery bolus that can easily slide through the esophagus without damaging the mucosa. The enzymatic digestion of carbohydrates and triglycerides are also initiated in the food bolus (Salt and Schenker, 1976; Hamosh and Burns, 1977). The water content of the food bolus does not seem to be the main factor for the initiation of swallowing (Watanabe and Dawes, 1988). It is more likely that the cohesive forces between the food particles in the food bolus determine when the bolus is to be swallowed. Thus, the optimal moment for swallowing appears to occur when the cohesive forces between the food particles in the bolus are strongest. The cohesive forces are both a product of the food particle size reduction and saliva secretion (Prinz and Lucas, 1997).

## Saliva and swallowing

The essential functions of swallowing are to clear the oral cavity of saliva and act as a transport mechanism of ingested food or liquid. Classically, the swallowing

process is divided into three continuous phases (Miller, 1982; Thexton and Crompton, 1998). The first phase, the oral phase, is the movement of saliva, liquid or a prepared food bolus posteriorly in the oral cavity, and the tongue sweeping the bolus or liquid through the faucal arches. This phase is considered to be voluntary. The second phase of swallowing, the pharyngeal phase, is entirely elicited by reflex (Figure 2). The pharynx elevates and contracts followed by a peristaltic wave movement of the musculature in a caudal direction, so that the saliva or food bolus descends into the esophagus. Simultaneously, the larynx elevates and moves anteriorly, thereby contributing to laryngeal closure, and the epiglottis is folded down to cover the entrance of the laryngeal vestibule and the trachea during swallowing, so that the lower respiratory tract is protected from the entry of saliva or food particles, while they pass through in the pharyngeal phase (Ertekin *et al*, 2001). The third phase is the esophageal phase, which involves a sequential contraction of the esophagus; a peristaltic movement in a cranial-caudal direction. This process is also a reflex (Logemann, 1988; Thexton, 1992). Stimulation of the posterior part of the mouth, the faucal arches and the oropharynx initiates the pharyngeal and esophageal phases. It has been shown that intact oropharyngeal sensitivity is important for the swallowing to be elicited, and if sensitivity is impaired it will cause difficulty in swallowing (Mansson and Sandberg, 1975a). One of the peripheral sensory stimulations for inducing a swallow is leakage of food, liquid or saliva into the vallecula, which is a depression placed posterior to the dorsum of the tongue and anterior to the epiglottis in the pharynx (Thexton, 1992). In these areas, the glossospharyngeal and vagal nerves innervate the sensory receptors and transmit a signal to a swallowing central pattern generator in the bilateral reticular formation of the medulla oblongata in the brainstem (Figure 2). If a pattern recognition system in the medulla oblongata identifies the incoming stimulus as appropriate for swallowing, then it triggers a reflex for the pharyngeal and esophageal phases of swallowing. The glossopharyngeal and vagal nerves control the pharyngeal and the esophageal phase, respectively (Logemann, 1988; Altschuler, 2001). Swallowing is also influenced by the cerebral cortex (Martin *et al*, 2001) (Figure 2).

In healthy individuals, the swallowing frequency is on average 600 times during a 24-h period, but demonstrates wide interindividual variations. It decreases to about six times an hour during sleep because of the decrease in salivary secretion (Lear, Flanagan and Moorrees, 1965). Oropharyngeal swallowing characteristics are independent of the wide range of normal salivary flow rates (Sonies, Ship and Baum, 1989). Swallowing of food most likely occurs when two thresholds are satisfied, a food particle size threshold obtained by chewing, and a lubrication threshold obtained by the flow of saliva into the oral cavity (Hutchings and Lillford, 1988). Thus, as noted earlier, the swallowing process apparently initiates when the cohesive forces between the food particles in the bolus are strongest (Prinz and Lucas, 1995). If particle size and concentration of food particles in the ingested food bolus are increased, the number of chews necessary before swallowing increases and the chewing frequency decreases (Prinz and Lucas, 1997). With a normal dentition and salivary flow, swallowing will happen after approximately 20–30 chews (Lucas and Luke, 1986). It has been hypothesized that delayed swallowing causes excessive salivary secretion, which reduces cohesion between food particles and dissolves the bolus, resulting in reduced swallowing efficiency and decreased oral clearance. On the other hand, difficulty in swallowing and risk of choking may also arise if the peak cohesive force between food particles is not reached because of an early swallowing. The latter is naturally also influenced by food texture, salivary flow rate, salivary composition, and salivary viscosity (Prinz and Lucas, 1997). Studies on the relationship between swallow frequency and salivary flow rate have revealed a substantial increase in salivary flow and swallowing frequency after stimulation with the muscarinic cholinergic agonist bethanechol, and a significant decrease after stimulation with the antagonist, atropine (Kapila *et al*, 1984).

The swallowing of saliva can be elicited by an adequate stimulus such as a certain amount of saliva or a critical thickness of the salivary film in the oral cavity, or when the saliva reaches peripheral receptors at the vallecula, the tongue base or in the oropharyngeal region (Mansson and Sandberg, 1975b). It has been shown that experimental infusion of 1–3 ml of water into the oral cavity elicits a swallow (Ertekin *et al*, 2001). Experimental fluid infusion in the oral cavity also increases the volume of fluid swallowed with each swallow and the frequency of swallowing. The critical thickness of the salivary film separating the oral mucosa when the mouth is closed increases to approximately 100 μm before eliciting a swallow. However, the rheology of this film varies greatly between the various parts of the oral cavity. The residual volume of saliva separating the oral mucosa after a swallow is estimated to be on average 60 μm thick (Lagerlöf and Dawes, 1984; Collins and Dawes, 1987). It has been shown that individuals who have relatively high salivary flow rates also have the shortest swallowing intervals as compared with individuals who have relatively low salivary flow rates (Rudney, Ji and Larson, 1995). Overall, there is a strong evidence of the importance of saliva both in the initiation, frequency and efficiency of swallowing.

## Saliva and digestion of starches and lipids

The most characteristic enzyme of saliva is α-amylase, or ptyalin, which breaks carbohydrates (starches) down to maltoses by cleaving the α-1-4 glycosidic bindings (Robyt and French, 1970). This breakdown to simple hexoses occurs in two phases. The luminal phase starts in the oral cavity with the initial digestion of starch by salivary α-amylase, and the second occurs in the upper small intestine as pancreatic α-amylase reaches the chyme. Salivary α-amylase is considered to be of minor

significance in the polysaccharide digestion by healthy individuals because of its rapid inactivation of gastric acid. It has its pH optimum at 6.8, but short-chain glucose polymers in the diet may stabilize the enzyme and allow maintenance of activity at acid pH during the first period in the stomach (Rosenblum, Irwin and Alpers, 1988). Accordingly, the activity of salivary α-amylase may be of importance to patients suffering from chronic pancreatic insufficiency and neonates with insufficient development of the pancreas (Alpers, 1987). Salivary α-amylase is secreted upon autonomic nerve stimulation mainly from the serous acinar cells of the parotid and to a lesser extent from the cells of the submandibular gland. Both glycosylated and non-glycosylated isoenzymes have been identified. Depending on the degree of glycosylation, their molecular weights are 54–57 kDa (Kauffman *et al*, 1970). In parotid saliva α-amylase makes up about one-third of the total protein content, whereas the content in secretions from the mixed salivary glands is much lower (Ferguson, 1999). The concentration of α-amylase increases with the salivary flow rate. Salivary α-amylase is also considered to play a role in dental health, as it binds to streptococci, and is involved in modulating the adhesion of bacteria on oral surfaces (Scannapieco, Torres and Levine, 1993).

Another salivary digestive enzyme is lingual lipase, which is secreted from acinar cells of the serous von Ebner's glands located on the posterior region of the tongue and beneath the circumvallate papillae (Hamosh and Scow, 1973). Lingual lipase breaks down a small fraction of dietary triglycerides in the oral cavity and stomach (Hamosh and Burns, 1977). Intake of a high fat diet and the act of suckling stimulate the enzymatic activity of lipase and it may act synergistically with pancreatic lipase (Harries, 1982). Lingual lipase is, however, considered to be of limited significance in lipolysis of healthy individuals, whereas it may be of particular importance in patients with cystic fibrosis and exocrine pancreatic insufficiency who exhibit varying degrees of steatorrhea because of the lack of pancreatic lipase activity (Abrams *et al*, 1984). In addition, preduodenal lingual lipase activity may also compensate for developmental deficiency in pancreatic lipase in neonates (Smith *et al*, 1986).

## Interactions between salivary gland dysfunction and GI functions

Salivary gland dysfunction, resulting in inadequate saliva composition and/or reduced salivary flow (hyposalivation), may be temporary or permanent. Hyposalivation is a term based on objective measures of the saliva secretion, where the flow rates are significantly lower than the generally accepted 'normal values'. Flow rates of unstimulated whole saliva, $\leq 0.1$ ml min$^{-1}$, and those of chewing-stimulated whole saliva, $\leq 0.5$–$0.7$ ml min$^{-1}$, fulfil the criteria for hyposalivation (Heintze *et al*, 1983; Sreebny, 2000). Inadequate salivary function is often associated with the sensation of dry mouth referred to as xerostomia. Xerostomia may occur without signs of hyposalivation (in mouth breathing, for example, xerostomia is related to mucosal dehydration), and hyposalivation may, in turn, occur without symptoms of xerostomia (Fox, Busch and Baum, 1987; Ship, Fox and Baum, 1991). Altered salivary composition may occur even when salivary flow is unaffected (Nederfors, Dahlöf and Twetman, 1994). Salivary gland dysfunction can be a manifestation of various systemic disorders or it can be a result of local functional or morphological pathology (Table 2; also see earlier article in this series by Ship). Temporary causes of salivary dysfunction include depression, salivary gland infections or side-effects of prescribed medication. Medications, and especially antidepressants, antianxiety agents, antihypertensives, diuretics, and antihistamines, are the most common cause of both hyposalivation and xerostomia (Sreebny and Schwartz, 1997). They may exert specific effects on different receptor systems on the salivary glands, such as the muscarinic cholinergic receptor, or induce compositional changes via their action on the salt and water transport and balance

**Table 2** Principal causes reportedly resulting in salivary gland dysfunction

| |
|---|
| Iatrogenic |
| Medications, e.g. antidepressants, antihistamines, and antihypertensives, polypharmacy, chemotherapy, radiation therapy of head and neck tumors, surgical trauma, graft-versus-host-disease |
| Chronic inflammatory autoimmune diseases |
| Sjögren's syndrome: primary and secondary associated with other rheumatologic and autoimmune disorders including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective tissue disease, sarcoidosis, and amyloidosis, Crohn's disease, ulcerative colitis |
| Endocrine diseases |
| Diabetes mellitus (labile), hyper- and hypothyroidism, Cushing's syndrome, Addison's disease |
| Neurological disorders |
| Mental depression, narcolepsy, Parkinson's disease, Bell's palsy, Alzheimer's disease, Holme's–Adie syndrome |
| Genetic disorders and congenital anomalies |
| Ectodermal dysplasia, cystic fibrosis, Prader–Willi's syndrome |
| Malnutrition |
| Eating disturbances, anorexia nervosa, bulimia, anemia, atrophic gastritis, dehydration, alcohol abuse |
| Infections |
| HIV/AIDS, epidemic parotitis, Epstein–Barr virus, bacterial sialoadenitis, tuberculosis |
| Other conditions |
| Hypertension, fibromyalgia, chronic fatigue syndrome, burning mouth syndrome, compromised masticatory performance |

(Clemmesen, 1988; Nederfors, Twetman and Dahlöf, 1989). Radiation therapy of head and neck cancer induces irreversible damage to the salivary gland tissue resulting in hypofunction (Valdez *et al*, 1992; see earlier article in this series by Nagler). Also, patients undergoing chemotherapy may experience the consequences of impaired salivary secretion (Main *et al*, 1984). Table 2 includes a variety of systemic disorders that affect the salivary gland tissue and function directly, such as Sjögren's syndrome, an autoimmune exocrinopathy (Pedersen and Nauntofte, 2001; also see the next article in this series by Jonsson *et al*), and cystic fibrosis (Davies *et al*, 1991), or by compromising the innervation of the glands, such as in Holme's–Adie syndrome (Kimber, Mitchell and Mathias, 1998) and Bell's palsy (Blom and Ekstrand, 1981). Examples of disorders that indirectly affect the salivary gland function are hormonal disturbances, inflammatory GI diseases, and malnutrition (Table 2). Several systemic disorders and conditions may not only be the primary cause of salivary dysfunction, they may also aggravate other conditions, thereby inducing salivary gland dysfunction. An example of such mutual interactions between salivary gland dysfunction and GI dysfunction is gastroesophageal reflux disease (GERD). GERD is characterized by retrograde movement of gastric contents through the lower esophageal sphincter because of abnormal function of the latter, delayed gastric emptying, salivary hypofunction and decreased oral and esophageal clearance. Symptoms associated with GERD include heartburn, nausea, dysphagia, dysgeusia, pharyngitis, laryngitis, fear of eating (Storr, Meining and Allescher, 2000). Decreased salivary flow rate and the concomitant decreased oro-esophageal clearance and mucosal protection may increase the risk of developing oral ulcerations, dental erosions, GERD, and gastric ulceration (Jarvinen *et al*, 1988; Biagini *et al*, 1991; Geterud *et al*, 1991; Korstein *et al*, 1991; Rourk *et al*, 1994). Given the symptoms of GERD, the disorder itself may aggravate salivary dysfunction through loss of appetite, decreased mastication and ultimately, malnutrition.

Regardless of the cause, salivary hypofunction often leads to increased risk of caries, and ultimately loss of teeth, and increased risk of oral infections, especially candidiasis (Table 3; see also earlier article in this series by Ship). The oropharyngeal functions may also be impaired resulting in speech difficulties, taste disturbances, dysphagia, esophageal acid reflux, considerable oral discomfort, and consequently, impairment of the quality of life (Gilbert, Heft and Duncan, 1993; Pedersen, Reibel and Nauntofte, 1999b). These alterations may, as with GERD, lead to further aggravation of GI dysfunctions including loss of appetite, fear of eating, special food preferences, weight loss, malabsorption and malnutrition. An important determinant of quality of life is the ability to enjoy a meal. Altered taste sensations, decreased lubrication and difficulty in swallowing because of salivary gland hypofunction, may lead to behavioral changes avoiding certain foods that are dry, spicy or crunchy and develop a preference for sweet food stuffs. Altered diet may lead to nutritional intake problems, atrophy of the masticatory muscles and decreased masticatory ability (Loesche *et al*, 1995; Dusek *et al*, 1996).

Increased caries activity is a prevalent manifestation of salivary hypofunction (Rundegren *et al*, 1985; Papas *et al*, 1993; Spak, Johnsson and Ekstrand, 1994; Pedersen *et al*, 1999a; Young *et al*, 2001) and seems primarily attributed to decreased oral clearance. A recent study of human saliva and caries-induced tooth demineralization showed that the unstimulated whole saliva flow rate rather than the saliva composition determines the rate of tooth demineralization (Bardow *et al*, 2001). Thus, lack of mechanical salivary flushing results in accumulation of food debris and dental plaque, thereby promoting an aciduric and acidogenic oral microflora that promotes the development of caries (Brown *et al*, 1975; Loesche *et al*, 1995; Almståhl and

**Table 3** Salivary dysfunction: some common symptoms and related clinical findings

| *Symptoms* | *Clinical findings* |
|---|---|
| Oral mucosal dryness and soreness | Atrophic, glazed, dry and red oral mucosa |
| Labial and pharyngeal dryness | Atrophy of the filiform papillae |
| The tongue sticks to the palate | Lobulated or fissured appearance of the tongue |
| Sensation of thirst, frequent sipping of liquid | Dry vermillion border, cracked lips |
| Burning oral sensation | Increased frequency of oral infections (e.g. recurrent oral candidiasis), angular cheilitis |
| Increased adherence of food and dental plaque to dental surfaces | Increased activity of caries (caries lesions on cervical, incisal and cuspal tooth surfaces) |
| Difficulty in speech (dysphonia) | Pharyngitis, laryngitis |
| Difficulty in wearing removable dentures | Mucosal ulcerations, denture stomatitis |
| Difficulty in swallowing (dysphagia) | Atrophic oral mucosa, esophageal dysmotility |
| Impaired masticatory function | Atrophy of the masticatory muscles |
| Taste disturbances (dysgeusia or hypogeusia) | Impairment of suprathreshold taste detection |
| Acid reflux, heartburn and nausea | Esophagitis, dental erosions |
| Bad breath | Halitosis, accumulated oral debris |
| Change in diet, for example avoiding dry, spicy foods | Malnutrition, constipation, weight loss |
| Impaired quality of life | Depression |

Wikstrom, 1999). Saliva also protects the teeth against tooth wear by erosion, attrition, and abrasion (Young *et al*, 2001). For example, the risk of developing dental erosions is five times more frequent in patients with unstimulated whole saliva flow rates $\leq 0.1$ ml $min^{-1}$ (Jarvinen, Rytomaa and Heinonen, 1991). Caries, erosion and attrition may lead to loss of teeth and a reduction in masticatory function. A further complicating factor is that absence of teeth, ill-fitting dentures, and pain in relation to eating often lead to a significant involuntary weight loss, which indirectly aggravates the salivary gland hypofunction (Sullivan *et al*, 1993). Mucosal inflammation and infections, of which oral candidiasis is the most prevalent, are often caused by a decreased salivary flow rate and concomitant reduction of salivary antimicrobial activity (Navazesh, Wood and Brightman, 1995; Abraham, Al-Hashimi and Haghighat, 1998; Almståhl, Wikstrom and Kroneld, 2001). Dysphagia is another common consequence of salivary hypofunction, but may also, among other factors, be caused by congenital or acquired neurological damage including myasthenia gravis, multiple sclerosis, Parkinson's disease or cerebrovascular accident. It has been shown that patients with Parkinson's disease have lower salivary flow rates than healthy individuals indicating that drooling in Parkinson's disease is caused by decreased swallowing efficiency and frequency (Pfeiffer, 1998; Bagheri *et al*, 1999).

## Concluding remarks

Saliva is implicated in a wide variety of physiological and biological processes that are crucial to the initial digestion in the upper parts of the GI including lubrication, cleansing, enzymatic digestion and maintenance of dental and mucosal integrity. Accordingly, salivary dysfunction is particularly detrimental to the upper GI tract, but GI dysfunction may also affect the salivary gland function. Evaluation of salivary gland function should therefore be a routine part of any oral examination in order to manage and prevent serious oral and pharyngeal consequences of salivary gland dysfunction.

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