Chapter 1

Introduction and Historical Perspective

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1.1 INTRODUCTION

All environmental nutrients and airborne chemicals required for life enter our bodies by the nose and mouth. The senses of taste and smell monitor the intake of such materials, not only warning us of environmental hazards, but determining, in large part, the flavor of our foods and beverages, largely fulfilling our need for nutrients. These senses are very acute; for example, the human olfactory system can distinguish among thousands of airborne chemicals, often at concentrations below the detection limits of the most sophisticated analytical instruments (Takagi, 1989). Furthermore, these senses are the most ubiquitous in the animal kingdom, being present in one form or another in nearly all air-, water-, and land-dwelling creatures. Even bacteria and protozoa have specialized mechanisms for sensing environmental chemicals – mechanisms whose understanding may be of considerable value in explaining their modes of infection and reproduction (Jennings, 1906; Russo and Koshland, 1983; van Houten, 2000).

While the scientific study of the chemical senses is of relatively recent vintage, the important role of these senses in the everyday life of humans undoubtedly extends far into prehistoric times. For example, some spices and condiments, including salt and pepper, likely date back to the beginnings of rudimentary cooking, and a number of their benefits presumably were noted soon after the discovery of fire. The release of odors from plant products by combustion was likely an early observation, the memory of which is preserved in the modern word *perfume*, which is derived from the Latin *per* meaning "through" and *fumus* meaning "smoke." Fire, with its dangerous and magical connotations, must have become associated early on with religious activities, and pleasant-smelling smoke was likely sent into the heavens in rituals designed to please or appease the gods, as documented in later civilizations, such as the early Hebrews. Importantly, food and drink became linked to numerous social and religious events, including those that celebrated birth, the attainment of adulthood, graduation to the status of hunter or warrior, and the passing of a soul to a better life.

In this chapter I provide a brief historical overview of the important role that tastes and odors have played in the lives of human beings throughout millennia and key observations from the last four centuries that have helped to form the context of modern chemosensory research. Recent developments, which are described in detail in other contributions to the *Handbook*, are briefly mentioned to whet the reader's appetite for what is to follow. Although an attempt has been made to identify, rather specifically, major milestones in chemosensory science since the Renaissance, some important ones have undoubtedly been left out, and it is not possible to mention, much less discuss, even a small fraction of the many studies of this period that have contributed to our current fund of knowledge. Hopefully the material that is presented provides some insight into the basis for the present Zeitgeist. The interested reader is referred elsewhere for additional perspectives on the history of chemosensory science (e.g., Bartoshuk, 1978, 1988; Beauchamp, 2009; Beidler, 1971a, b; Boring, 1942; Cain, 1978; Cloquet, 1821; Corbin, 1986; Doty, 1976; Douek, 1974; Farb and Armelagos, 1980; Farbman, 1992; Frank, 2000; Garrett, 1998; Gloor, 1997; Harper et al., 1968; Harrington and Rosario, 1992; Jenner, 2011; Johnston et al., 1970; Jones and Jones, 1953; Luciani, 1917; McBurney and Gent, 1979; McCartney, 1968; Miller, 1988; Moulton and Beidler, 1967; Moulton et al., 1975; Mykytowycz, 1986; Nagel, 1905; Ottoson, 1963; Pangborn and Trabue, 1967; Parker, 1922; Pfaff, 1985; Piesse, 1879;

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Schiller, 1997; Simon and Nicolelis, 2002; Smith et al., 2000; Takagi, 1989; Temussi, 2006; Vintschgau, 1880; Wright, 1914; von Skramlik, 1926; Zippel, 1993).

1.2 A BRIEF HISTORY OF PERFUME AND SPICE USE

The relatively rich history of a number of ancient civilizations, particularly those of Egypt, Greece, Persia, and the Roman Empire, provides us with examples of how perfumes and spices have been intricately woven into the fabric of various societies. Thousands of years before Christ, fragrant oils were widely used throughout the Middle East to provide skin care and protection from the hot and dry environment, and at least as early as 2000 BCE, spices and fragrances were added to wine, as documented by an inscription on a cuneiform text known as the *Enuma elish* (Heidel, 1949). During the greater part of the 7th to 5th Centuries BCE, Rhodian potters developed vast quantities of perfume bottles in the form of animals, birds, and human heads and busts that were shipped throughout the mediterranian area (Figure 1.1). In Egypt, incense and fragrant substances played a key role in religious rites and ceremonies, including elaborate burial customs, and whole sections of towns were inhabited by men whose sole profession was to embalm the deceased. As revealed in the general body of religious texts collectively termed the "Book of the Dead" (a number of which predate 3000 BCE; Budge, 1960), the Egyptians performed funeral ceremonies at which prayers and recitations of formulae (including ritualistic repeated burning of various types of incense) were made, and where the sharing of meat and drink offerings by the attendees occurred. Such acts were believed to endow the departed with the power to resist corruption from the darkness and from evil spirits that could prevent passage into the next life, as well as to seal the mystic union of the friends and loved ones with the dead and with the chosen god of the deceased. The prayers of the priests were believed to be carried via incense into heaven and to the ears of Osiris and other gods who presided over the worlds of the dead (Budge, 1960).

Figure 1.1 Example of a horse head perfume bottle manufactured in Rhodes circa 580 BCE. © Heritage Images (Image ID: 2-605-015).

As noted in detail by Piesse (1879), the ancient Greeks and Romans used perfumes extensively, keeping their clothes in scented chests and incorporating scent bags to add fragrance to the air. Indeed, a different scent was often applied to each part of the body; mint was preferred for the arms; palm oil for the face and breasts; marjoram extract for the hair and eyebrows; and essence of ivy for the knees and neck. At their feasts, Greek and Roman aristocrats adorned themselves with flowers and scented waxes and added the fragrance of violets, roses, and other flowers to their wines. As would be expected, perfume shops were abundant in these societies, serving as meeting places for persons of all walks of life (Morfit, 1847). In Grecian mythology, the invention of perfumes was ascribed to the Immortals. Men learned of them from the indiscretion of Aeone, one of the nymphs of Venus; Helen of Troy acquired her beauty from a secret perfume, whose formula was revealed by Venus. Homer (8th century BCE) reports that whenever the Olympian gods honored mortals by visiting them, an ambrosial odor was left, evidence of their divine nature (Piesse, 1879). Interestingly, bad odors were a key element of a number of myths, including that of Jason and the Argonauts (Burket, 1970). As a result of having been smitten with the wrath of Aphrodite, the women of Lemnos developed a foul odor, which drove their husbands to seek refuge in the arms of Thracian slave girls. The women were so enraged by their husbands' actions that one evening they slew not only their husbands, but all the men of the island. Thereafter, Lemnos was a community of women without men, ruled by the virgin queen Hypsiple, until the day when Jason and the Argo arrived, which ended the period of celibacy and returned the island to heterosexual life.

Perfumes were not universally approved of in ancient Greece. Socrates, for example, objected to them altogether, noting, "There is the same smell in a gentleman and a slave, when both are perfumed," and he believed that the only odors worth cultivating were those that arose from honorable toil and the "smell of gentility" (Morfit, 1847). Nevertheless, the use of perfumes became so prevalent in ancient Greece that laws were passed in Athens in the 6th century BCE to restrain their use. Despite this prohibition, however, their use grew unabated, and the Greeks added greatly to the

stock of fragrant plants from the East that made up the core of the perfume industry.

Perfume and incense had religious significance to the followers of Zoroaster, the Persian religious leader of the 6th century BCE, who offered prayers before altars containing sacred fires to which wood and perfumes were added five times each day (Piesse, 1879). It is noteworthy that, to this day, sandalwood fuels the sacred fires of the Parsees (modem Zoroastrians) in India and that similar rituals were required of the early Hebrews, as indicated by the following instructions from God to Moses (Exodus 30:1, 7–9. 34–38; King James version):

> And thou shalt make an altar to burn incense upon: of shittim wood shalt thou make it. And Aaron shall burn thereon sweet incense every morning: when he dresseth the lamps, he shall burn incense upon it [the altar]. And when Aaron lighteth the lamps at even, he shall burn incense upon it, a perpetual incense before the Lord throughout your generations. Ye shall offer no strange incense thereon, nor burnt sacrifice, nor meat offering; neither shall ye pour drink offering thereon.
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> And the Lord said unto Moses, take unto thee three sweet spices, stacte, and onycha, and galbanum; these sweet spices with pure frankincense; of each shall there be a light weight. And thou shalt make it a perfume <or incense>, a confection after the art of the apothecary, tempered together, pure and holy: And thou shalt beat some of it very small, and put of it before the testimony in the tabernacle of the congregation, where I will meet with thee: it shall be unto you most holy. And as for the perfume which thou shalt make, ye shall not make to yourselves according to the composition thereof: it shall be unto thee holy for the Lord. Whosoever shall make like unto that, to smell thereto, shall even be cut off from his people.

Given such instructions from God and the Christian emphasis on cleansing the soul of evil spirits, as well as the fact that Christ himself, after his crucifixion, had been embalmed in pleasant-smelling myrrh, aloe, and spices (John 19: 39–40), it is perhaps not surprising that bad smells came to signify the unholy at various times in Christian history. Indeed, St. Philip Neri reportedly found the stench emanating from heretics so great that he had to turn his head (Summers, 1926).

One of the more interesting, and tragic, uses of bad smells was to identify witches and warlocks in Europe in the late 1500s. Remy, a distinguished appointee of Charles III to the Provosts of Nancy (a court that judged all criminal cases for some 72 villages in the Nancy region of France), wrote the following in his classic 1595 monograph *Demonolatry*:

> In the Holy Scriptures the Devil is constantly referred to as Behemoth, that is to say, "the impure animal and the unclean spirit" (see S. Gregory, in *Memorabilia*, *Matthew XII, Mark I and V*, *Job XI*). It is not only because the Devil is, as all his actions and purposes show, impure in his nature and character that we should consider this name to be aptly applied to him; but also because he takes immoderate delight in external filth and uncleanliness. For often he makes his abode in dead bodies; and if he occupies a living body, or even if he forms himself a body out of the air or condensation of vapours, his presence therein is always betrayed by some notable foul and noisome stench. The gifts of the Demon are also fashioned from ordure and dung, and his banquets from the flesh of beasts that have died . . . for the most part [he] has for his servants filthy old hags whose age and poverty serve but to enhance their foulness; and these ... he instructs in all impurity and uncleanliness …. Above all he cautions them not to wash their hands, as it is the habit of other men to do in the morning; for he tells them that to do so constitutes a sure obstruction to his incantations. This is the case whether it is the witches themselves who wash their hands, as we learn from the answer freely given to her examiners by Alexia Galaea of Betoncourt at Mirecourt in December 1584, and by countless others whose names I have not now by me; or whether it is the intended victims of their witchcraft who wash their hands, as was stated by Claude Fellet (Mersuay, February 1587) and Catharina Latomia (Haraucourt, February 1587).

In contrast to the detection of witches and warlocks by stench was the verification of sainthood by a pleasant odor, the so-called "odor of sanctity." If a saint had been an impostor, a nauseating smell, rather than a delectable one, was present upon exhumation of his body (Rothkrug, 1981). This concept bears a striking resemblance to the Greek myths of the pleasant odors left by the Olympian gods who visited mortals and may well stem from the same tradition.

It should be noted, however, that cleanliness was not always the vogue for Christianity, as described by McLaughlin (1971) in a series of interesting accounts from the Middle Ages. Thus, in their repudiation of Roman values and their desire to avoid lust and sins of the flesh, early Christians often went unbathed. Every sensation offensive to humans was believed acceptable to God, and the custom of bathing the limbs and anointing them with oil was condemned. Monks shaved their hair, wrapped their heads in cowls to avoid seeing profane objects, and kept legs naked except in the extreme of winter. St. Jerome criticized a number of his followers for being too clean,

and St. Benedict, a key administrator of the early church, pronounced solemnly that "to those that are well, and especially to the young, bathing shall seldom be permitted." St. Agnes reportedly had never washed throughout her life, and a pilgrim to Jerusalem in the 4th century is said to have boasted that her face had gone unwashed for 18 years so as not to disturb the holy water used at her baptism.

During the Middle Ages, perfumery and the widespread use of spices and flavoring agents was little known in Europe, being practiced mainly by Arabs in the East. Marco Polo, visiting the China of Kublai Khan (1216–1295), noted that pleasantly perfumed silk paper money was used for exchange within Khan's kingdom (Boorstin, 1985). The dearth of smell in Europe was to change dramatically, however, as a major element of the Renaissance was the relentless search for perfumes and spices, a number of which were more valuable than silver or gold. The quest was not only for aesthetic enjoyment; some of these agents made it possible, much like cooking itself, to exploit a wider and more diverse range of foodstuffs, including ones that otherwise were unsafe or had little gastronomic appeal. In this regard, it is of interest that at the siege of Rome in 408 BCE, Alaric, the victorious king of the Goths, demanded 3000 pounds of pepper as ransom for the city, and when the Genoese captured Caesarea in 1101 BCE, each soldier received two pounds of pepper as his share of the spoils (Verrill, 1940).

Perfume was introduced, at least in a widespread sense, to medieval Europe by the crusaders. After the downfall of the Roman Empire, the perfume industry moved to the Eastern Roman Empire, and Constantinople became the perfume center of the world. Reportedly, Avicenna (CE 980–1036), the great Arab scientist, philosopher, and physician, discovered a way to extract and maintain the fragrances of plants and invented rose water (Takagi, 1989). In 1190, King Philip II (Philip Augustus, r. 1180–1223) of France granted the first charter to a perfume maker. King Charles V (Charles the Wise, r. 1364–1380) subsequently planted large fields of flowers in France to obtain perfume materials, and Charles VIII (r. 1483–1498) was reportedly the first French monarch to appoint a court perfumer. The soil, climate, and location of southern France made it a natural place for the cultivation of flowers for the perfume industry, which gained world supremacy from the late 1700s – supremacy that has continued to the present time (Vivino, 1960).

According to Piesse (1879), perfumes lost their popularity in England for more than a century prior to the Victorian era, unlike the case in France, Italy, and Spain. Related to this loss of popularity was an act, introduced into the English parliament in 1770, that warned women of the use of scents and other materials in the seduction of men (Piesse, 1879, p. 20):

> That all women, of whatever age, rank, profession, or degree, whether virgins, maids, or widows, that shall, from and after such Act, impose upon, seduce or betray into matrimony, any of his Majesty's subjects, by the scents, paints, cosmetic washes, artificial teeth, false hair, Spanish wool, iron stays, hoops, high-heeled shoes, and bolstered hips, shall incur the penalty of the law now in force against witchcraft and the like misdemeanors, and that the marriage, upon conviction, shall stand null and void.

The influences of such attempts to ban perfumes in England were short-lived, as perfume vendors thrived, although the state taxed them and required them, in 1786, to have licenses. By 1800 approximately 40 companies were making perfumes in London. Importantly, in the 19th century the revolution that occurred in organic chemistry ensured the continuance of perfume manufacturing in Britain; the first important successful synthetic odorant, coumarin, was prepared in 1863 by the British chemist Sir William Henry Perkin (Vivino, 1960).

Interestingly, for some time the odor of coffee, when first introduced into London, was viewed as offensive. Thus, a formal complaint was lodged in 1657 by the inhabitants of the parish of St. Dustant's in West London against a barber, James Farr, "for making & Selling of a Drinke called Coffee whereby in making the same he annoyeth his neighbors by evill smells" (Jenner, 2011). As with perfume manufacturing, however, such concerns were relatively short-lived. Thus, in 1708 the English historian Edward Hatton pointed out, in relation to the Farr incident, "who would then have thought London would ever have had nearly 3000 such Nusances, and that Coffee would have been (as now) so much Drank by the best of Quality, and Physicians" (Jenner, p. 30).

1.3 THE CHEMICAL SENSES AND EARLY MEDICINE

The close association between odors, spices, and medicine was undoubtedly forged long before recorded history and was likely fostered not only by stenches associated with plagues and death, but by the utility of essential oils and spices in warding off insects and microbes. Indeed, one reason why perfumes and spices were major objects of international trade in the ancient world was their medicinal properties (van der Veen and Morales, 2014). According to Morris (1984), such properties may have been as important to early civilizations as the development of the X-ray or discovery of penicillin was to our own, as modern studies confirm that numerous essential oils and spices are very effective in controlling pathogens, including *Staphylococcus* and tuberculosis bacilli. Apparently

this observation first came to the attention of European scientists in the latter half of the 19th century, when the perfumery workers at Grasse, France, were found to have a much lower rate of cholera and tuberculosis than the rest of the European population. As noted by Morris (1984, p. 15):

> Essential oils have shown startling fungitoxic properties. Oil of clove is toxic to specific growths, and oil of geranium is effective against a broad range of fungi. *Cymbopogon* grasse*s*, an Indian genus of aromatic grasses, have been found effective against *Heuninthosporium oryzae*, a source of food poisoning, *Aspergillus niger*, a cause of seborrheic dermatitis of the scalp, *Absidia ramosa*, a cause of otitis, and *Trichoderma viride*, another cause of dermatitis. Man has long guessed that these oils that the plant secreted to protect itself from insect, fungal, and microbial dangers could serve him as well. Thus it is that the story of perfumery is intimately linked to the story of pharmacy. Our ancestors could not formulate the germ theory of disease, but they assumed that whatever smelled clean and healthy must be of use in hygiene.[1]

The history of hygiene and public health is closely associated with the view that bad odors were the source, indeed often the cause, of diseases and pestilence. Places of filth and stench were, in fact, associated with a higher incidence of diseases. The stenches that developed in the cities of Europe during the Middle Ages are unimaginable to us today. Conditions were so bad that, for example, the monks of White Friars in London's Fleet Street complained that the smell from the Fleet River overcame all the frankincense burnt at their altars and killed many of their brethren (McLaughlin, 1971). Such problems were the backdrop of the spread of the plague epidemics that traversed Europe and England in the 12th to the 17th centuries. As chronicled by Corbin's (1986) fascinating account of the history of hygiene and odors in 18th-century France, health administration of that era was based on a catalog of noxious odors. Indeed, authorities sought to locate the networks of miasmas by "mapping the flux of smells that made up the olfactory texture of the city" (p. 55). The desire to localize odors and to eliminate them in an effort to ward off diseases may well have been one reason why so many odor classification schemes arose during the 18th century, including those of von Haller (1756), Linnaeus (1765), Lorry (1784/85), and Fourcroy (1798).

Throughout this period, as well as in earlier times, infection was believed to be stemmed by wearing a perfume or by burning aromatic pellets in special perfume pans, thereby masking the odors that were considered unhealthy. Lemery's *Pharmacopee universelle* (1697) cataloged the therapeutic value of aromatics and perfumes and suggested the prescription of "apoplectic balms" because "what is pleasing to the nose, being composed of volatile, subtle, and penetrating parts, not only affects the olfactory nerve, but is spread through the whole brain and can deplete its pituita and other overcourse humors, increasing the movement of animal spirits" (Corbin, 1986, p. 62). During outbreaks of the plague, defenses included the burning of incense, juniper, laurel leaves, cypress, pine, balm, rosemary, and lavender, although, if effective, they were only marginally so. Various plague waters, to be poured on handkerchiefs or into pomanders, were invented, including the original eau de cologne. Unpleasant agents were also believed to keep away the plague, and the members of many households crouched over their privies inhaling the fumes in attempts to avert the disaster (McLaughlin, 1971). Specialized plague Physicians wore garmets designed to protect them from the odors emanating from plague victums who were touched by long canes, some of which were hollow to allow for listening to the heart (Figure 1.2). Even in the late 1800s, smells were associated with illnesses, as exemplified by the belief that decaying organic matter in swamps produced malaria (mal = bad, aira = air). This theory, apparently initially proposed by Varro (116-28 BCE) and Palladius (4th century CE), was brought to the more modern stage by Morton (1697) and Lancisi (1717), but was largely abandoned after the French physician Alphonse Laveran (1881) described the responsible parasite and Sir Ronald Ross (1923) demonstrated, a few years later, its transmission by the female anopheline mosquito.

In the history of medicine, both odors and tastes have been used at various times in the diagnosis of diseases (Doty, 1981; Whittle et al., 2007). Even today, diabetes is diagnosed in some areas of the world on the basis of the patient's acetone-like breath and sweet-tasting urine, although, in general, the use of odor and taste in diagnosis has become a lost art. In addition, certain smells and tastes were known to elicit symptoms of some diseases,

[1] Billing and Sherman (1998) provide empirical support for the hypothesis that the amount of spice in foodstuffs from various world cuisines is better explained on the basis of their antibacterial than their sensory properties. These investigators quantified the frequency of use of 43 spices in the meat-based cuisines of 136 countries for which traditional cookbooks could be found. A total of 4578 recipes from 93 cookbooks was examined, along with information on the temperature and precipitation in each country, the ranges of spice plants, and the antibacterial properties of each spice. As mean annual temperatures (an index of relative spoilage rates of unrefrigerated foods) increased, the proportion of recipes containing spices, number of spices per recipe, total number of spices used, and use of the most potent antibacterial spices all increased, both within and among countries. The estimated fraction of bacterial species inhibited per recipe in each country was positively correlated with annual temperature. Although alternative hypotheses were considered (e.g., that spices provide macronutrients, disguise the taste and smell of spoiled foods, or increase perspiration and thus evaporative cooling), the data did not support any of these alternatives.

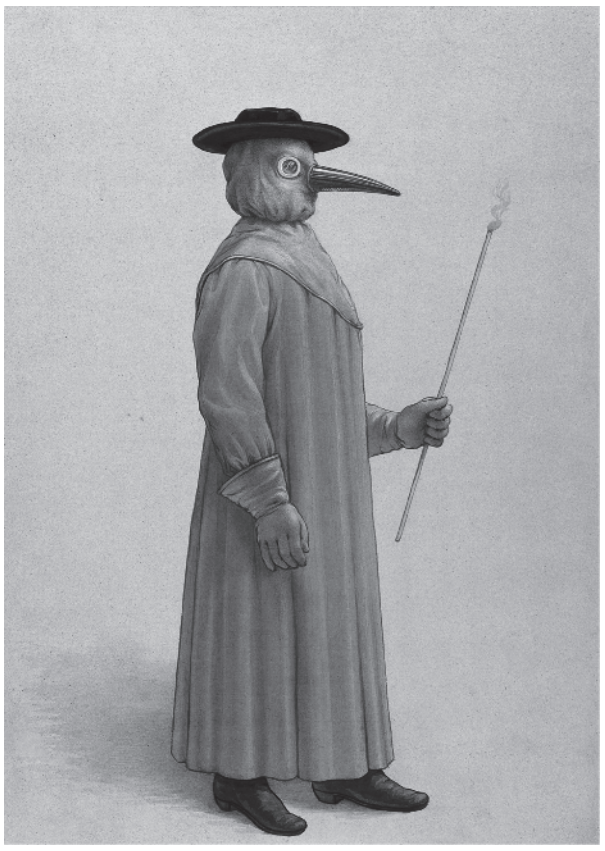

Figure 1.2 Picture of a plague doctor in his protective garb. This costume was invented in France in 1619. It was comprised of a heavy overcoat rubbed in beeswax, glass eye openings, and a beak-like extension which contained scents, such as ambergris, camphor, cloves, mint, and rose petals, to breathe through in an effort to protect the wearer from miasmatic bad air. A cane pointer was used to touch the patient. Courtesy of the Wellcome Library, London.

including epilepsy and hysteria. A classic example is reported by the Roman historian Caius Plinius Caecilius Secundus (Pliny) in his *Historia Naturalis* (circa 50 CE), where sulfur and burning bitumen (asphalt) were noted to induce seizures (Bailey, 1932), a phenomenon that has also been noted in more modern times (West and Doty, 1995). Alum (alumen), which contained aluminum, was used as a deodorant in the Roman empire, predating the use of aluminum salts as deodorants in the United States in the 1880s, as evidenced by the following quotation of Pliny, which extols its values (Bailey, 1932, p. 103):

> ...Liquid alumen has astringent, hardening, and corrosive properties. Mixed with honey, it heals sores in the mouth, pustules, and itchy eruptions. In the latter case, the treatment is applied in a bath to which honey and alumen have been added in the proportion of two to one. Alumen diminishes offensive odours of the axilla, and reduces sweating in general.

To my knowledge, there are no pre-Renaissance treatises on chemosensory dysfunction, *per se*, although descriptions of loss of olfactory function are found in the writings of the ancient Greeks and Romans, as well as in the Bible. In 2 Samuel 19:31–37, a story is told about an 80-year-old man who complained to the king that his ability to taste (or smell) had faded, along with his hearing. Theophrastus noted, in the 3rd century BCE, the following (Stratton, 1917, p. 84):

> . . . it is silly to assert that those who have the keenest sense of smell inhale most; for if the organ is not in health or is, for any cause, not unobstructed, more breathing is to no avail. It often happens that man has suffered injury [to the organ] and has no sensation at all.

Although the early Greeks routinely used surgical intervention for the treatment of polyps and other intranasal obstructive problems (for review, see Wright, 1914), the first description of the use of surgery to specifically correct anosmia was apparently made during the Renaissance by Forestus (1591; cited in Lederer, 1959):

> If it [anosmia] is from ethmoidal obstruction, or from the humor discharged from a catarrh, the latter must first be cured. If from the flesh growing from within the nose . . . it is to be cured by the surgeons by operative procedures, either with a cutting instrument, or cautery, or snare.

Claudius Galenus (Galen; 130–200 CE), whose writings had a major impact on Western medicine in general, attributed anosmia to obstruction of the foramina within the cribriform plate (an attribution made by a number of early Greeks, including Plato and Hippocrates). He correctly described the role of the nose in warming and filtering the air and alluded to empirical studies noting the permeability of the dura matter around the cribriform plate to both water and air (Wright, 1914). He believed that the organ for smell was located in the ventricles of the brain and that particles responsible for olfactory sensations passed through the foramina of the cribriform plate during inhalation. As discussed in more detail later in this chapter, this compelling idea continued until the 18th century, when light microscopy revealed that the nasal secretions came from secretory cells within the epithelium. In terms of taste, he posited that the lingual nerve communicated gustatory sensations, in accord with modern perspectives (see Chapters 29 and 32).

1.4 THE RENAISSANCE AND THE BIRTH OF MODERN STUDIES OF TASTE AND SMELL

As is evidenced throughout the volume, major advances have been made in the last quarter century in understanding the senses of taste and smell – advances that follow on the footsteps of a long tradition of scientific observations stemming from treatises written in the 16th century. Indeed, the sense of smell did not escape the attention of Leonardo da Vinci (1452–1519), who, in the *Codex Atlanticus,* presented nine diagrams next to one another in which he compared the behavior of light, the force of a blow, sound, magnetism, and odor (Riti, 1974). Cardinal Gasparao Contarini (1482–1542), an alchemist, wrote about the elements and their combinations in five brief volumes published posthumously in 1548 by Ioannes Gaignaeus. The last of these was dedicated to flavors, odors, and colors. Contarini believed that there were eight flavors or tastes and argued that cooking food or preserving fruit can produce flavors not found in nature. He felt the sense of smell was imperfect and noted that the names of flavors are often employed to explain the variety of odors. Andrea Vesalius devoted one and a half large pages to the sense of smell in his classic anatomy treatise *De Humani Corporis Fabrica* (1543), although he failed to observe the olfactory fila. In 1581, Fernel listed nine types of basic taste qualities, including the seven of Aristotle and Galen (sweet, bitter, sour, salty, astringent, pungent, harsh) and "fatty" and "insipid," the latter apparently reflecting the lack of other taste qualities (Bartoshuk, 1978). During this period, *Two Books on Taste, Sweet and Bitter* was published by Laurence Gyrllus (1566), conceivably being the first work solely devoted to taste. In 1609, Casserius described the detailed structure of the tongue, and Malpighi (1664), Casserius, 1609 and Bellini (1665) associated the sense of taste with lingual papillae. Taste buds were first identified on the barbels and skin of fishes by Leydig (1851), and later were described in mammals (Loven, 1868; Schwalbe, 1868). In 1587, Iohannes Camerarius presented a thesis to the University of Marburg entitled "Themata Physica de Odorum Natura et Affectionibus." In this work, he discussed odor classification, the relationship between taste and smell, a mechanism for explaining the function of olfaction, the ability of smelling in water, and the effect of heat from the sun on odors (Kenneth, 1928).

In 1673 Robert Boyle wrote an article on "Nature, Properties, and Effects of Effluvia" in which he provides vivid and accurate observations on such topics as olfaction in birds, odor tracking in dogs, and the physical nature of the materials released from various odor sources. In his 1675 paper, "Experiments and Observations About the Mechanical Production of Odours," he addresses some simple issues of odorant mixtures and observes that the quality and intensity of odors can be related. He provides, in his "Experiments and Considerations About the Profity of Bodies" (1684), perhaps the first description of intravascular olfaction or taste (i.e., the smelling or tasting of substances that are initially blood-borne):

> One of the notablest instances I ever met with of the porosity of the internal membranes of the human body, was afforded to me by that British nobleman, of whom our famous Harvey tells a memorable, not to say matchiless story. This gentleman, having in his youth by an accident, which that doctor relates, had a great and lasting perforation made in his thorax, at which the motion of his heart could be directly perceived, did not only out-live the accident, but grew a strong and somewhat corpulent man; and so robust, as well as gallant, that he afterwards was a soldier, and had the honour to command a body of an army for the King.
>
> This earl of Mount-Alexander . . . gave me the opportunity of looking into his thorax, and of discerning there the motions of the cone, as they call it, or mucro of the heart . . . Having then made several inquiries fit for my purpose, his lordship told me, that, when he did, as he was wont to due from time to time, (though not every day) inject with a syringe some actually warm medicated liquor into his thorax, to cleanse and cherish the parts, he should quickly and plainly find in his mouth the taste and smell of the drugs, wherewith the liquor had been impregnated. And I further learned, that, whereas he constantly wore, upon the unclosed part of his chest, a silken quilt fluffed with aromatic and odoriferous powders, to defend the neighboring parts and keep them warm; when he came, as he used to do after several weeks, to employ a new quilt, the fragrant effluvia of it would mingle with his breath in expiration, and very sensibly perfume it, not, as I declared I suspected, upon the score of the pleasing exhalations, that might get up between his cloathes and his body, but that got into the organs of respiration, and came out with his breath at his mouth, as was confirmed to me by a grave and judicious statesman, that happened to be then present, and knew this general very well.

Another early depiction of what seems to be an example of intravascular olfaction is described by Cloquet (1821). Cloquet notes that Dupuytren, a famous surgeon of the time, performed an ad hoc experiment in which he injected an odorous fluid into a vein of a dog. Soon thereafter, the dog began running around sniffing.

Unfortunately, many of the studies and observations of the period from the 1500s to the mid-1800s confused taste with flavor (which is largely dependent on the sense of smell), thereby obscuring the clear focus needed for

optimal scientific progress. In these periods, research on gustation was much more limited in scope than that on olfaction, although notable advances were made in taste research, including (1) the discovery that dissimilar metals, when placed on the tongue, produced an "electric taste" sensation (Sulzer, 1752; Volta, 1792), (2) the observation that taste sensations are localized to papillae (Malpighi, 1664; Bell, 1803), (3) the identification of the chorda tympani as the nerve that mediates taste in the anterior tongue (Bellingeri, 1818; see Bartoshuk, 1978), and (4) the demonstration that different regions of the oral cavity are differentially sensitive to different taste qualities (Horn, 1825). As noted above, the observation that taste buds exist within the papillae of the mammalian tongue and depend on an intact nerve supply came in the latter half of the 19th century (see Chapter 29; Loven, 1868; Merkel, 1880; Schwabe, 1867; Vintschgau and Hönigschmied, 1877), as did the painstaking mapping of the sensitivity of individual papillae to stimuli representing the four basic taste qualities (Öhrwall, 1891; Kiesow, 1894).

One reason for the comparatively greater interest in olfaction than taste during the post-Renaissance period stemmed from the compelling, albeit erroneous, conceptual framework in which olfactory functioning, disease, and nasal secretions were viewed. For smelling to occur, odorous bodies had to enter the brain via the foramina of the cribriform plate – the same foramina through which body humors flowed to produce nasal mucus. From this perspective, blockage or alterations in this passageway (e.g., by the changes in the viscosity of the humors) were closely related to diseases that caused (1) anosmia, (2) running noses, (3) high fever, and (4) general ill feeling.There is no doubt that the major conceptual chemosensory advance of this period, indeed perhaps of the entire modern era, was refutation of this ancient concept. The compelling nature of this theory and its adaptation to a more modern era is illustrated by Descartes' (1644) description of how olfaction works (Haldane and Ross, 1955, p. 292):

> . . . two nerves or appendages to the brain, for they do not go beyond the skull, are moved by the corporeal particles separated and flying in the air – not indeed by any particles whatsoever, but only by those which, when drawn into the nostrils, are subtle and lively enough to enter the pores of the bones which we call the spongy, and thus to reach the nerves. And from the diverse motions of these particles, the diverse sensations of smell arise.

Interestingly, convincing evidence for this notion continued to be amassed during this period, as the following quotation from Thomas Willis (1681, p. 100) indicates:

> The Sieve-like Bone in divers Animals is variously perforated for the manifold necessity and difference of smelling. A Process from the Dura Mater and manifold nervous Fibres pass through every one of its holes, and besmear the inside of the Nostrils. But as the impressions of sensible things, or sensible Species, confined as it were by the undulation or waving of the animal Spirits, ascend through the passages of these bodies stretched out from the Organ towards the Sensory; so the humidities watring the same bodies, for as much as some they may be more superfluous than usual, may distil into the Nostrils through the same ways. For indeed such humors as are perpetually to be sent away from the brain, ought so copiously to be poured upon the Organs of Smelling, as we shall shew hereafter, when we shall speak particularly of the smelling Nerves; in the mean time, that there is such a way of Excretion opening into the Nostrils, some observations, taken of sick people troubled with Cephalick diseases, do further perswade.
>
> . . . A Virgin living in this City, was afflicted a long time with a most cruel Headach, and in the midst of her pain much and thin yellow Serum daily flowed out from her Nostrils; the last Winter this Excretion stopped for some time, and then the sick party growing worse in the Head, fell into cruel Convulsions, with stupidity; and within three days dyed Apoplectical. Her Head being opened, that kind of yellow Latex overflowed the deeper turnings and windings of the Brain and its interior Cavity or Ventricles . . . I could here bring many other reasons, which might seen to perswade, that the Ventricles of the Brain, of the Cavity made by the complicature or folding up of its border, is a mere sink of the excrementitious Humor; and that the humors there congested, are purged out by the Nose and Palate.

The idea of movement of humors from the brain to the nasal cavity was most likely supported by other types of evidence as well. For example, demonstrations that dyes (e.g., Indian ink), after injection into the subarachnoid space or the cerebral spinal fluid, travel to the nasal mucosa via the cribriform plate were made in the 19th century, and there is no reason to believe that such information was not available in earlier times (see Jackson et al., 1979, for review).

It is not clear who deserves the credit for identifying the olfactory nerves in the upper nasal cavity, although, according to Wright (1914), the 7th-century Greek physician Theophilis gave one of the better anatomical accounts of their distribution, despite the potential political ramifications of going against Galen's dictates. Graziadei (1971) credits Massa, in 1536, as having first demonstrated the olfactory nerves in humans, and Scarpa, in 1789, as having shown that the fine fila olfactoria actually end in the regio olfactoria (note, however, Scarpa's 1785 article). Wright

(1914), on the other hand, notes that the Italian Anatomist Alessandro Achillini, who died in 1512, had described their intranasal distribution.

Regardless of who is responsible for their first description, there was considerable disagreement, which spanned over a century and a half, among authorities as to whether the processes that extended from the olfactory bulbs into the nasal cavity were, in fact, nerves. Indeed, even after they were generally accepted as nerves, debate lasted into the 1840s as to whether they mediated smell sensations. Francois Magendie (1824) was the primary proponent of the idea that such sensations were mediated via the trigeminal nerve, whereas Sir Charles Bell believed that the olfactory nerves subserved such sensations (Shaw, 1833). As late as 1860, experiments appeared in the literature that addressed this point (e.g., Schiff, 1860), although the more authoritative general physiology and medical textbooks from the 1820s to the 1850s correctly noted that the olfactory nerve mediates qualitative odor sensations and the trigeminal nerve somatosensory sensations (e.g., Good, 1822; Kirkes, 1849).

Schneider (1655) and Lower (1670) are generally credited as being the first to show that nasal secretions arise from glands, rather than being secreted through the cribriform plate. However, a century earlier Berenger del Carpi, who taught surgery at Bologna (1502–1527), broke the Hippocratic and Galenic tradition and denied that fluids passed through these foramina, suggesting that they actually passed through the sphenoid sinus (Wright, 1914). The evidence that nasal secretions came from glands, rather than through the cribriform plate, was clearly an important observation in the history of medicine. Collectively, the aforementioned studies placed the first nails in the coffin of the theory propagated largely by Galen that the cribriform plate is pervious to odors and that the sense of smell lies within the ventricles of the brain. Other major studies before 1890, a number of which are now considered classic, contributed the remaining nails to this coffin and include, in chronological order, those by Hunter (1786), Sömmerring (1809), Todd and Bowman (1847), Schultze (1856, 1863), Ecker (1856), Eckhard (1858), Clarke (1861), Hoffman (1866), Martin (1873), Krause (1876), von Brunn (1875, 1880, 1889, 1892), Sidky (1877), Exner (1878), Ehrlich (1886), and Cajal (1889).

An important 17th century discovery was that exocrine glands were responsible for the saliva of the oral cavity, a finding that preceded the aforementioned discovery that similar glands were responsible for nasal secretions. This discovery resulted from the identification of the ducts of the submandibular and parotid glands by Wharton in 1656 and Stensen (Latinized to Nicolaus Stenonis) in 1661, respectively. In 1677, de Graaf employed chronic salivary fistula for collecting saliva from conscious dogs. He and Bordeu (1751) recognized that smell and taste of food, as well as its mastication, increased salivary flow, preceding the classic and defining studies of Pavlov of this phenomenon in the early 1900s. However, investigators at that time did not pay much attention to the neural innervation of the salivary glands, largely due to the belief that saliva arose solely from the small arteries by the opening of pores, being then filtered by the acini (Haller, 1744). This "particle and pore theory" continued until Carl Ludwig discovered, in 1850, that electrical stimulation of the chorda-lingual nerve induced considerable flow of saliva from the submandibular gland in the dog. Ludwig also found that the secretory pressure in the submandibular duct could exceed the arterial pressure, a finding that disproved the particle and pore theory. Claude Bernard followed up Ludwig's discovery by studying reflex salivation and the role of the medulla in altering such salivation, introducing the concept of the salivary reflex arc in 1856.

Since these early studies saliva has been found to serve numerous functions, including ones related to digestion, lubrication, protection of oral tissues, and thermoregulation. In 1963, McBurney and Pfaffmann demonstrated, in a human psychophysical study, that salivary constituents (namely sodium and chloride) could affect taste sensitivity to NaCl. This important study led to the realization that saliva is not only a solvent for tastants, but forms the external milieu of the taste receptors. Their study evolved from previous speculations that lowered sodium content of the blood, such as occurs after adrenalectomy, might directly lower the threshold sensitivity of the salt receptors (e.g., Young 1949). Previously Richter and MacLean (1939) had raised the possibility that the taste threshold might be determined by the salt content of saliva. After McBurney and Pfaffmann's research, the effects of salivary constituents on taste function became the focus of numerous human psychophysical and animal electrophysiological studies. These studies led to the realization that saliva affects not only the perception of salty tasting stimuli, but also the taste of stimuli that induce the other classic taste qualities, as well as fatty tastes and tactile sensations such as astringency (Spielman, 1990; Matsuo, 2000; Bradley and Beidler, 2003).

The studies by Schultze of the olfactory neuroepithelium (1856, 1863) deserve special mention. Despite the lack of modern stains and fixatives, Schultze painstakingly provided the first comprehensive accurate description and drawings of the olfactory receptor cells and supporting cells (Zippel, 1993). He clearly identified the cilia. As noted in his 1856 paper, "… each of the various fiber cells, lying on a refracting knoblet, bears six to ten of these long hairlets which, under resting conditions, appear bristly and extend freely to the nostril air" (Zippel, p. 67). Schultze noted species differences in cilia and identified the non-ciliated supporting cells, as well as basal cells near the lamina propropria. Moreover, he noted the irregularities

in the epithelium – irregularities that were further defined by von Brunn in his 1880 and 1882 papers as follows, "… the olfactory region can be compared to a continent which has a sometimes greater, sometimes lesser density of large lakes, extends into peninsulas and splits and contains numerous islands" (Zippel, p. 71). The basal cells were named by Krause (1876). Evidence that the receptor cells arise from the periphery and grow towards the bulb was provided by His (1889).

It is of interest that many of these olfactory studies were performed in an era when the human sense of smell was not highly regarded as important to many notables, a stigma that remains today. For example, Charles Darwin, who might have been expected to champion an exploration of human olfactory studies, indicated the following in 1871 (p. 32):

> '… <human olfaction> is of extremely slight service, if any, even to savages, in whom it is generally more highly developed than in the civilised races. It does not warn them of danger, nor guide them to their food; nor does it prevent the Esquimaux from sleeping in the most fetid atmosphere, nor many savages from eating half-putrid meat'.

Darwin's negative perspective on human olfaction was forshadowed nearly a century earlier by Immanuel Kant, the renowned German philosopher, who stated in 1798:

> 'To which organic sense do we owe the least and which seems to be the most dispensable? The sense of smell. It does not pay us to cultivate it or to refine it in order to gain enjoyment; this sense can pick up more objects of aversion than of pleasure (especially in crowded places) and, besides, the pleasure coming from the sense of smell cannot be other than fleeting or transitory'.

Leading 19th century physicians similarly denigrated the human sense of smell. In 1870, Notta pointed out that smell dysfunction did not represent a life-threatening infliction (Notta, 1870) and three years later Legg indicated, in *The Lancet*, that smell loss "barely amounts to a discomfort" (Legg, 1873). In 1881, Althaus, also writing in *The Lancet* (p. 771), stated the following (p. 771):

> if Prince Bismarck and M. Gabetta were to become suddenly blind and deaf, the destinies of Europe would no doubt be changed; while if these two men were to lose their smell and taste, things would probably go on much in the same manner as they do now.

Leading comparative anatomy of the late 19th century fueled, to some degree, the argument that the human sense of smell is not very important and that olfaction is largely a primitive element of the brain. Broca (1878), using the rhinal fissure as a dividing line, separated the brain into a basal (rhinencephalon) and a superior (pallium) portion. Animals with a large basal region were termed "osmatic" and were assumed to have a keen sense of smell. Those with a small basal brain region were termed "anosmatic" and were assumed to have little or no smell function (Schiller, 1997). Broca extended this concept into human mental development, concluding that the basal, i.e., limbic, part of the brain represented the emotional "brute," whereas the newer cerebral lobes represented the development of intelligence.[2] In 1890, Turner further refined Broca's schemata by dividing animals into three groups, described as follows (p. 106):

1. Macrosmatic, where the organs of smell are largely developed, a condition which is found, for example, in the Ungulata, the proper Carnivora and indeed in the majority of mammals.
2. Microsmatic, where the olfactory apparatus is relatively feeble, as in the Pinnipedia, the Whalebone Whales, Apes, and Man.
3. Anosmatic, where the organs of smell are apparently entirely absent, as in the Dolphins, and it may be in the Toothed Whales generally, though, as regards some genera of Odontoceti, we still require further information.

That being said, considerable efforts were made in the 19th century to quantify human smell and taste function, particularly in Germany where Hermann von Helmholtz's student, Wilhelm Wundt, founded the first experimental psychology laboratory in 1879. Indeed, the dawn of human chemosensory psychophysics occurred in the mid-to-late 19th century, as illustrated by studies in which specific taste qualities were painstakingly mapped on the tongue by Öhrwall (1891) and Kiesow (1894). Although Boring (1942) credits Fischer and Penzoldt (1886) as having measured the first absolute threshold to an odorant, Valentin, in 1848, described a procedure that assessed olfactory sensitivity that predated even Fechner's development of formal threshold methodology by a dozen years. Zwaardemaker (1925), who invented the important draw-tube olfactometer (Chapter 11) and who performed sophisticated studies on a wide range of topics, including adaptation and cross-adaptation, credited Passy (1892) as having made an important step in the development of olfactometry. In essence, Passy dissolved a given amount of odorant in alcohol in a 1:10 ratio. This new solution was then again diluted in such a ratio, and this was repeated

[2]This dichotomy was rejuvenated by subsequent investigators, including Maclean's triune brain in which sectors of the brain were divided into the reptilian, paleomammalian (limbic system), and neomammalian (neocortex) complexes (Maclean, 1990).

over and over to provide a series of dilution steps. For testing, a small amount of solution at each concentration was placed in liter bottles which were heated slightly to evaporate the alcohol. Such bottles were then sampled from highest concentration to lowest concentration until no smell was discernible to the subject. Zwaardemaker, however, expressed concern that the alcohol diluent used by Passy might influence the perception of the test odorant. This potential problem was eliminated to a large degree in the successive dilution series described by Toulouse and Vaschide (1899) and Proetz (1924), where water and mineral oil, respectively, served as the diluents.

From the clinical perspective, the more scholarly physicians of the 18th and 19th centuries were very much aware of the major types of olfactory disorders that we recognize today. Good (1822), for example, classified disorders of olfaction into the following categories: *Parosmia acris* (acute smell), *Parosmia obtusa* (obtuse or distorted smell), and *Parosmia expers* (anosmia or lack of smell). Good (1822, pp. 260–261) notes the following regarding *Parosmia obtusa*:

> The evil is here so small that a remedy is seldom sought for in idiopathic cases; and in sympathetic affections, as when it proceeds from catarrhs or fevers, it usually, though not always, ceases with the cessation of the primary disease. It is found also as a symptom of hysteria, syncope, and several species of cephalaea, during which the nostrils are capable of inhaling very pungent, aromatic, and volatile errhines, with no other effect than that of a pleasing and refreshing excitement.
>
> Where the sense of smell is naturally weak, or continues so after catarrhs or other acute diseases, many of our cephalic snuffs may be reasonably prescribed, and will often succeed in removing the hebetude. The best are those fond of the natural order verticillatae, as rosemary, lavender, and marjoram; if a little more stimulus be wanted, these may be intermixed with a proportion of the teucrium *Marum*; to which, if necessary, a small quantity of asarum may also be added: but pungent errhines will be sure to increase instead of diminishing the defect.

Good's observations concerning *Parosmia expers* were as follows:

> This species is in many instances a sequel of the preceding [Parosmis obtusa]; for whatever causes operate in producing the former, when carried to an extreme or continued for a long period, may also lay a foundation for the latter. But as it often occurs by itself, and without any such introduction, it is entitled to be treated separately. It offers us the two following varieties:
>
> Organica. Organic want of smell. From natural defict, or accidental lesion, injurious to the structure of the organ.
>
> Paralytica. Paralytic want of smell. From local palsy.
>
> The FIRST VARIETY occurs from a connate destitution of olfactory nerves, or other structural defect; or from external injuries of various kinds; and is often found as a sequel in ozaenas, fistula lachrymalis, syphilis, small-pox, and porphyra. The SECOND is produced by neglected and long continued coryzas, and a persevering indulgence in highly acrid sternutatories.

Among the more detailed and vivid descriptions of cases of anosmia in the 19th century literature are those of Ogle (1870). He describes in detail three cases of anosmia due to head injury in which taste function was intact, a case of anosmia associated with facial palsy, a viral-induced case of anosmia, a case of anosmia due to obstruction, and three cases of unilateral olfactory loss that were related to aphasia, agraphia, and seizure attributable to brain lesions. The olfactory losses due to head injury were believed to be caused by the shearing of the olfactory filaments at the level of the cribriform plate from movement of the brain produced by the blow. In this explanation of the problem, Ogle notes (p. 266) that "the anterior brain rests directly upon the bones of the skull, and is not separated from them as is the case elsewhere by the interposition of cerebro-spinal fluid."

1.5 THE MODERN ERA: 20th AND 21st CENTURY ADVANCES

The major progress in the field of chemosensory research that has taken place in the 20th and 21st centuries has largely been due to contemporaneous technical advances in other fields of science. Included among such advances, which are not mutually exclusive, are (1) the invention of sensitive methods for recording minute electrical potentials from the nervous system, including measurements taken from the scalp (e.g., electroencephalography) and recordings from single cells and isolated components of cell membranes, (2) development and refinement of statistical methodologies and experimental designs, such as those employed in epidemiology and pharmacology, (3) development of novel and sensitive psychophysical techniques, (4) the invention of new histological stains and radically novel histological procedures, such as those that utilize autoradiography, immunohistochemistry, and various tracing agents, (5) the development of biochemical techniques for assessing endocrine and neurotransmitter receptor events, including radioimmunochemistry, (6) the

continued development and refinement of microimaging systems, including the electron microscope, (7) advances in tissue preparation procedures that optimize such imaging technology, such as osmium preparations and freeze fracture techniques, (8) the invention of computerized tomography (CT), magnetic resonance imaging (MRI), and other noninvasive imaging tools useful for evaluating the structure of the brain in vivo, (9) the development of functional imaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional MRI (fMRI), and (10) innumerable advances in biology, including the development of the fields of animal behavior and, importantly, molecular biology and molecular genetics, where, for example, recombinant DNA techniques and gene manipulations have made it possible to identify and confirm the roles of many proteins involved in olfactory and gustatory function.

Obviously, in this introduction it is only possible to mention a few of the many important observations made in the last hundred and fifty years or so that have contributed to the present research climate. The areas selected for exposition were chosen, in part, on the basis of the amount of chemosensory research they have generated and are continuing to generate. These and other important events or areas of research are mentioned in more detail throughout the *Handbook.*

1.5.1 Electrophysiological Studies

A major 20th-century milestone that had a significant impact on modern chemosensory science was the development of means for electrophysiologically recording nerve impulses from the brain, including the olfactory and gustatory receptors and pathways. Although crude electrical recordings were obtained from the olfactory system in the late 19th century (e.g., Saveliev, 1892; Garten, 1900), the sophisticated equipment necessary for reliable recordings, including sensitive electrodes, was not available until well into the 20th century (e.g., the oscilloscope was invented in 1922; Erlanger and Gasser, 1937). The earliest extracellular recordings of single-cell gustatory primary afferent nerve activity were made by Zotterman (1935) and Pfaffmann (1941), the latter of whom was working in Lord Adrian's laboratory at the time. Kimura and Beidler (1961) and Tateda and Beidler (1964) were the first to record from single cells within the taste bud. Recordings of olfactory nerve fiber bundles were made by Beidler and Tucker (1955); recordings of single-cell olfactory receptor activity from extracellular electrodes were obtained by Hodgson et al. (1955) and Gesteland et al. (1963, 1965). The first evidence for between species differences in single-cell neural firing was presented by Beidler et al. (1955) and Pfaffmann (1955), a point that was later exploited by Frank (1973) in the use of the hamster as a model for species, such as the human, that exhibit salient responsiveness to sweet-tasting stimuli.

These observations were harbingers for the more recent discoveries of the receptors that largely defined their afferent activity. Other manifestations of this advance in technology include (1) the recording of multicellular summated potentials at the levels of the vertebrate olfactory mucosa [the electro-olfactogram (EOG); Hosoya and Yoshida, 1937; Ottoson, 1956] and insect antenna (the electroantennogram; Schneider, 1957a, b), (2) recording of transduction currents in isolated olfactory receptor cells (e.g., Kurahashi and Shibuya, 1987; Firestein and Werblin, 1989), (3) measurement of ion channel activity in restricted patches of olfactory or taste cell membranes (Nakamura and Gold, 1987; Kinnamon et al.,1988); (4) topographic analysis of responses within the olfactory epithelium and olfactory bulb (e.g., Kauer and Moulton, 1974; Kubie and Moulton, 1980; Leveteau and MacLeod, 1966; Mackay-Sim et al., 1982; Mozell, 1964, 1966; Moulton, 1976), (5) the application of voltage-sensitive dyes for recording electrical changes in chemosensory neural tissue (Kauer, 1988), (6) the recording of olfactory- and taste-evoked potentials in higher brain regions (e.g., Funakoshi and Kawamura, 1968, 1971; Kobal and Hummel, 1988; Kobal and Plattig, 1978; Plattig, 1968/1969), and (7) electrophysiological mapping, in animals, of local, as well as more global, olfactory, and gustatory brain circuits (e.g., Emmers et al., 1962; Getchell and Shepherd, 1975; Komisaruk and Beyer, 1972; Mori and Takagi, 1978; Motokizawa, 1974; Nicoll, 1971; Norgren, 1970; Pfaffmann et al., 1961; Rall et al., 1966; Scott and Pfaffmann, 1972; Shepherd, 1971, 1972; Tanabe et al., 1973, 1975).

The first studies to directly stimulate sectors of the human brain in conscious patients so as to map brain centers associated with taste and smell were those of Foerster (1936) and Penfield and Faulk (1955). These neurosurgeons identified key cortical regions associated with taste and somatosensory perception. Subsequently, numerous anatomical and electrophysiological studies in nonhuman primates confirmed that the primary "gustatory cortex" is located within the insular cortex and parietal operculum and that these regions contain cells sensitive to both gustatory and somatosensory inputs (e.g., Benjamin and Burton, 1968; Ogawa et al., 1989) (see Chapters 32 and 35).

1.5.2 Studies of Receptor Function

Remarkable progress has been made in the last 30 years in identifying the initial events that occur when odorant or tastant molecules activate receptor cells, as is evidenced by the studies reviewed in detail in Chapters 5, 6, 30,

31, and 40–42. A number of these studies have been performed solely at the molecular genetic or biochemical level, but many others have used electrophysiological measures, sometimes in combination with biochemical ones, to address conductance changes that occur in the cell membrane following receptor activation, including activation of single channels. Major technicial advances have made it possible to identify the olfactory and gustatory receptors, establish the involved second messengers and ion channels, and to understand phylogenetic associations and likely patterns of evolution. In olfaction, the discovery of a protein termed olfactory marker protein, which is expressed in mature olfactory receptor cells of a range of species, has proved invaluable to the study of olfactory transduction and the anatomy of the olfactory pathways (Margolis, 1972; Farbman and Margolis, 1980). Another protein, alpha-gusducin, has proved similarly useful in understanding taste transduction (McLaughlin et al., 1992a,b).

Soluble proteins have been identified within the olfactory mucus that may play multiple roles, most notably assisting in the transport of hydrophobic molecules to receptor regions or in stimulus removal and/or deactivation (Lee et al., 1987; Pevsner et al., 1988a, b; Schmale et al., 1990). Such "odorant binding proteins" are also found in insects, where they have been said to represent "a major evolutionary adaptation regarding the terrestrialization of the olfactory system, converting hydrophobic odorants into hydrophilic ones by increasing their aqueous solubility" (Vogt et al., 1991, p. 74). The role of mucus and saliva in early elements of olfactory and gustatory transduction are described in Chapters 3 and 28.

It is now appreciated that the interaction of stimulus molecules with the receptor membrane opens or closes, directly or indirectly (i.e., via second-messenger systems), membrane channels, resulting in a change in the flux of ions and alteration of the cell's resting potential (see Chapters 5, 6, 30, 31, 40–42) . Taste receptor cells possess a number of ion channels identical to some of those found in neurons (i.e., voltage-gated Na+, Ca^2+, and K+ channels, as well as Ca+-mediated cation channels and amiloride-sensitive Na+ channels) and release a neurotransmitter that activates the first-order taste neuron (Roper, 1989). In the case of olfaction, the receptor cell is the first-order neuron, so changes in membrane potential, if of sufficient magnitude, produce the action potentials. Bronshtein and Minor (1977) provided the first scientific evidence that these interactions occur on the olfactory cilia, an observation supported by subsequent workers (e.g., Rhein and Cagan, 1980, 1983; Lowe and Gold, 1991; Menco, 1991; see Chapters 3–7). In taste, such interactions occur on microvillae associated with apical portions of the taste receptor cell (Avenet and Lindemann, 1987, 1990; Heck et al., 1984), a region whose importance was apparently first stressed by Renqvist in 1919 (see Kinnamon and Cummings, 1992). Although occluding junctions among cells in the apical region of the taste bud restrict most stimuli to that region, molecules of low molecular weight may permeate these junctions (Holland and Zampighi, 1991). Interestingly, actin filaments are found around the taste pore, suggesting that taste buds may contract or expand, possibly in response to the type of taste stimulus that they encounter (Ohishi et al., 2000). Until the application of electron microscopy to taste buds in the 1950s (de Lorenzo, 1958; Engström and Rytzner, 1956a, b), taste buds were believed to contain cilia, not microvillae.

In the 1980s and 1990s, a number of important findings led to a fuller understanding of the initial events in olfactory transduction. A calcium sensitive enzyme adenylyl cyclase (type III), which is usually coupled to a G-protein, was found to be highly active in olfactory cilia (Kurihara and Koyama,1972; Pace et al., 1985). Several laboratories found that odorants increase, in a dose-related manner, intracellular cyclic adenosine 3′,5′-monophosphate (cAMP) in olfactory receptor cells, triggering the opening of cAMP-gated cation channels (Bruch and Teeter, 1989; Nakamura and Gold, 1987; Pace et al., 1985; Pace and Lancet, 1986; Sklar et al., 1986). In addition to cAMP, cGMP was found to play a likely role in the modulation of the sensitivity of olfactory receptor neurons, such as during adaptation (Leinders-Zufall et al., 1996). A positive correlation was noted between an odorant's ability to activate adenylyl cyclase in a frog ciliary preparation and both the magnitude of the EOG response it produces in frog epithelia (Lowe et al., 1989) and its perceived odor intensity to humans (Doty et al., 1990), suggesting a gross association between the amount of adenylate cyclase activated and the intensity of odor perception.

In 1989, Jones and Reed (1989) isolated a guanine nucleotide-binding protein (G-protein) in olfactory cilia, thereby lending strong support to the view that odorant receptors are G protein-coupled receptors. This protein had 88% sequence identity to conventional G_s and was termed $G\alpha_{olf}$ or G_{olf}. Although G-proteins other than G_{olf} (e.g., G_{i2} and G_o) have been identified in olfactory receptor cells, they appear not to be involved in early transduction events, presumably assisting in such processes as axonal signal propagation, axon sorting, and target innervations (Wekesa and Anholt, 1999).

In 1991, the identification of the primary receptor family responsible for vertebrate olfactory transduction was made by Buck and Axel (1991). This work was the basis for the 2004 Nobel Prize in Medicine or Physiology. Under the assumption that olfactory receptors have elements in common with a large superfamily of surface receptors that evidence seven transmembrane domains and linkage to G-proteins and second-messenger systems, these investigators synthesized oligonucleotides that coded for conserved

(i.e., nearly invariant) amino acid sequences found among receptors from sensory systems other than olfaction. These oligonucleotides were then used as molecular probes. Eighteen clones were found that coded for proteins with seven transmembrane domains within olfactory tissue, but not within brain, retina, or various non-neural tissues. The variability in the amino acid sequences was found to be in regions of the molecule believed to be important in the binding of ligands in other receptor proteins with seven transmembrane domains. Based on this information, it was concluded that a large number of diverse receptors were involved in olfactory transduction and that such receptors comprised a very large multigene family that "encodes seven transmembrane domain proteins whose expression is restricted to the olfactory epithelium."[3]

Subsequent work has found that the number of functional olfactory receptors varies among species, being nearly 2000 in the African elephant, over 1000 in murine rodents, and around 400 in humans and chimpanzees (Glusman et al., 2001; Zozulya et al., 2001; Young and Trask, 2002; Zhang and Firestein, 2002; Niimura et al., 2014). The number of genes appears to be influenced by the environment to which a given species is adapted. In the mid-1990s, it was found that each receptor gene is expressed in only a small percentage of neurons (Ressler et al., 1994) and that a given neuron expresses only one allele of a single receptor gene (Malnic et al., 1999; Lomvardas et al., 2006), although this generalization does not apply to all vertebrates (e.g., fish; see Chapter 23). It was also found that neurons that express the same odorant receptor gene converge on the same glomeruli (Ressler et al., 1994; Mombaerts et al., 1999). Such findings, along with those from other studies (e.g., Johnson and Leon, 2000), have largely clarified the topographic relationships between olfactory receptor cells and the olfactory bulb – relationships that were incompletely and only grossly known from earlier anatomical and physiological studies (e.g., Adrian, 1953; Le Gross Clark, 1951; Døving and Pinching, 1973).

It is important to note that the gene family encoding insect olfactory receptors likely evolved independently from that encoding vertebrate olfactory receptors. This is reflected by the fact that genes of these two families lack sequence homology (Wistrand et al., 2006). One major difference between the two families was discovered in Drosophila, where a "chaperone" receptor (Or83b), unlike other olfactory receptors, was found to be expressed in all olfactory receptor neurons. Instead of binding volatile ligands, this receptor forms dimers with other olfactory receptors, resulting in ligand-detecting receptor complexes that enhance receptor sensitivity (Benton et al., 2006; Larsson et al., 2004; Neuhaus et al., 2005).

Trace amine-associated receptors (TAARs), a specific family of G-protein coupled receptors, have been identified that function as chemosensory receptors for several volatile amines in mice (Liberles and Buck, 2006) and a range of other vertebrate species (Hashiguchi and Nishida, 2007). TAARs are expressed in the olfactory epithelium, being most abundant in fish and less abundant in tetrapods. Humans express only five putatively functional TAARs, in contrast to zebrafish, who express 109 such TAARs (Hashiguchi and Nishida, 2007). The function of these receptors is yet to be determined, although amines are found among a number of biological secretions in rodents.

As described in detail in Chapter 5, the olfactory-specific receptor guanylyl cyclase D (GC-D, *Gucy2d*) was cloned in the mouse by Fulle et al. (1995). Less than 0.1% of the bipolar olfactory receptor neurons express the GC-D transcript, and these neurons appear to be randomly dispersed among the classic olfactory receptor neurons. Their axons project to unique glomeruli that form a "necklace-like" structure in the caudal olfactory bulb. The function of these unique neurons, which mainly employ cGMP as their second messenger, is poorly understood, although there is evidence that they detect natriuretic peptides from the urine of conspecifics, as well as atmospheric CO2 (Hu et al., 2007).

A number of olfactory, taste, and vomeronasal organ receptors have now been deorphened (Glatz and Bailey-Hill, 2011; Kratuwurst et al., 1998; Malnic et al., 1999; Touhara, 2007; Touhara et al., 1999; Wetzel et al., 2001; Zhao et al., 1998; for invertebrates, see Carlson, 2001). For example, Zhao et al. (1998) used an adenovirus-mediated gene transfer procedure to increase the expression of a specific receptor gene in an increased number of receptor neurons in the rat olfactory epithelium, demonstrating ligand-specific increases in EOG amplitude. Krautwurst et al. (1998) employed a polymerase chain reaction (PCR) strategy to generate an olfactory receptor library from which cloned receptors were screened for odorant-induced responsiveness to a panel of odorants, as measured by an assay sensitive to intracellular Ca^{2+} changes. Several receptor types with ligand specificity were found, including one differentially sensitive to the (−) and (+) stereoisomers of citronella. More recently, Saito et al. (2009) deorphanized 10 human and 52 mouse olfactory receptors. Some were broadly tuned to a range of odorants ("generalists") whereas others were narrowly tuned ("specialists") to a small number of structurally related odorants.

[3]It is now known that receptor-encoding complement DNA can be expressed in some non-neuronal cells, which, when stimulated with appropriate ligands, generate second-messenger responses (e.g., Raming et al., 1993). The same receptor genes described by Buck and Axel (1991) have now been identified in tissues far removed from the olfactory cilia, including sperm (Parmentier et al., 1992) and the heart (Hillier et al., 1996).

An explosion in the identification of taste receptor genes has occurred in the last decade. Nearly 50 taste receptor genes have been identified and more than 2,000 genes have been associated with primate taste buds (Hevezi et al., 2009). Receptors on three main classes of taste cells have been defined. Type I cells, which are involved in neurotransmitter clearance and ion redistribution and transport, mediate salty taste sensations via specialized Na^+ channels (Chaudhari and Roper, 2010). Type II cells harbor G-protein-coupled receptors that produce sweet, umami (monosodium glutamate-like), and bitter sensations, the latter being mediated by a family of ∼30 such receptors. Type III cells have been found to have specialized proton channels for hydrogen ions and mediate sour sensations (Chang, Waters, and Liman, 2010). Of considerable importance is the discovery that sweet receptor genes are compromised in a wide range of vertebrtate species, including bats, horses, cats, chickens, zebra finches, and the western clawed frog (Li et al., 2005; Zhao et al., 2010), as are bitter and umami receptors for dolphins (Feng et al., 2014) (see Chapter 43). During the early part of the 21st century the sequencing and functional expression of umami human taste receptors for glutamate were made, solidifying the concept that umami represents a fifth taste quality (Chaudhari, Landin and Roper, 2000; Nelson et al., 2002; Li et al., 2002). Kikunae Ikeda (1909) was the first to identify glutamic acid as the agent associated with the umami taste, a word derived from the Japanese adjective Umai, meaning delicious (Lindemann, Ogiwara and Ninomiya, 2002).

It has now become apparent that both bitter and sweet taste-related receptors, heretofore believed to occur only in taste buds, are present elsewhere in the body, most notably in the alimentary and respiratory tracts. In pioneering work, Hofer and Drenckhahn (1998), Hofer et al. (1996) discovered that α-gustducin, the taste-specific G-protein α-subunit, is expressed in so-called brush cells within the rat stomach, duodenum, and the pancreatic duct system. Such cells, which were first described in the trachea by Rhodin and Dalham in 1956, have been found in olfactory epithelium (where they are termed microvillar cells; Okano et al., 1967; Moran et al., 1982), lung (Meyrick and Reid, 1968), pancreas (Nakagawa et al., 2009), gall bladder (Luciano and Reale, 1979), and, in nonhumans, the vomeronasal organ (Adams, 1978). Although they have no direct contact with neurons, brush cells are rich in nitric oxide (NO) synthase. NO defends against xenobiotic organisms, protects the mucosa from acid-induced lesions, and, in the case of the gastrointestinal tract, stimulates vagal and splanchnic afferent neurons. NO further acts on nearby cells, including enteroendocrine cells, absorptive or secretory epithelial cells, mucosal blood vessels, and cells of the immune system (Hofer et al., 1998).

Wu et al. (2002) were the first to identify members of the T2R family of bitter receptors within the gastrointestinal tract and in enteroendocrine cell lines. Sweet taste receptors of the T1R family were first found in the intestinal tract and the STC-1 enteroendorine cell line by Dyer et al. (2005). Mace et al. (2007) found that all members of the T1R family were expressed in Paneth and other cells in rat jejunum and were involved in the stimulation of glucose absorption. That same year, Margolskee et al. (2007) and Jang et al. (2007) demonstrated that T1R3 receptors and gustducin play decisive roles in the sensing and transport of dietary sugars from the intestinal lumen into absorptive enterocytes via a sodium-dependent glucose transporter and in regulation of hormone release from gut enteroendocrine cells. Shah et al. (2009) identified a number of T2R bitter receptors in the motile cilia of the human airway that responded to bitter compounds by increasing their beat frequency. Recently, Lee et al. (2012) demonstrated that the T2R38 taste receptor is expressed in human upper respiratory epithelia and responds to acyl-monoserine lactone quorum-sensing molecules secreted by *Pseudomonas aeruginosa* and other gram-negative bacteria. Importantly, they found that differences in T2R38 functionality, as related to TAS2R38 genotype, correlated with susceptibility to upper respiratory infections in humans.

1.5.3 Studies of the Olfactory Pathways in Transport of Agents from the Nose to the Brain

A very important empirical observation, made in the first half of the 20th century, was that the olfactory nerve can serve as a conduit for the movement of viruses and exogenous agents from the nasal cavity into the brain (see Chapters 19 and 20). This route is direct, since the olfactory neurons lack a synapse between the receptive element and the afferent path. The existence of this pathway for viral infection of the brain has been recognized for some time, as evidenced by a number of studies from the 1920s and 1930s (see Clark, 1929; Hurst, 1936). For example, mice intraperitoneally inoculated with louping ill virus showed the first signs of CNS localization of the virus in the olfactory bulbs. Mice whose olfactory mucosa was cauterized with sulfate were partly protected against such infection (Burnet and Lush, 1938). Poliomyelitis virus, placed in the noses of primates, travels to the olfactory bulbs via the axoplasm of the olfactory nerves, rather than along the nerve bundle sheaths (Bodian and Howe, 1941a, b). In a pioneering paper, Armstrong and Harrison (1935) reported that monkeys could be protected against intranasal inoculations of poliomyelitis virus by previous lavage of the nose with solutions of alum or picric acid (or both). Subsequent studies (e.g., Schultz and Gebhardt, 1936) found that zinc sulfate gave a longer-lasting and higher

degree of protection from poliomyelitis, leading to the prophylactic spraying of noses of children with this agent during poliomyelitis outbreaks in the late 1930s (Peet et al., 1937; Schultz and Gebhardt, 1937; Tisdall et al., 1937). Unfortunately, such spraying produced long-lasting, presumably permanent, anosmia in some individuals (Tisdall et al., 1938).

Related to the observation that the olfactory nerves are a major carrier of viruses is the fact that the receptive elements of the olfactory system are exposed, to a large degree, to the vagaries of the external environment, making them susceptible to damage from bacteria, viruses, toxins, and other foreign agents. As reviewed in detail in Chapters 3 and 19, numerous studies have demonstrated that the olfactory mucosa is rich in enzymes that likely minimize the deleterious influences and uptake of most xenobiotic agents into the olfactory receptor cells, including cytochromes P-450, flavin-containing monooxygenase, and aldehyde dehydrogenases and carboxylesterases.

1.5.4 The Discovery that Taste Buds and Olfactory Receptor Cells Regenerate

Another important 20th-century development is the discovery that the gustatory and olfactory receptor cells regenerate periodically. Beidler and Smallman (1965) provided the first scientific demonstration that the sensory cells of the taste bud are in a dynamic state of flux and are constantly being renewed, with the more recently formed cells of the periphery migrating centrally to act as receptors for very limited periods of time. The observation that olfactory receptor cells, which are derived from ectoderm and which serve as the first-order neurons, can regenerate after they are damaged was first noted in mice by Nagahara (1940) and later confirmed in primates by Schultz (1960). This observation is particularly significant, in that it is in conflict with the long held notion that neurons in the adult animal are irreplaceable and suggests that the olfactory system may contain the key to producing neural regeneration in a variety of neural systems (Farbman, 1992). However, questions remain as to why metaplastic respiratory epithelium often invades the region of the damaged olfactory epithelium and, when such metaplasia occurs, the epithelium in that region may never convert to olfactory epithelium. Recent studies, in which the olfactory epithelia of rodents were exposed to airborne or systemically administered toxic agents, may shed some light on this question. Thus, the type of repair seems to correlate with the degree or extent of the initial epithelial damage (Keenan et al., 1990). For example, when the basilar layer of the mucosa is completely damaged, then metaplastic replacement with a respiratory-like epithelium occurs. When the damage is not marked or the toxic insult is not sustained, regeneration, usually with fewer or irregularly arranged cells, occurs. It is currently believed that horizontal basal cells and globose basal cells near the basement membrane of the epithelium are responsible for the generation of all neuronal and non-neuronal cell types within the epithelium (Chapter 7).

Closely related to the discovery of regeneration within the olfactory epithelium is the important observation made by Andres (1966, 1969) that mitotic cells, young sensory cells, mature sensory cells, and dying cells coexist within the olfactory epithelium (see Farbman, 1992, for a review). This suggested to Andres the hypothesis that the olfactory receptor cells were continually being replaced. The notion that olfactory receptor cells were in a state of flux received subsequent support by others (Chapter 7; Moulton et al., 1970; Thornhill, 1970; Graziadei and Metcalf, 1971) and led to the idea that they are relatively short-lived. Hinds et al. (1984), however, found that a number of the olfactory receptor cells of mice reared in a pathogen-free environment survived for at least 12 months and hypothesized that olfactory nerve cell turnover involves recently formed or immature receptor cells that fail to establish synaptic connections with the olfactory bulb. This hypothesis implies that environmental agents play an important role in dictating which elements of the receptor sheet become replaced and that the rate of regeneration of the olfactory receptor cells is not genetically predetermined, as previously supposed (see Chapter 7). The observation that improvement in olfactory function after cessation of chronic cigarette smoking occurs over a period of years and is dose-related (Frye et al., 1990) suggests, under the assumption that the olfactory epithelium is involved, that either turnover of the olfactory epithelial cell complement takes a much longer time than previously supposed or growth of olfactory epithelium into damaged areas is relatively slow and dependent on the extent of prior trauma, or both.

The study of the regeneration of the olfactory neurons has been greatly enhanced by the ability to culture the olfactory mucosa in vitro (for review, see Mackay-Sim and Chuah, 2000). This was first demonstrated in the culture of olfactory organs from embryonic mice (Farbman, 1977) and used to show the importance of olfactory bulb in promoting differentiation of the olfactory sensory neurons (Chuah and Farbman, 1983). The next major development came with the investigations of dissociated cultures from embryonic and newborn rats (Calof and Chikaraishi, 1989; Pixley, 1992a). This allowed the growth factors regulating olfactory neurogenesis to be explored in the developing olfactory epithelium (DeHamer et al., 1994; Mahanthappa and Schwarting, 1993) and in the adult (MacDonald et al., 1996; Newman et al., 2000).

Interestingly, normal targeting of glomeruli by olfactory receptor axons has been demonstrated in mice lacking functional olfactory cycle nucleotide-gated channels

(Lin et al., 2000) and in mice lacking most intrabulbar GABAergic interneurons (Bulfone et al., 1998). Thus, establishment of the topographical map from the receptor cells to the glomeruli seems to require neither normal neural activity in these pathways nor cues provided by the major neural cell types of the bulb.

More recently, as described in detail in Chapter 7, considerable progress has been made in understanding the regulation of neurogenesis within the olfactory epithelium. Among the more important discoveries was the finding that horizontal basal cells are neural stems cells with the capacity to regenerate both neuronal and non-neuronal elements of the epithelium, including the olfactory receptor nerve precusors, globose basal cells (Leung et al., 2007).

Human olfactory neuronal progenitors have now been grown *in vitro* (Wolozin et al., 1992) and this has been exploited to study biochemical changes in Alzheimer's disease (Wolozin et al., 1993). Primary cultures of human olfactory mucosa (Féron et al., 1998; Murrell et al., 1996) have lead to investigations into the etiology of schizophrenia (Féron et al., 1999), and the vitro growth of olfactory ensheathing cells (Chuah and Au, 1991; Pixley, 1992b; Ramon-Cueto and Nieto-Sampedro, 1992). The latter glial cells assist sensory neuron regeneration (Doucette, 1984) and have, in fact, been employed in cell transplantation therapy for the damaged nervous system (Li et al., 1998; Lu et al., 2001; Ramon-Cueto et al., 2000; Ramon-Cueto and Nieto-Sampedro, 1994).

1.5.5 The Discovery that Some Olfactory Bulb Cells Regenerate

A long-held dogma regarding the nature of the CNS of vertebrates is now known to be false; namely, that the adult brain does not exhibit neurogenesis (for review, see Gross, 2000). Although early studies found mitotic figures within the walls of the lateral ventricle (e.g., Allen, 1912; Globus and Kuhlenbeck, 1944; Öpalski, 1934; Rydberg, 1932), definitive evidence that such cells represented neurogenesis awaited the development of the tritiated thymidine technique, the electron microscope, and immunohistochemistry (Gross, 2000). In the 1960s, Altman and his associates published a series of classic studies based upon tymidine autoradiography that demonstrated neurogenesis in several brain regions of young and adult rats, including the olfactory bulb (Altman, 1969), the neocortex (Altman, 1963, 1966a,b), and the dentate gyrus of the hippocampus (Altman, 1963; Altman and Das, 1965). Regarding the olfactory bulb, proliferating cells were found within the subventricular zone lining segments of the lateral ventricles. These cells were found to reach the core of the olfactory bulb via the rostral migratory stream. Subsequent studies have confirmed and extended these observations (e.g., Luskin, 1993; Lois, Garcia-Verdugo and Alvarez-Buylla, 1996; O'Rourke, 1996), noting that the precursor cells invade the granule and perioglomerular layers of the bulb, where they differentiate into local interneurons. A major differentiation is into GABAergic granule cells – the most numerous cells of the bulb.

These stem-cell-related phenomena are of considerable significance, as they indicate that the plasticity of the olfactory system goes far beyond simply replacing damaged neuroepithelial cells, and that continual cell replacement may play an integral role in olfactory perception. It is now known, for example, that reducing the numbers of interneurons recently generated via this process impairs the ability of an animal to discriminate among odorants (Gheusi et al., 2000). Moreover, enriching the odorous environment of mice enhances such neurogenesis and improves odor memory (Rochefort et al., 2002). The degree to which such processes influence, or are influenced by, endocrine state and various social processes is not well known, although interestingly glucocorticoids decrease, and estrogens increase, the rate of such neurogenesis within the hippocampus (Gould and Tanapat, 1999; Tanapot et al., 1999).

1.5.6 Functional Imaging Studies

A significant and rapidly evolving modern development in the study of the chemical senses is that of functional imaging. It has long been known or suspected that brain circulation changes selectively with neuronal activity (e.g., Broca, 1879; Mosso, 1881, 1884; Roy and Sherrington, 1890; Fulton, 1928), but was not until the late 1950s and early 1960s, the development of the [^{131}I]trifluoroiodomethane ([^{131}I)CF$_3$1]CF$_3$1) method provided a potential and novel means for quantitatively examining the influences of sensory, cognitive, and motor processes on local blood flow within regions of the brain (Landau et al., 1955; Freygang and Sakoloff, 1958; Kety, 1960; Sakoloff, 1961). This early work led in the development of the [^{14}C]2-deoxy-D-glucose (2-DG) autoradiographic method for determining regional glucose consumption in animals (Reivich et al., 1971; Kennedy et al., 1975; Sakoloff et al., 1977), and set the foundation for modern human functional imaging studies. Reivich et al. (1979) introduced the [^{18}F] flurorodeoxyglucose method for assessing regional glucose metabolism, and Lassen et al. (1963) and Ingvar and Risberg (1965) subsequently developed and applied a procedure in which regional blood flow measurements could be established in humans by using scintillation detectors arrayed over the surface of the scalp. The refinement of such approaches led to the practical development of positron emission tomography (PET) (Ter-Pogossian et al., 1975; Hoffman et al., 1976), which was made possible by the earlier invention of X-ray computed tomography (CT) in 1973 (Hounsfield, 1973). The coincidence of these techniques provided the

capability of mapping the regions with increased blood flow or glucose metabolism to specific regions of the brain in three-dimensional coordinates.

Magnetic resonance imaging (MRI) technology emerged contemporaneously with the latter developments (e.g., Lauterbur, 1973). Based upon a set of earlier principles (Block, 1946; Fox and Raichle, 1986; Lauterbur, 1973; Pauling and Coryell, 1936), Ogawa et al. (1990) were able to demonstrate that changes in blood oxygenation could be detected, in vivo, with MRI, setting the stage for the development of functional MRI (fMRI). This phenomenon, known as the blood oxygen level dependent (BOLD) signal, reflects the fact that blood flow changes more than oxygen consumption does in an activated region, reflected by a reciprocal alteration in the amount of local deoxyhemoglobin that is present, thereby altering local magnetic field properties. Details of fMRI, as well as other imaging procedures, are presented in Chapters 13, 35, and 46.

The first study to employ functioning imaging in the chemical senses was that of Sharp et al. (1975). These investigators injected four rats intravenously with 2-DG and immediately placed them in a sealed glass jar containing glass wool saturated with pentyl acetate. After 45 minutes the animals were sacrificed, and sections of the bulbs were appropriately prepared and autoradiographed. Two regions of heightened optical density were noted bilaterally which tended to be centered in the glomerular layer, with variable spread into the external plexiform and olfactory nerve layers. Subsequent studies more clearly defined the regions of apparent activation (e.g., Sharp et al., 1977; Stewart et al., 1979), and resulted in the identification of a unique set of glomeruli in weanling rats responsive to odorants in their mothers' milk (Teicher et al., 1980).

The first published human olfactory PET study was that of Zatorre et al. (1992). These investigators found that odorants increased regional cerebral blood flow (rCBF) bilaterally in the piriform cortex, as well as unilaterally in the right orbitofrontal cortex. The first taste study employing PET was that of Small et al. (1997). Increased rCBF was noted, in response to citric acid, bilaterally within the caudolateral orbitofrontal cortex, and unilaterally within the right anteromedial temporal lobe and the right caudomedial orbitofrontal cortex. The first published fMRI report on olfaction was that of Yousem et al. (1997), who demonstrated (a) odor-induced activation of the orbitofrontal cortex (Brodmann area 11), with a mild right-sided predominance (in accord with the earlier PET study of Zatorre et al., 1992) and (b) unexpected cerebellar activation. Sobel et al. (1998a) noted that olfactory stimulation activated lateral and anterior orbito-frontal gyri of the frontal lobe, and that sniffing behavior, regardless of whether an odor is present, induces piriform cortex activation. These investigators, following up on the unexpected observation of cerebellar activation by odorants, subsequently demonstrated concentration-dependent odorant activation in the posterior lateral cerebellar hemispheres, and activation from sniffing alone in the anterior cerebellum, most notably the central lobule (Sobel et al., 1998b). More recent advances are summarized in Chapters 13 and 35).

1.5.7 Optogenetics

Optogenetics is an emerging technology with potential for elucidating neural processes associated with smell and taste function. In this technology, which was pioneered by Deisseroth and his associates (e.g., Boyden et al., 2005), photoresponsive microbial proteins are genetically expressed in neurons whose action potentials can then be altered by exposure, in vivo, to various wavelengths of light delivered by fiberoptics to the target neurons. Defined trains of spikes or synaptic events with millisecond-timescale temporal resolution can be induced by brief pulses of light.

To my knowledge, the first application of this technology to an element of the olfactory system, notably the piriform cortex, was by Choi et al. (2011). These investigators found that both appetitive and aversive behaviors could be classically conditioned in mice to light activation of small subsets of piriform neurons that expressed channelrhodopsin. Different sets of neurons could be independently conditioned to elicit distinct behaviors, suggesting that this cortex can produce learned behavioral outputs independent of sensory input. These findings have shed considerable light on the mechanisms by which the piriform cortex associates odors with behavioral responses.

1.5.8 The Animal Behavior Revolution

Another large area of research activity that must be mentioned as having had a profound impact on modern chemosensory research is that of animal behavior (see Chapters 19, 21–27). This field, which grew in geometric proportions after World War II, is a major contributor to chemosensory studies. In addition to providing detailed explications of the many rich and often complicated influences of chemical stimuli on wide range of invertebrate and vertebrate behaviors (including, in mammals, behaviors related to aggression, alarm, suckling and feeding, mating, predator–prey relationships, social status appraisal, territorial marking, and individual and species recognition), this field has provided important methodology for assessing olfactory, gustatory, and vomeronasal function in animals, including preference paradigms (e.g., Richter, 1939; Mainardi et al., 1965), classical conditioning paradigms (Pavlov, 1927), conditioned aversion paradigms (e.g., Garcia et al., 1955), habituation paradigms

(e.g., Krames, 1970), sniff rate analysis paradigms (e.g., Teichner, 1966), and operant conditioning paradigms using positive or negative reinforcers (Skinner, 1938). Furthermore, behavioral studies have been instrumental in the demonstration of the close association between neuroendocrine and chemoreception systems in both vertebrates and invertebrates, and are critical for demonstrating the effects of various gene manipulations on smell- or taste-mediated behaviors. A number of the chapters of this volume directly relate to this vast literature and, in some cases, provides means for assessing responses of animals to odorants (Chapters 21–27) and tastants (Chapters 38 & 41–44). The reader is referred to the many general reviews of this topic (Albone, 1984; Doty, 1974, 1975, 1976, 1980, 1986; Johnston, 2000; Johnston et al., 1970; Leon, 1983; Meredith, 1983; Mykytowycz, 1970; Slotnick, 1990; Smith, 1970; Stevens, 1975; Vandenbergh, 1983; Verendeev and Riley, 2012; Wysocki, 1979).

According to Stürckow (1970), the studies by Barrows (1907), von Frisch (1919), and Minnich (1921) were seminal for the development of studies of insect chemosensory behavior and physiology, even though earlier, more equivocal, studies had been performed (e.g., Hauser, 1880). Barrows (1907) devised the first insect olfactometer and found, in the pomice fly (*Drosophila ampilophila*), that different degrees of responding were obtained from different concentrations of chemical attractants. Von Frisch (1919) demonstrated that bees could be trained to fly to a fragrant odor using simple reinforcement and later found the location of the olfactory sensilla to be on the eight distal segments of the antennae (von Frisch, 1921, 1922). Minnich (1921, 1926, 1929) explored the responses of various body parts of butterflies, certain muscid flies, and the bee to taste solutions. For example, he found that they extended their proboscises when their tarsi or certain mouth parts were touched with a sugar solution. These and other studies led to electrophysiological studies of the chemoreceptive systems of insects by Dethier (1941), Boistel (1953), Boistel and Coraboeuf (1953), Kaissling and Renner (1968), and Schneider (1955, 1957a, b).

A number of important studies, published in the 1950s, 1960s, and early 1970s, demonstrated a close association between olfaction, social behavior, and reproductive processes in rodents and other mammalian forms. Pioneering reports on this topic include those which showed that odors from male and female mice influence the timing of estrous cycles (Lee and Boot, 1955; Whitten, 1956; Whitten et al., 1968), that urine odor from unfamiliar male mice can block the pregnancy of female mice (Bruce, 1959; Bruce and Parrott, 1960), and that chemical stimuli can accelerate the onset of puberty in mice (Vandenbergh, 1969). Other important studies demonstrated that olfactory bulbectomy, anesthetization, or damage to the olfactory receptor region vomeronasal organ or nervus terminalis, alone or in combination, can dramatically influence mating behavior, depending on the species involved (e.g., in the male or androgenized female hamster, anesthetization or damage of these systems can eliminate male copulatory behavior; Doty and Anisko, 1973; Doty et al.,1971; Murphy and Schneider, 1970; Powers and Winans, 1973, 1975; Winans and Powers, 1974). Such phenomena have been demonstrated to one degree or another in a wide variety of mammals and have important implications for animal ecology, husbandry, and perhaps even human behavior.

Other studies of this period that had a considerable impact on the field of mammalian social behavior include those that examined, in a systematic manner, sexual odor preferences in rodents. Godfrey (1958), for example, found that estrous female bank voles *(Clethrionomys*) preferred homospecific male odors over heterospecific male odors and that hybrids were discriminated against. Le Magnen (1952) demonstrated that adult male rats *(Rattus norvegicus*) prefer the odor of receptive females to nonreceptive ones, whereas prepubertal or castrated males do not (unless they have been injected with testosterone). Beach and Gilmore (1949) noted that sexually-active male dogs, but not a sexually-inactive male dog, preferred estrous to non-estrous urine. This and other work led to a number of carefully designed studies by Carr and his associates in the 1960s which sought to determine the influences of sexual behavior and gonadal hormones on measures of olfactory function. Carr and Caul (1962) demonstrated that both castrate and noncastrate male rats can be trained to discriminate between the odors of estrous and nonestrous females in a Y-maze test situation, implying that the preference phenomenon observed by Le Magnen (1952) was not due to castration-related influences on olfactory discrimination ability, per se. Carr et al. (1965) subsequently demonstrated the important role of sexual experience in producing strong preferences in male rats for estrous over diestrous odor and in female rats for noncastrate male odors over castrate male odors. These investigators also showed that sexually inexperienced females preferred male noncastrate odors if they were administered gonadal hormones that induced estrus.[4] These general findings have been observed in a wide range of species, although some species differences do exist and castration has been shown to mitigate the increase in detection performance of rats that follows repeated testing (Doty and Ferguson-Segall, 1989; for reviews, see Brown and Macdonald, 1985; Doty, 1974, 1976, 1986).

Animal behavior studies in the 1980s contributed significantly to the understanding of the function of

[4]In an unpublished M.A. thesis, Keesey (1962) found that sexually experienced, but not sexually inexperienced, male rats preferred the odor of female urine collected during proestrus than that collected during diestrus.

vomeronasal organ which was described histologically in many species in the 19th century, but whose function was unknown (for review of the early literature, see Wysocki, 1979). In the mouse, removal of the vomeronasal organ eliminates the surge in luteinizing hormone (LH) and subsequent increase in testosterone that ordinarily follows exposure of male mice to an anesthetized novel female mouse or her urine. However, this does not occur following exposure to an awake female mouse, suggesting several sensory cues can produce the LH surge (Coquelin et al., 1984; Wysocki et al., 1983). In both mice and hamsters, vomeronasal organ removal impairs male sexual behavior, particularly in animals that have had no prior adult contact with females (Meredith, 1986; Wysocki et al., 1986). In mice whose vomeronasal organs have been removed soon after birth, long-lasting influences on male sexual behavior in adulthood have been noted (Bean and Wysocki, 1985). Vomeronasal organ removal also greatly decreases aggression in male house mice, particularly those that have not had much fighting experience with other males (Bean, 1982; DaVanzo et al., 1983; Wysocki et al., 1986).

While there is now incontrovertible evidence that most adult humans have a rudimentary vomeronasal organ (VNO) whose opening is present at the base of the nasal chamber, no neural connection exists and the structure is generally considered vestigial (Doty, 2001; Smith and Bhatnagar, 2000; Bhatnagar and Meisami, 1998; Brown, 1979). The presence of a regressive human VNO fits into the general idea that humans have lost much chemosensory capacity, at least relative to many other mammals, over the course of evolution. However, aside from the VNO, the concept of lesser smell function has come under vigorous debate and some animal behavioral studies have suggested that the divide between humans and other mammals is not as great as often believed (Laska et al. 2000) (see Chapter 27). Contributing to this notion is a reassessment of the relationship between nasal cavity structure and both the size and density of the olfactory neuroepithelium of primates, throwing into question the classic distinction between macrosmatic and microsmatic mammals (Smith et al. 2004).

A significant event for the field of odor communication was the coining of the term "pheromone" in insects for "substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process" (Karlson and Lüscher, 1959, p. 55). The pheromone concept, which has permeated most areas of biology, has been applied by some workers to nearly any chemical involved in chemosensory communication. The term pheromone replaced an earlier term (ectohormone) and conjures up the idea that the social organization of animals is akin to the endocrine organization of an organism, with disparate parts being influenced by chemicals that circulate within the social milieu. For many, but not all, insects, this term seems appropriate, given the high degree of stereotypic behavior and evidence for comparatively simple stimuli that induce behavioral or endocrinological changes. However, for many vertebrates, particularly mammals, this concept has questionable utility since it assumes simple associations between stimuli and responses which rarely, if ever, exist. As discussed in *The Great Pheromone Myth* (Doty, 2010), this concept suffers from a range of basic problems when applied to mammals. For example, it leads to the nominal fallacy, i.e., the tendency to confuse naming with explaining, and assumes that a few species-specific molecules of innate origin, largely impervious to learning and distinct from other types of stimuli, are the motive influences. Importantly, it inappropriately dichotomizes complex behaviors and stimuli into simple classes and fails to take into account the complexity of chemical stimuli and the influences of experience in determining their meaning. Despite possibly one or two such claims, no single chemical or set of chemicals has been identified in mammals that can be truly considered analogous to an insect pheromone. A number of phenomena in humans that have been attributed to pheromones, such as menstrual synchrony, have been found to be based upon statistical artifact, further denigrating the usefulness of this popular but flawed concept (Schank, 2006; Strassmann, 1997; Wilson, 1992).

Pioneering behavioral studies of mammalian taste function began in the 1930s, heralded by experiments that sought to explain so-called specific hungers, e.g., salt craving in patients with adrenal gland hypofunction. In seeking to determine whether alterations in taste function are responsible for increased NaCl intake of adrenalectomized rats, Richter (1936, 1939) developed the two-bottle taste test (see also Richter and Campbell, 1940). In this test, differential fluid intake from two bottles, one of which contains a tastant (e.g., a NaCl solution) and the other water alone, is recorded over a period of time. The lowest concentration of the tastant that produces a differential intake is taken as the threshold measure.

Although this behavioral procedure provided a means for measuring a preference threshold, postingestional factors may alter the behavioral response and such a threshold is conceptually different from a sensory threshold. Thus, a lack of preference between two solutions need not reflect an inability to discriminate between them [see Stevens (1975) for reviews of analogous procedures for olfaction]. Subsequent workers, including Carr (1952), Harriman and MacLeod (1953), Morrison (1967), and Morrison and Norrison (1966), utilized shock avoidance paradigms or operant conditioning paradigms that provided positive reinforcement to establish NaCl threshold values – values that were much lower than those obtained using Richter's

procedure and which corresponded more closely to neural thresholds. Numerous modifications of behavioral procedures for assessing taste function in mammals have since been developed which incorporate general principles that evolved from these pioneering behavioral studies (e.g., Brosvic et al., 1985, 1989; Spector et al., 1990). Analogous procedures have been developed in olfaction (e.g., Bowers and Alexander, 1967; Braun et al., 1967; Braun and Marcus, 1969; Eayrs and Moulton, 1960; Goff, 1961; Henton, 1969; Moulton, 1960; Moulton and Eayrs, 1960; Pfaffmann et al., 1958; Slotnick and Katz, 1974; Slotnick and Ptak, 1977; Slotnick and Schellinck, 2002). Another noteworthy development in behavioral testing was that of the conditioned aversion paradigm (Garcia et al., 1955, 1974). In one variant of this technique, an animal is allowed to drink or smell a novel tastant or odorant and is then injected with an agent that produces nausea (e.g., lithium chloride). The animal quickly learns to avoid the novel stimulus as a result of a single aversive conditioning experience, even if the aversion occurs long after the presentation of the sensory stimulus. This procedure can be used to establish whether detection of a given stimulus is present and is particularly useful for assessing cross-reactivity of stimuli (i.e., the extent to which a stimulus has elements in common with other stimuli). One of the more novel applications of this technique was by Smotherman (1982), who demonstrated that the olfactory system of rats is functional in utero. In this study, unborn rat pups (gestation day 20) received in utero injections of apple juice and lithium chloride. After birth, these individuals showed evidence of having developed a conditioned aversion to the odor of apple juice (see Chapter 14).

1.5.9 Clinical Chemosensory Studies

Considerable progress in understanding chemosensory disorders has been made in the last few decades, as reviewed in detail in Chapters 16–20, 28, and 36–40. The proliferation of clinical studies has been fueled, in large part, by the development wide-spread commercial availability of standardized psychophysical tests of olfactory function that first occurred in the early 1980s (e.g., Doty et al., 1984a, Doty, 2000, 2001; Kobal et al., 1996; Hummel et al., 1997; for review, see Doty, 2007). It is now widely appreciated that smell loss is markedly depressed in elderly persons (Doty et al., 1984b), and that most common causes of *permanent* smell loss are (1) upper respiratory viral infections, (2) head trauma, and (3) nasal and sinus disease (e.g., Deems et al., 1991). Moreover, it appears that these disorders largely reflect damage to the olfactory neuroepithelium, as revealed by autopsy and biopsy studies (Douek et al., 1975; Hasegawa, Yamagishi and Nakano, 1986; Jafek et al., 1989, 1990; Moran et al., 1992). Most complaints of taste loss reflect the loss of olfactory function, and flavor sensations are largely derived from retronasal stimulation of the olfactory system during active deglutition (Mozell et al., 1969; Burdach and Doty, 1987).

We now know that the olfactory system seems more susceptible to damage than the taste system, although damage to regional lingual afferents is particularly striking in old age (Matsuda and Doty, 1995), and taste sensitivity is directly related to the number of taste buds or papillae stimulated, regardless of whether stimulation is by chemicals or by electrical current (Doty et al., 2001; Miller et al., 2002; Zuniga et al., 1993). Moreover, it has become increasingly apparent that many medicines, including a number of antibiotics, antidepressants, antihypertensives, antilipid agents, and psychotropic drugs, can produce alterations of the taste system (e.g., severe dysgeusia), alone or in combination with alterations in the smell system (Schiffman, 1983; Schiffman et al., 1998, 1999a,b, 2000). Importantly, recent studies suggest that damage to one of the major taste nerves (e.g., one chorda tympani) may release inhibition on other taste nerves (e.g., the contralateral glossopharyngeal nerve), resulting in hypersensitivity to some tastants and the production of phantom dysgeusias (Lehman et al., 1995; Yanagisawa et al., 1998).

A major advance in the last few years is the discovery that smell loss is among the first, if not the first, signs of such common neurodegenerative diseases as Alzheimer's disease (AD) and idiopathic Parkinson's disease (PD), and that disorders sharing similar motor signs, such as progressive supranuclear palsy (PSP) and MPTP-induced Parkinsonism (MPTP-P), are largely unaccompanied by such loss (see Chapter 18). Such observations imply that olfactory testing can be of value not only in the detection of some neurodegenerative disorders early in their development, but in differential diagnosis. Indeed, odor identification testing accurately differentiates between patients with AD and those with major affective disorder (i.e., depression) (Solomon et al., 1998; McCaffrey et al., 2000). Interestingly, longitudinal studies have now appeared indicating that olfactory dysfunction can be predictive of AD in individuals who are at risk for this disorder, particularly when considered in relation to other risk factors (Bacon et al., 1998; Graves et al., 1999; Devanand et al., 2000). The only neurodegenerative disorder for which a definitive physiological basis has been found to date, however, is multiple sclerosis, where a -0.94 correlation has been observed between odor identification test scores and the number of plaques, as measured by MRI, in the subtemporal and subfrontal regions of the brain (Doty et al., 1997, 1998, 1999).

Among the many diseases or disorders in addition to those noted above that are associated with smell dysfunction include severe alcoholism, amyotrophic lateral sclerosis (ALS), chronic obstructive pulmonary disease,

cystic fibrosis, epilepsy, the Guam ALS/PD complex, head trauma, Huntington's disease, Kallmann's syndrome, Korsakoff's psychosis, myasthenia gravis, pseudohypoparathyroidism, psychopathy, restless leg syndrome, schizophrenia, seasonal affective disorder, and Sjogren's syndrome. Neurological disorders in which olfactory seems to be spared in addition to PSP and MPTP-induced PD are corticobasal degeneration, depression, panic disorder, essential tremor, and multiple chemical hypersensitivity (for review, see Doty, 2012). In addition to traditional medical means for treating or managing diseases responsible for decreased olfactory function, surgical intervention at the level of the olfactory neuroepithelium (e.g., by selectively ablating or stripping away the diseased tissue) or the olfactory bulb (e.g., by removal of one or both olfactory bulbs in an anterior cranial approach) has successfully eliminated or markedly reduced the symptoms of some forms of chronic dysosmia or phantosmia (see Chapter 27). Recent advances in understanding the deleterious influences of oxygen radicals on neural tissue, as well as changes that occur in olfactory tissue at menopause, have led to ongoing studies of the prophylactic potential of antioxidants, hormones, and other agents in mitigating toxin-induced damage to the olfactory (e.g., Dhong et al., 1999).

1.6 CONCLUSIONS

In this introduction, a brief description of the significant role that tastes and odors have played throughout the course of human history has been presented. In addition, a number of key studies, events, and trends have been identified which form the backdrop of much of today's chemosensory research enterprise, providing perspective for the chapters that follow. The chapters of this volume provide a detailed contemporary information related to most of these trends and address the important role of chemosensory science in both basic and applied (e.g., clinical) situations. Until recently, the chemical senses have engendered, relative to the other major senses, comparatively little attention on the part of the scientific and medical communities. This has clearly changed, as reflected in the chapters that follow.

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