CHAPTER 1
Introduction: what is chemesthesis?

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1.1 A brief history

The coolness of peppermint, the warmth of cinnamon, the heat of chilis, the tingling of carbonated beverages, the sting from a bee, the itch from a mosquito bite, the pungency of sniffed ammonia, the pain from an inflamed joint – these diverse sensations all share a common basis in chemesthesis. Not limited to the nose and mouth but experienced throughout much of the body, chemesthesis might simply be described as the chemical sensitivity of the body that is *not* served by the senses of taste or smell. But such a definition would not convey either the neurobiological complexity or the varied and important functions of chemesthesis. These and the concept of chemesthesis can be better appreciated by first considering the venerable concept that it replaced: "the common chemical sense".

For much of the 20th century, researchers in the chemical senses and related fields considered the common chemical sense to be a third specialized chemosense in addition to taste and smell. The concept was proposed by the Harvard zoologist G.H. Parker (1912) to describe the chemical sensitivity of the integument of fish and amphibians, which had previously simply been referred to as "the chemical sense" or "the undifferentiated chemical sense". By cutting individual cranial nerves and observing behavioral responses to concentrated solutions of HCl, NaOH, NaCl, and quinine applied to the bodies and tails of two species of fish, Parker concluded the sensitivity to chemical irritants was a property of "ordinary spinal nerves" rather than of the gustatory and olfactory nerves. He further proposed that the common chemical sense was a sensory system in vertebrates "as distinct as smell or taste" (Parker, 1912, p. 221), though closer in sensitivity and function to taste than to smell. A few years later, Crozier (1916) performed experiments on frogs that he argued provided further support for a common chemical sense. Some decades later, in his book titled *The Chemical Senses*, Moncrieff (1944) lent further credence to the concept by describing the common chemical sense as a separate modality that functions in concert with taste and smell.

However, some researchers were unhappy with the concept and argued instead that the chemical sensitivity of the skin and mucus membranes was a property of

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the sense of pain. Among them was M.H. Jones (1954), who conducted a study of her own after complaining that "the 'common chemical sense' is accepted by some writers without much tangible evidence and summarily rejected by others without much better evidence" (Jones, 1954, p. 696). Jones found that application of cocaine to the mucosal surface of the lower lip in humans reduced sensitivity to mechanical pain as well as to chemical pain, and so concluded that both forms of stimulation were sensed by cutaneous nerve endings of the pain system. In support of this conclusion, Jones quoted from Carl Pfaffmann's (1951) chapter on the chemical senses in Stevens' *Handbook of Experimental Psychology* in which he wrote, "Pain and the common chemical sensitivity appear…to be mediated by the same nerve endings" (Pfaffmann, 1951, p. 1144). It is notable, however, that this quotation was taken from a section in the chapter with the heading "The Common Chemical Sense", in which Pfaffmann went on to say, "On the other hand, it is quite clear that such chemical sensitivity is distinct from touch, and in the mouth and nose, distinct from taste and smell" (p. 1145). Pfaffmann's use of the term and affirmation of a chemical sensitivity separate from taste and smell may have helped to sustain the concept of a common chemical sense despite the clear evidence of its relationship to pain.

Further sustaining the terminology (if not Parker's original concept) were papers by Keele and others (Armstrong *et al.*, 1953; Bleehen and Keele, 1977; Keele, 1962) on the chemical sensitivity of pain, in which the possibility of specific "chemonociceptors" was proposed. While this body of work demonstrated beyond a doubt that chemosensory irritation was mediated at least in part by receptors of the pain sense, it also implied that the common chemical sense was in fact a specialized chemical sensitivity within the pain sense. Indeed, Keele titled his 1962 paper "The common chemical sense and its receptors". Other work published around the same time on the neurophysiological and perceptual response to capsaicin, the spicy-hot constituent of chilis (Jancso *et al.*, 1968; Szolcsanyi, 1977; Szolcsanyi *et al.*, 1988; Szolcsanyi and Jancso-Gabor, 1973), further strengthened the connection between pain and chemical irritation by showing that sensitization or desensitization by capsaicin also affected the sensitivity to both mechanical pain and heat pain (Green, 1986; Szolcsanyi, 1977; Szolcsanyi, 1985; Szolcsanyi *et al.*, 1988). This work paralleled and supported Jones' earlier evidence that cocaine reduced the sensitivity to both mechanical and chemical pain. Thus, whether or not specialized chemonociceptors existed, the evidence was clear that chemical irritants also stimulate nonspecific (polymodal) nociceptors, and thus are not sensed exclusively by a chemosensitive sub-modality of pain.

At about the same time the chemical sensitivity of the temperature senses was being brought to light through studies which showed that menthol evokes its sensory cooling effect by direct stimulation of cold fibers and not merely by evaporative cooling (Green, 1985; Schafer *et al.*, 1986; Schafer *et al.*, 1989). Remarkably, the sensitivity of cold fibers to menthol had been demonstrated decades before in electrophysiological studies of the gustatory nerves (Dodt *et al.*, 1953; Hensel and Zotterman, 1951), but the earlier findings had not found their way into published discussions of the common chemical sense. Evidence that warm fibers could also be chemically stimulated was less clear (Foster and Ramage, 1981), although experiments showing

that capsaicin-sensitive receptors played a role in thermoregulation, and that capsaicin increased the perceived temperature of warm or hot water sipped into the mouth, suggested that capsaicin could modulate the excitability of the warmth system (Green, 1986; Szolcsanyi and Jancso-Gabor, 1973).

It was at this stage of understanding that a symposium on "chemical irritation" was held at the Monell Chemical Senses Center in 1988. The symposium brought together leading researchers in diverse fields of study to present their latest findings and to discuss current understanding and future research directions. Dissatisfaction with the concept of the common chemical sense surfaced throughout the symposium and was a central topic in the closing discussion, but no agreement was reached on an alternative terminology. Not until the proceedings of the meeting were being edited was the term "chemesthesis" coined and offered in the preface of the published volume as an alternative concept (Green *et al.*, 1990). Defined as the chemical *sensibility* of the skin and mucus membranes rather than as a chemical sense, the term was intended to communicate what the collective evidence had by that time shown, namely that cutaneous chemical sensitivity is multimodal in nature and derives primarily from chemically-sensitive receptors of the senses of pain and temperature.

Because it is defined as a property of the somatosensory system, chemesthesis serves as a unifying concept that includes chemosensory stimulation throughout the body, not just within the nose and mouth, where research on chemosensory irritation had most often been focused. Indeed, with the exception of the work of Keele and his colleagues, virtually all prior data on chemosensory irritation in humans had come from studies of oral and nasal sensitivity. Reflecting this research emphasis, chemosensory scientists routinely described chemicals that evoked sensations other than taste or smell as "trigeminal stimuli", since the nasal mucosa and the anterior regions of the oral cavity are both innervated by the trigeminal nerve (CN V). Tasteless and largely odorless chemicals such as vanilloids and aldehydes were typically described as "trigeminal irritants", and taste and odor stimuli that in high concentrations also produced sensations such as burning, stinging, or tingling (e.g., salts, acids, alcohols) were said to have a "trigeminal" component or quality. This terminology is still in use today and is appropriate and even preferable when the stimulus is limited to areas innervated solely by the trigeminal nerve (Hummel, 2000; Just *et al.*, 2007; Prah and Benignus, 1984; Scheibe *et al.*, 2006). Nonetheless, reference to trigeminal sensitivity can also oversimplify the neurobiology of oral and nasal chemosensory irritation. Because somesthesis on the back of the tongue is served by the glossopharyngeal nerve (CN IX) (Nagy *et al.*, 1982; Yamada, 1965; Zotterman, 1935), and the vagus nerve (CN X) innervates the airways and esophagus, when stimuli are either swallowed or inhaled they can be sensed by at least one other nerve that contains somatosensory, and thus chemosensory, receptors.

1.2 What is its relevance today?

As is evident from the varied contents of the chapters in the present volume, in the quarter century since the concept of chemesthesis was introduced, our understanding of the perception and neurobiology of this sensibility have advanced dramatically.

Whereas a serious topic of debate at the 1988 symposium was whether "trigeminal" stimulation had qualitative as well as quantitative dimensions, the clear evidence that chemicals can evoke tactile and thermal sensations as well as many varieties of painful sensations (e.g., burn, sting, bite, tingle) has settled the debate emphatically (e.g., Dessirier *et al.*, 2000; Green, 1991; Klein *et al.*, 2011; Zanotto *et al.*, 2007). Most relevant to the concept have been the discoveries that chemicals in the sanshool family can stimulate mechanoreceptors as well as nociceptors (Albin and Simons, 2010; Bryant and Mezine, 1999; Lennertz *et al.*, 2010), making chemesthesis a property of all three primary somatosensory modalities of touch, temperature, and pain, and that thermoreceptive and nociceptive sensory neurons express members of the transient receptor potential (TRP) family of receptors that are sensitive to chemicals and pH (Caterina *et al.*, 1997; Gerhold and Bautista, 2009; Koltzenburg, 2004; Patapoutian *et al.*, 2003; Peier *et al.*, 2002; Stucky *et al.*, 2009).

In addition, the discovery of extra-oral T2R "bitter" taste receptors in the mammalian and human airways that appear to play protective roles against inhalation of dangerous chemicals via sensory (i.e., apnea triggered by trigeminal or vagal afferents) and non-sensory (e.g., in motile cilia of the lung) mechanisms (Finger *et al.*, 2003; Gulbransen *et al.*, 2008; Tizzano *et al.*, 2010; Tizzano *et al.*, 2011) has further broadened understanding of the neurobiological basis and function of chemesthesis. But more than just increasing the scope and importance of the concept, these discoveries point to the role of chemesthesis as one of the body's important defenses against biological and chemical threats in the environment. Within this broader scope, chemesthesis can be considered part of the immune system via the sensitivity of pain fibers to endogenous inflammatory mediators (Jancso-Gabor *et al.*, 1980; Rang *et al.*, 1991), which were originally studied in the skin by Keele and his colleagues (Armstrong *et al.*, 1953; Bleehen and Keele 1977; Keele, 1962). We now know too that sensitivity to inflammation and tissue damage throughout the body is mediated in part by the same classes of multimodal pain receptors that respond to capsaicin and many other exogenous irritants, for example, TRPV1 (Blackshaw, 2014) and TRPA1 (Dhaka *et al.*, 2009; Talavera *et al.*, 2009; Wang *et al.*, 2010; Willis *et al.*, 2011). Accordingly, it was recently proposed that chemesthesis be considered as the sensory component of what might be termed the body's "chemofensor complex" (Green, 2012), the array of chemical defense mechanisms that function both together and separately to protect and rid the body of harmful chemicals and bacterial agents.

It is interesting to consider that this modern view places chemesthesis on an equal footing with taste and smell, though in terms of Gibson's (1966) pioneering concept of shared functionality within a perceptual system rather than shared categorization as special senses. One could argue that within the domain of chemical defenses, chemesthesis has the broadest range of functions of these three chemosensory components, having both an exteroceptive sentinel function and an interoceptive function as a signal of tissue damage and/or infection. Running as it does against the theme of specialized sensory systems that has historically dominated research in sensory neuroscience, an understanding of chemesthesis has evolved more slowly than in the classical sense modalities, where workers have been able to focus on specific sensory mechanisms serving specific stimuli and functions. Yet

the wide ranging research presented in this volume testifies to the growing emphasis on multidisciplinary and multisensory approaches to the study of human sensory perception, which has contributed significantly to the broader and deeper understanding of chemesthesis that has begun to emerge.

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