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# Optimizing Oral Medications for Children

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## Abstract

**Background—**Active pharmaceutical ingredients that taste bitter and/or irritate the mouth and throat are aversive to children as well as many adults. Effective methods of avoiding unpleasant tastes for adults (eg, encapsulating the medicine in pill, capsule, or tablet form) are problematic because many children cannot or will not swallow these. The unpalatable flavor of the medicine can thwart the benefits of even the most powerful of drugs. Failure to consume medication may do the child harm and can even be life-threatening.

**Objectives—**This article provides an overview of the current knowledge of the sensory capabilities and preferences of children as it relates to flavor, defined here as the combined input of taste, smell, and chemical irritation. The methods used to evaluate flavor perception in children are reviewed. Recent scientific advances are summarized that shed light on why the bitter taste of oral pharmaceuticals is an ongoing formulation problem and how discoveries of novel flavor molecules and modulators of bitter tastes hold considerable promise for the future. Alternative methods for evaluation of the palatability of medicines are described.

**Methods—**The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development sponsored a Pediatric Formulation Initiative workshop on December 6 and 7, 2005, in Bethesda, Maryland. Information for this article was gathered from literature reviews that were then discussed during this workshop as well as during several conference calls with the Taste and Flavor Working Group members. Terms for the MEDLINE search (1970-2007) included infant, children, taste, olfaction/smell, flavor, chemical senses, palatability, sensory testing, pharmaceutical, and *medicines*.

**Results—**Children have well-developed sensory systems for detecting tastes, smells, and chemical irritants, and their rejection of unpalatable medications is a reflection of their basic biology. Sugars, salt, and other substances reportedly reduce the bitterness of several pharmaceuticals. Adding pleasant flavor volatiles such as bubble gum may help induce children to consume a medicine, but such volatile compounds are not effective in suppressing the strong bitter tastes associated with some medications. Also, because individual experiences and culture mainly determine which odors are attractive, a universally appealing volatile flavoring agent may be difficult to identify. Sensory panelists who are sensitive to the pediatric palate, which is different from adults, and new techniques involving animal models, isolated parts of the receptor cells, and even electronic devices that detect taste and flavor are among the tools that may be used to evaluate the palatability of medications and predict compliance among pediatric populations.

**Conclusions—**Although there are no easy solutions to this dilemma, children's acceptance of many medicines can be improved by applying the knowledge gleaned from basic research in the chemical senses. Further development and validation of sensory methods will provide a better understanding of the sensory world of the child. This understanding, combined with new technologies and results



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of animal model studies, will enhance drug acceptance and compliance in pediatric populations. A better understanding of the scientific basis for distaste and how to ameliorate it is a public health priority.

**Keywords**

taste; flavor; children; medicines

## INTRODUCTION

Children and adults are subject to many of the same ailments and diseases, and by necessity, may be treated with the same drugs. However, only a small fraction of these drugs has been adequately tested in children and, consequently, most drugs lack approval by the US Food and Drug Administration for pediatric labeling for safety and efficacy. [1] Adequate testing is confounded by the requirement that the formulation of the drug meets the unique needs of children. One such need is that the medicine be palatable.[2,3] Active pharmaceutical ingredients may taste bitter and/or irritate the mouth and throat and thus are aversive not only to children but to many adults.

Encapsulating the medicin—in pill, capsule, or tablet form—may be an effective method of avoiding unpleasant tastes for adults but is problematic for children because many cannot or will not swallow these. However, pill-swallowing training interventions are available.[4] Crushing or splitting pills can enhance acceptance in some cases but may cause dosing inaccuracies and impair bioavailability.[5] Because younger children often consume medicine in liquid or suspension formulations, attempts have been made to mask or cover the unpalatable active ingredients.

One such method, adding sweeteners, may increase palatability, but in addition to not being completely efficacious, it can be problematic for several reasons. First, some children may need to restrict sugar intake. Second, added sweeteners may render the medicine too palatable and can lead to overconsumption. Third, the medical and dental communities have called for use of noncariogenic substitutes in children's medicines because chronic usage is associated with excessive dental disease.[6] However, many of these noncaloric, noncariogenic sweeteners (eg, saccharin, aspartame, acesulfame K, cyclamate) have a bitter taste component and, to some, an aversive metallic aftertaste, particularly at higher concentrations, which may be needed to mask the active ingredients. [7]

The rejection of unpalatable medications is a reflection of the child's basic biology. From an evolutionary perspective, the senses that evaluate what is put into the mouth have likely evolved to reject that which is harmful and seek out that which is beneficial. In particular, rejection of bitter-tasting and irritating substances is thought to have evolved to protect the animal from being poisoned and the plant producing these chemicals from being eaten. Many toxic substances, including pharmaceuticals, are by their nature bitter and hence distasteful.[8] The unpleasant taste of a medicine is a sensory expression of its pharmacologic activity; the more potent the drug, the more bitter and/or irritating it will be.[9] The more bitter and irritating its flavor, the more likely the drug will be rejected by children.

Several working groups were established as part of the Pediatric Formulation Initiative (PFI), an ongoing program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) aimed at exploring a range of issues and challenges in creating pediatric formulations. One such group was the Taste and Flavor Working Group. This article briefly reviews the principles of flavor perception, which were defined as the combination of the senses of taste, smell, and chemosensory irritation. This review served as a foundation for

the group's discussion on the current knowledge of the sensory world of children, with a particular focus on bitter and sweet tastes, the appropriateness of current sensory methodologies for children, and the need for validated methods. The group also considered how recent scientific advances in understanding flavor perception shed light on why the bitter taste of oral pharmaceuticals is an ongoing formulation problem and how discoveries of novel flavor molecules and modulators of bitter tastes hold considerable promise for the future.

## MATERIALS AND METHODS

The NICHD sponsored a PFI workshop that was held on December 6 and 7, 2005, in Bethesda, Maryland. Information for this article was gathered from literature reviews that were then discussed during this workshop as well as during several conference calls with the Taste and Flavor Working Group members. Terms for the MEDLINE search (1970-2007) included infan, children, taste, olfaction/smell, flavor, chemical senses, palatability, sensory testing, phamzaceutical, and *medicines*. The literature in this area is vast, and only a small fraction of it was used herein. When appropriate, review articles are referenced that will lead the reader to the wider literature.

## WHAT IS FLAVOR?

The perceptions arising from the senses of taste, smell, and chemical irritation combine in the oral cavity to determine flavor. [10] These perceptions are often confused and misappropriated with odor sensations, such as bubble gum or strawberry volatile compounds (flavoring ingredients in children's medicines in the United States), erroneously being attributed to the taste system per se when, in fact, much of the sensory input is due to retronasal olfaction.

It is generally agreed that there are a small number of primary taste qualities (ie, sweet, sour, salty, bitter, umami) that are detected by specialized receptors in the tongue and other parts of the oral cavity. Umami, the fifth basic taste, is the savory taste sensation imparted most dramatically by glutamate, which is present in free form in foods such as mushrooms, tomatoes, soy sauce, aged cheeses, meats, and even breast milk. [11,12] In contrast, there is a much larger number of odor qualities, such as the aforementioned bubble gum or strawberry. Odor stimuli can reach the olfactory receptors in 2 ways: they can enter the nostrils during inhalation (orthonasal route) or travel from the back of the oral cavity toward the roof of the nasal pharynx (retronasal route). It is the latter route that leads to the predominant flavor sensations individuals experience. In other words, a medicine does not "taste" like bubble gum. Rather, it is flavored with bubble gum, and the sensation experienced is due to the retronasal perception of bubble gum odors combined with a sweet taste. Plugging a child's nose while taking medicine may eliminate some of its unpleasant odors, but this will do little to diminish its bitter taste. Flavoring the medicine with pleasant odors may mask the bitterness of some medicine but will not be effective for most of the very bitter ones. We present here a brief review of the sensory systems that contribute to flavor. Other researchers have reviewed this in extensive detail. [13-16]

### Taste

Taste receptors are composed of modified epithelial cells and are found most frequently on the papillae of the tongue and throughout the oral cavity, on the hard and soft palates, the pharynx, the larynx, the epiglottis, and the esophagus. Peripheral innervation of these cells is via branches of 3 different cranial nerves: the facial (VII), glossopharyngeal (IX), and vagus (X). Taste molecules interact with these receptors after they dissolve in saliva. Taste can be separated into 5 primary taste qualities: sweet, sour, salty, bitter, and umami or savory. Although there are regional differences in the oral cavity in the relative sensitivity to these different taste qualities, virtually all can be perceived on all areas of the tongue. Other qualities

that have been attributed to taste are either due to stimulation of other sensory systems (eg, chalky) or remain controversial as to how they are recognized (eg, metallic, fatty),[17]

Major progress has been made in identifying the initial events in taste recognition. It appears that 2 different strategies have evolved to detect taste molecules. For salty and sour tastes, it is widely believed that ion channels serve as receptors. Here sour and salty ions are thought to flow through the channels into the cell and thereby activate the cell to send an electrical message to the brain. However, for both of these taste qualities, the molecular identity of the receptors and their exact mechanism is still unknown. For sweet, umami, and bitter tastes, G-protein-coupled receptors (GPCRs) appear to play the most prominent roles. These GPCRs bind taste molecules in a "lock and key mechanism," thereby activating the taste cell to send an electrical message to the brain. For sweet and umami, a family of 3 GPCRs—TIR1, TIR2, and TIR3—act in pairs (TlRl + TlR3 for umami and TIR2 + TIR3 for sweet) to detect molecules imparting these taste qualities. A substantially larger family of GPCRs, the T2R receptors (n = 26), constitutes the bitter receptors.

Each of the T2R receptors likely recognizes one compound or a few structurally related compounds. [18] Presumably, there are many bitter receptors because there are so many structurally different compounds that are potentially harmful. Thus, it is not surprising that the bitter and unpleasant taste of oral pharmaceuticals is an ongoing formulation problem. Because the chemical structure of a drug determines both its pharmacologic efficacy and its bitterness, it cannot be modified to increase its palatability.[9] Consequently, research has focused on 2 alternatives to reducing or eliminating bitter tastes: bitter blocking (pharmacologic antagonism of bitter compound activation or transduction pathways) and bitter masking (psychological interference with bitterness perception). [19,20]

One method of blocking bitter taste involves the use of sodium salts, which not only impart a desirably salty taste but reduce the bitterness and unpleasantness of many, but not all, bitter compounds.[21,22] Although the mechanisms underlying sodium's effectiveness as a bitter blocker remain unknown, studies in adults revealed that sodium is the most effective cation at inhibiting bitterness of several oral pharmaceuticals (eg, ranitidine, acetaminophen, pseudoephedrine), presumably by acting at the peripheral taste level and not by cognitive effects.[20] Sodium salts also reduced the bitterness of liquids for young children.[23] Because children prefer salted solutions even more than adults,[23] the use of sodium salts may be an especially effective strategy for reducing the bitterness of pharmaceutical liquids designed for the pediatric population. Moreover, the intensity of the sweetness of a liquid formulation may be enhanced by the addition of a sodium salt, presumably by blocking bitterness and thereby releasing sweetness from cognitive suppression.[21] Concerns about the negative consequences of consuming excess sodium and intolerance of sugars for some children could limit the usefulness of this approach.

Additional blockers of bitterness have been identified, both in research publications and in the patent literature (eg, phosphatidic acid-β-lactoglobulin, glutamate, adenosine monophosphate [AMP]). [19,20,24] With progress in understanding the molecular mechanisms underlying bitter taste perception and how bitter blockers function to suppress bitterness, it may be possible to predict the efficacy of these blockers for a drug of interest. This will be discussed further at the end of the article.

## Smell

Smell or olfaction occurs when chemicals stimulate olfactory receptors located on a relatively small patch of tissue located high in the nasal cavity. The human olfactory epithelium lines the roof of the nasal cavity, part of the nasal septum, and the superior turbinates, and may extend to the middle turbinates. The organization of the olfactory system reflects the need to recognize

a wide range of odors and to discriminate one odor from another. In fact, the olfactory receptors (7-transmembrane GPCRs) are encoded by the largest mammalian gene superfamily consisting of >1000 genes, a discovery by Linda B. Buck and Richard Axel that was awarded the 2004 Nobel Prize in Physiology or Medicine.[25]

Experience is a means by which the olfactory system can be tuned to respond more strongly to stimuli that are relevant to an individual's environment. In other words, it is through experiences and the context of such experiences that odors may acquire personal significance.[26,27] As will be discussed later, such associational learning forms the basis for differences among cultures in the types of flavors and odors that are preferred and accepted in foods, beverages, and medicines.

### Chemical Irritation

Sensations resulting from chemicals stimulating receptors and free nerve endings of the trigeminal and vagus nerves lead to oral perceptions such as pain, heat, coolness, tingling, tickle, and itch. Recent research has shown that a family of transient receptor potential (TRP) channels is involved in detecting many of these chemicals.[28] These channels also respond to actual heating and cooling. Apparently, plants have evolved defensive strategies involving chemicals that affect these channels as a protective device. For example, chili peppers contain capsaicin that burns (ie, stimulates the same receptors which are stimulated by noxious heat) and hence are avoided by potential predators. Other irritants include menthol, which interacts with channels sensitive to cooling; mustard oil; black pepper; and even $CO_2$ (carbonation). Irritants, in addition to bitter compounds, can provide sensory problems in pharmaceutical preparations. For example, ibuprofen when given in liquid formulation irritates the throat more than the mouth, and its quality in the throat is characterized primarily as a sting/prick, itch, or tickle, often leading to a cough.[29] Many volatile compounds also stimulate irritant receptors in the nasal cavity, producing a characteristic sting. Indeed, most—but not all—volatiles that are odorants at low concentrations cause irritation at higher concentrations.

Because there is virtually no research on the ontogeny of trigeminally mediated oral or nasal responses to irritating chemicals, the next section focuses on the ontogeny of taste and smell. Because "irritating" sensations are critical in food and flavor acceptability and most likely have a huge impact on the acceptance of medications by children, this void is puzzling. Developmental studies here are certainly indicated.

## SENSORY WORLD OF CHILDREN

There is a misperception that infants are tabula rasae when it comes to smells, tastes, and flavors. Some believe that children do not display any affective responses to odors and flavors until mid-childhood. The findings gleaned from basic research suggest otherwise. Indeed, the chemical senses are functioning early in development. Taste and olfactory receptors are capable of conveying information to the central nervous system by the last trimester of pregnancy, and this information is available to systems organizing changes in sucking, facial expressions, and other affective behaviors. Because this body of research has been reviewed extensively elsewhere,[15,30] only a brief overview is presented here.

### Taste

The taste system is well developed before birth and continues to mature postnatally. Specialized taste cells first appear in the human fetus at 7 to 8 weeks of gestation, and morphologically mature receptor cells are recognizable at 13 to 15 weeks. Within hours after birth, infants reject bitter tastes and prefer sweet and umami tastes.[31-33] Adult-like sensitivity to salt does not emerge until the infant is ~4 months of age, however.[34] In other words, infants are neither

blank slates nor miniature adults, as their sense of taste continues to develop during infancy and childhood.

With regard to bitter taste, human newborns can detect and tend to reject several bitter compounds, as shown by studies on facial expressions [32,33] and inhibition of sucking. [35] Many of these studies use very strong (to adults) stimuli. Some data suggest that responses to various bitter compounds mature postnatally and that some children may be even more sensitive to bitter tastes than adults. [35,36] However, because of the paucity of research on the ontogeny of bitter taste sensitivity, the extent of the differences in perception between adults and children is unknown. In addition, there is some indication that there may be sensitive periods, such that early experiences with bitter tastes and other flavors predispose individuals to be more accepting of these flavors later in life. [37] Whether similar phenomena exist for acceptance of medications remain unknown. More research is needed to fill this void.

Perhaps the most striking taste difference between children and adults is the child's stronger liking for foods and beverages that taste sweet,[38] salty,[39] and, in some cases, sour,[40] and the dislike of all that tastes bitter. Is the strong preference that children have for sweets mainly a product of modern marketing, technology (eg, sugar refining), and availability? Probably not. Liking for sweets is innate and presumably evolved to attract plant-eating species to energy sources. The child's heightened liking, relative to adults, probably reflects the need for energy during periods of maximal growth, as many foods rich in energy (eg, breast milk, fruits) taste sweet.

According to both cross-sectional and longitudinal studies, the preference for sweets remains heightened throughout childhood[36] and then declines to adult levels during late adolescence. [41] In a cross-sectional study that measured sweet preference in >750 participants, 50% of the children and adolescents, but only 25% of the adults, selected the 0.60-M sucrose concentration as their favorite solution.[41] To put this in perspective, a 0.60-M sucrose concentration is equivalent to ~12 spoonfuls of sugar in 230 mL of water (an 8-ounce glass), whereas a typical cola is about half of this sucrose concentration (or sucrose equivalent). Not only do children prefer sweet tastes, but sweet-tasting solutions in the oral cavity reportedly reduce pain in both infants and children,[42,43] presumably via the involvement of the endogenous opioid system. Thus, it is not surprising that many oral formulations for children are sweetened.

## Smell

The olfactory system is well developed before birth. The olfactory bulbs and receptor cells attain adult-like morphology by week 11 of gestation, and the olfactory marker protein, a biochemical correlate of olfactory receptor functioning, has been identified in the olfactory epithelium of human fetuses at 28 weeks of gestation. (See Ganchrow and Mennella[30] for an indepth review.) Because the epithelial plugs that obstruct the external nares open between gestational weeks 16 and 24, there is a continual turnover of amniotic fluid—and the odor and taste molecules contained within—through the nasal passages.

At birth, infants are as sensitive as adults, if not more so, to a wide range of odors. Within hours after birth, mothers and infants can recognize each other through the sense of smell alone. [44] This recognition of and preference for maternal odors may playa role in guiding the infant to the nipple area and facilitating early nipple attachment and breastfeeding.[45] The early state of maturity, as well as the plasticity of the olfactory system, favors its involvement in the adaptive responses to the challenges of development. The finding that olfactory learning begins early in life is evidenced by the infants' preferential response to the flavors of foods consumed by their mother during pregnancy and lactation.[46] The flavors of foods mothers consume transmit to the fetus through amniotic fluid and to infants through breast milk. [47,48] Infants cannot only detect these odors but experience can bias their behavioral responses to the odor component

of flavor later in life. Thus, experience with flavors in amniotic fluid and mother's milk may be one of the first ways infants become familiar with, and learn to prefer, the flavors of their culture.[44-46]

Humans continue to learn and develop preferences and aversions for flavors and foods experienced later in life. However, it is during childhood that the flavors and foods acquire meaning. That is, children learn in part what constitutes a food, how it should be prepared and flavored, by whom it should be eaten, and at what time of day it should be consumed. As a consequence, flavorings are differentially associated with particular foods among cultures. The same can be applied to cultural practices in medicine. For example, lemon-flavored hot drinks containing decongestants (ie, Lemsip [Reckitt Benckiser, Slough, Berkshire, United Kingdom]) are common cold and flu remedies in England and Australia, and herbal infusions of manzanilla (ie, chamomile) are used to treat acute diarrhea and other pediatric ailments in Mexico.[49] In the United States, bubble gum and cherry flavors are added to medicines,[50,51] toothpaste, and other pediatric products. Because of these differences, developing a universal flavor for medications for older-aged children may be problematic for those who have already experienced a particular flavored medicine or for whom flavors have already acquired a cultural meaning. Indeed, there is probably no universal "favorite flavor" for children.

How much a person likes or dislikes the odor component of a food, beverage, or pharmaceutical flavor is highly influenced by individual experience. Nevertheless, it is possible that, as is the case for taste, individuals may be innately biased toward some odors in a positive or negative direction. For example, odors containing sulfur are generally disliked, whereas those associated with some foods and plants are generally liked. [52] Recently, it has been suggested that the chemical structure of a volatile may predict its pleasantness.[52] More research is needed to determine how preferences and aversions to the odor components of flavor change over an individual's life span. Also unknown is whether medication usage and disease state modify taste and smell perception. Although the etiologic factor contributing most to taste and smell dysfunction in adults appears to be medication use,[53,54] there are few reports in pediatric populations. [15] For adults, not all individuals taking a particular drug are affected the same way, and the mechanisms by which chemosensory function is altered are not well understood. Whether a drug alters chemosensory function and how this affects compliance in children is yet another important area for future research.

### Chemical Irritation

Although little is known about the ontogeny of this chemical sense and whether children are more responsive to oral irritants, there is some evidence that susceptibility to skin irritants is inversely proportional to age.[55] Children aged <8 years may be more vulnerable to skin irritation while reactivity becomes normal as they age.[56] More research is needed in this area as well.

## METHODS TO TEST PEDIATRIC POPULATIONS

Sensory studies can provide data relevant to 2 aspects of chemical sensation: the sensitivity of the system to chemical stimuli and the hedonic valence of the sensation. In studies on adults, the distinction between the 2 is usually unambiguous. Measures of sensitivity include thresholds, just noticeable differences, intensity judgments, and sensory adaptation, whereas measurements involving a hedonic dimension usually consist of estimates of pleasantness, liking, or preference. In studies of children aged <4 to 5 years, these 2 classes of responses to chemical stimuli can be more difficult to distinguish. Many response measures are associated with acceptance or rejection and, thus, presumably involve a hedonic component.

Sensory evaluation methods for children have been published in standard guides[57] and review articles.[58] However, there has been little to no peer-reviewed research studies that systematically determine the validity of many of these methods among children of varying ages.[59] We provide here a review of some of the methods that have been used for pediatric populations, as well as an overview of the methodologic issues that need to be incorporated into research designs.

Contemporary research on the ontogeny of the chemical senses is based on more than a century-long legacy examining behavioral responsiveness and determining functional maturity. (A more detailed review has been published elsewhere. [30]) The most widely used reflex-like responses for evaluating taste and smell in nonverbal infants include changes in salivation, the lateral tongue reflex, head and body orientation, sucking measures, heart rate, and facial expressions. [30] The most widely used consummatory responses include the multiple-bottle preference test (single test day) and one-bottle tests (multiple test days).[30] Data from such consummatory tests may be variable and inconsistent if basic stimulus (eg, concentration, temperature, volume and type of diluent) and methodologic (eg, degree of satiation and experience) parameters are not controlled. However, many of these issues can be resolved by controlling for these variables and using a within-subject design. Although each measure has its limitations, the convergence of findings from different methodologies gives confidence to conclusions and has repeatedly revealed the innate preference of sweets and rejection of bitter, as described earlier.

In older children (ie, those aged ≥5 years), methods that do not confound sensitivity and hedonics are possible. For example, paired-comparison methods can be used to assess pairs of samples that differ in taste or flavor quality to determine which is preferred.[60] More complicated tasks, such as scaling tests, forcedchoice tracking procedures, and rank order tests, are used to measure sensitivity and hedonic responses to tastes, odors, and flavors, [57] but their use in children aged <5 years is problematic.[59,61]

Forced-choice tracking procedures can be used to determine both sensitivity and preferences in children older than 4 to 5 years. [36,62] This technique has been shown to be sensitive enough to detect developmental, genetic, and race-related differences in taste preferences. In brief, subjects are presented with pairs of solutions that differ in taste concentration. They are instructed to taste, without swallowing, each solution and then point to which of the pair they like better (or tastes stronger). The procedure continues until the subject chooses either a given concentration of a tastant when it is paired with a higher and lower concentration or the highest or lowest solution 2 consecutive times. The entire task is then repeated with stimulus pairs presented in reverse order. By comparing the solution chosen in the first and second (reverse order) task, one can determine reliability within a subject. Estimates of reliability should be incorporated into all pediatric studies, but unfortunately they are not. The forced-choice tracking procedure is especially useful because memory requirements are minimized, unlike tests where the child has to remember sequentially presented stimuli about which relative judgments are to be made.

In rank order methods, either a sample is removed from the set after being selected, or a bifurcated approach is used in which the child is first asked to place the sample into either a “good/like” or a “bad/dislike” category.[40,63,64] The degrees of like or dislike are then scaled. Hedonic rating scales, some of which include series of faces ranging from happy (“smiley”) to sad (“frowning”), are also frequently used in pediatric studies. Some marketing research firms and researchers claim success with 7- to 9-point face scales with 5- to 7-year-old children. However, little is known about the validity and reliability of these scales[59] and at what age children use the entire scale and not just the anchors.

In conducting research in children, there are several methodologic issues that need to be addressed. First, young children are more prone to attention lapses and have shorter memory spans. Therefore, any method relying on sustained attention that places demands on memory could yield spurious findings. Second, because young children tend to answer questions in the affirmative,[65] a forced-choice categorization procedure is generally preferred. Age-appropriate tasks, embedded in the context of a game that is fun for children and minimizes the impact of language and cognitive development, are particularly effective.[27,66] Third, before the actual testing and after a period of acclimation, the experimenter should ascertain whether the child comprehends the task. Screening tools need to be developed to determine whether a given child has the ability to do the task.[59] Reproducibility of the measures over time should be built into the design of the study. Fourth, because children are reluctant to participate in a research study when the first stimulus is "unpleasant,"[66] none of the trials should begin with an unpleasant odor or taste. Fifth, when evaluating children's preference regarding odors, the experimenter should present the odor directly to the child and monitor his or her breathing, as previous research has shown that children may exhale air when asked to sniff an odor bottle or jar.[66] Sixth, videomicroscopy of the tongue has revealed that the fungiform papillae-rich anterior region does not attain adult size until children are 8 to 10 years of age, while the posterior region continues to grow until ~15 years of age.[67] Thus, evaluation of taste solutions that are applied directly to small portions of the tongue versus the whole mouth could lead to different results for taste palatability and sensitivity in children when compared with adults.

Appropriate study designs and methods depend on the objectives of the study. For pediatric formulations, methods specially suited for children must be used and the reliability of such methods within and among individuals must first be established. In some cases, the question may need to be asked several ways, and the convergence of findings from different methodologies will give confidence to the conclusions.

Several additional questions and issues should be addressed in future research. What methods yield data that can predict initial acceptance versus long-term compliance of a medication? How do medication usage and disease state modify flavor perception in children? Is there a disparity between branded and generic drugs when it comes to flavor and acceptance by children? There is a need to identify measures that systematically evaluate the palatability issues of medications, as well as parental perceptions and biases, so that they can be incorporated into clinical trials. The reporting of formulation information is needed in all future drug trials that include children to improve validity and reliability of findings. [5] Moreover, it is important that pediatric drug trials provide sufficient information on the methods used so that the results can be reproduced in other clinical trials and implemented in clinical practice. Further development of valid and reliable methods for testing children will improve our understanding of the sensory world of the child. These testing techniques, along with new technologies that will be developed to enhance drug acceptance in pediatric populations, should lead to improvements in compliance.

## PROSPECTUS

To enhance the palatability of oral medications for children, one must diminish or eliminate the bitter taste and, in some cases, sensory irritation of those medications. Although testing children directly is the most obvious approach to developing potentially more palatable drug formulations, there are major difficulties. Much of the very strong bitter and irritating sensations from drugs are most evident in the back of the mouth and throat. [29,68] Thus, for adequate testing, the child must be induced to swallow the substance of interest. Swallowing raises many issues of toxicity that are important even when adults are testing the formulations but are even more concerning when testing is conducted in children. Alternative systems for

screening are needed, at least to identify potentially useful candidates and thereby compliment direct tests with children.

## Adult Sensory Panels

Historically, adults have been used to test for palatability of products, even those primarily aimed for pediatric markets. The advantages of using adults are obvious. Adults can easily follow instructions and articulate responses. Furthermore, there is a long history of developing sensory testing procedures for adults.[69-71] Finally, it is likely that adults and children are quite similar in their responses to many flavor components.[27,66] Nevertheless, as outlined earlier, there are also significant age-related differences in how children and adults respond to flavors, and in some cases adult sensory panels may not be able to predict flavors that children prefer and those they will reject because of these differences in flavor perception. More psychophysical research in the chemical senses is needed to determine what types of adult sensory panels and which methods are most appropriate for predicting acceptance and compliance by pediatric populations.

## In Vivo Animal Models

The use of animal model systems for drug screening is an attractive approach. [13,72] Currently, the most prominent model system, the mouse, is being used throughout biology because of the animal's relatively small size, the fact that the mouse genome has been fully identified, the availability of many genetically characterized mouse strains, and the ability of investigators to genetically engineer those strains. A description of various types of mouse behavioral tests has been reviewed elsewhere. [13] The advantages of using mice as a screening tool include reduced cost, minimized safety issues, and more rapid and efficient testing relative to human testing.

There are disadvantages, however. Mice and humans differ in responses to many flavors, and this is particularly the case for bitterness where evolutionary forces have shaped somewhat different sets of receptor repertoires. Indeed, even among mice, there are significant differences in response to bitter compounds that reflect strain differences in bitter receptor genotypes,[73,74] so results will depend in part on the strain of mouse being tested. If mice are being used to screen for flavor inhibitors—for example, bitter blockers—these compounds may also exhibit species differences, complicating interpretation. Nevertheless, use of mice as a first-pass screening tool is a promising approach that merits additional study. One particularly intriguing idea would be to genetically engineer a strain of mice for which the set of mouse bitter genes were exchanged for human ones. Theoretically, these animals could represent a better model system. Other model organisms, such as the fruit fly (*Drosophila melanogaster*)[75] or the worm (*Caenorhabditis elegans*),[76] may be useful tools for flavor screening, particularly if engineered to carry human receptor genes.

## In Vitro Test Systems

Olfactory[25] and taste receptors[74,77,78] and receptors for many irritants[28] were identified during the past decade. Bachmanov and Beauchamp [13] and Silver et al[79] have published reviews on these topics. Whether there is developmental variation among these receptors that contributes to age-related differences in flavor perception and, in turn, lead to problems with acceptance and compliance, is an important gap in knowledge that must be addressed.

Taking their cue from the pharmaceutical industry, some companies (eg, Senomyx, Inc., San Diego, California [www.senomyx.com]; Redpoint Bio Corporation, Ewing, New Jersey [www.redpointbio.com]) are developing assay systems that use receptors or other transduction elements in the taste cells to screen for alternative taste molecules, taste enhancers, and taste blockers. [80,81] For example, human bitter receptors can be expressed in human cell lines. One can challenge the cells with a bitter compound of interest and the same bitter compound along

with a putative bitter-blocking compound to determine whether, at the receptor level, this presumptive blocker works. Because a common pathway for several classes of taste stimuli is the TRPM5 ion channel,[82] compounds that interact with this channel may act as bitter blockers or taste enhancers. Indeed, in one important advance, this method was used to discover that AMP could be a potent blocker of many bitter compounds. [19] The advantage of such systems is that it is possible to screen thousands of compounds in a very short time. Vast libraries of chemicals can be tested in a search for potential bitter antagonists. It is thus possible to identify candidate blockers that merit further study, which could involve the aforementioned animal studies and/ or human sensory studies, depending on the compound. The obvious practical disadvantage of this approach is that it is likely to generate many false-positive results. Moreover, this approach necessarily cannot detect molecules that are active at sites other than the isolated receptor or the transduction pathway. Nevertheless, this is a potentially powerful approach that has great promise. [83]

An alternative to studying the isolated receptor is to study the intact receptor cell that has been placed in culture. For example, cultured trigeminal nerve cells[84] can be exposed to irritants and to irritants combined with potential inhibitory compounds in ways analogous to that described here for bitter compounds. One potential advantage of this approach, compared with isolated receptors or individual pathways in transduction sequence, is that tests are made on a more complete system. It has been particularly difficult to create long-term or immortalized cultures of chemosensory receptor cells. However, progress is being made and assay systems may have great potential.[85] Here, too, any interesting potential blocker must be further tested using in vivo systems.

### Artificial Sensor Systems

The idea of using sensors that do not involve actual chemosensory receptors has a long history. In an early attempt to develop an “artificial nose,” Tanyolac and Eaton[86] published an article in 1950 describing an artificial sensor for volatile compounds. In the ensuing years, many such devices have been used, and there remains considerable interest in their further development. These devices typically are arrays of sensors; the arrays of gas sensors are called electronic noses and the arrays of liquid sensors are referred to as electronic tongues.

The use of an electronic tongue to taste test active compounds has gathered interest and experimental support in recent years. [3,87,88] This area has been reviewed extensively.[89,90] The advantages of this approach include its speed, relatively low cost, and lack of risk. However, several problems may limit its current usefulness. Because these devices do not use biological receptors, it is difficult to predict whether they would be able to identify novel inhibitory molecules. Inhibition in biological systems most likely involves, for example, altering the binding characteristics of the receptor or other elements in the bitter transductive cascade. Thus, it appears unlikely that nonbiological systems would necessarily work in an analogous way. However, since this is an active area of research, it is quite possible that these devices might be useful in the future. Indeed, an instrument that actually makes use of immobilized taste, smell, or irritant receptors could be a very valuable screening tool.

## CONCLUSIONS

Many parents are faced with the daily challenge of getting their children to take a medicine. The unpleasant flavor of the medicine can thwart the benefits of even the most powerful drug, and failure to consume medication may do the child harm, and in some cases, may be life-threatening. Although there are no easy solutions to this dilemma, children’s acceptance of many medicines can be improved by applying the knowledge gleaned from basic research in the chemical senses. Better understanding of the scientific basis for distaste, and how to

ameliorate it, is a public health priority for advancing availability of formulations of drug products that will be accepted by children.

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