A STUDY OF THE POTENTIAL APPLICATIONS OF OLFACTORY RESEARCH IN MAN

MARCH, 1973

Prepared for

LIFE SCIENCES OFFICE
OFFICE OF THE CHIEF OF RESEARCH AND DEVELOPMENT
DEPARTMENT OF THE ARMY
WASHINGTON, D.C. 20310

CONTRACT NO. DAHC19-72-C-0010

The findings in this report are not to be construed as an official Department of the Army position

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FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20014
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. These reports are based upon comprehensive literature reviews and the perceptive observations of knowledgeable scientists engaged in work in the field. Although LSRO reports are recognized by FASEB as contributions to societal needs and most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the members of its six constituent societies. However, the report has been reviewed for policy matters by the LSRO Advisory Committee, which includes representatives of each constituent society.

This technical report was prepared for the Life Sciences Office, Office of the Chief of Research and Development, Department of the Army, by the staff of the Life Sciences Research Office, FASEB, in accordance with the provisions of U.S. Army Contract No. DAHC19-72-C-0010.

We acknowledge the contributions of the numerous investigators and consultants who have assisted with this study. The report reflects the opinions expressed by participants in an ad hoc study group that met at Beaumont House, FASEB, on September 19-20, 1972, and other consultants. The report has been reviewed by these scientists and a judicious attempt has been made to incorporate the different viewpoints and opinions.

The listing of the consultants' names in Section XII must not be construed as indicating that they are authors of the report or that they endorse the conclusions or recommendations. The authors accept full responsibility for the contents of this report.

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SUMMARY

This study provides a comprehensive review of the feasibility of developing and utilizing the chemical senses of the soldier. While biosensors and odor-sensing devices can supplement, they cannot replace the potential performance of the normal human olfactory system. There is no current program in the Army to train soldiers to use their chemical senses. Experience in other countries suggests that a soldier trained to recognize olfactory cues is more effective in the field, more responsive to hazards, and less likely to give olfactory information to the enemy than one whose chemical senses are underutilized.

Practical testing and training methods suited to the Army's needs have been lacking in the past, and basic knowledge of the mechanisms of olfaction and taste is incomplete. However, elements of a suitable technology have been identified in agencies such as the National Bureau of Standards and in certain industries. This technology appears suitable for further development within the Army research and development community. This report concludes that it is feasible for the Army to use these methods in determining classifications of personnel that require normal acuity of the chemical senses and to institute training programs.

In addition, regular testing for normal acuity of the chemical senses may uncover early cases of some illnesses, indicate extensive exposures to ionizing radiation, and categorize personnel as either suitable or unfit for certain Army duties. If administered at recruitment, these tests can be used later to document disability claims for service-related losses of olfaction and taste.
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I. THE PROBLEM

Visual and auditory proficiency are generally recognized as important requirements for the soldier, and are not only related to efficient performance in the military environment but also may be essential for survival. The military significance of these sensory modalities has been reviewed recently (Carr and Fisher, 1970, 1971, Carr et al., 1969, Fisher et al., 1969). On the other hand, acuity of the "chemical senses," olfaction and taste, has been less widely recognized as important, and the only available review of the subject related to Army interests was concerned mainly with animal biosensors (Smith and Coates, 1965). Another trend has been to substitute instruments for odor detection in the field without considering the performance potential of man.

Although some of the basic mechanisms of the neurophysiology of olfaction and taste are unknown, human skill in the recognition of odors and tastes can be enhanced by training and may be used efficiently by the soldier (Woods, 1968). The Army has sponsored major work related to olfaction and taste on nutrition, diet, food components, and acceptability of rations, but there has been little in-house military research on the potential contribution of the chemical senses to military performance.

When men are incapable of detecting odors of fire, toxic gases, or spoiled foods, this must obviously be a handicap to performance and even to survival. Most men are capable of detection, yet are often untrained in odor recognition. Failure to identify odors that characterize machine malfunctions, enemy operations, states of the environment or other situations could mean the difference between success or failure of a military mission. In general, any underutilization of sensory responses to environmental stimuli detracts from the quality of human performance. Woods (1968) has indicated that olfactory acuity is required for certain military duties in the British and Commonwealth armies. In contrast, in the United States Army, no military duties are specified as requiring a normal level of acuity and the chemical senses are not even tested.

A major requirement of this study was to identify aspects of the military environment in which normal acuity of olfaction and taste are important and factors that contribute to losses of these senses. In the past, a major difficulty has been inadequate testing methods to evaluate
acuity of olfaction and taste. Although many testing methods continue to be directed toward elucidation of basic mechanisms rather than evaluation of human capabilities, recent technical advances indicate that the latter objective should now be attainable.
II. SCOPE OF THE STUDY

Preliminary discussions with research investigators in universities and Army laboratories revealed many facets of the problems of understanding the mechanisms of human olfactory and taste systems, the nature of loss of acuity, recognition and detection levels, environmental and genetic influences, and analytical techniques employed in assessment of acuity in man.

From this background an agenda was developed for an ad hoc review group meeting convened at Beaumont House, Federation of American Societies for Experimental Biology, on 19-20 September 1972 (see Section XII-A). These reviews of the subject provided insight into the basic and applied aspects of olfactory and taste research and the Army programs related to these areas. The scope of this report emerged from these reviews.

The study includes a synopsis of the current limits of scientific and technical knowledge, especially of olfaction, and a more detailed assessment of opinions on how this information may be applied to Army needs. It was not deemed necessary to review current in-house Army research programs on food acceptability, biosensors, or odor-sensing devices. The study stresses the practical applications of human sensory acuity in olfaction and taste, rather than fundamental concepts and theories that are available in the literature.
III. COMPONENTS OF THE HUMAN OLFACTORY AND TASTE SYSTEMS

A. OLFACITION

1. Air Passages

The nose is a paired organ, like the eyes but unlike the mouth (Figure 1). The olfactory system is exquisitely sensitive; in nose-breathing, only 3 percent of the inspired air passes over the olfactory epithelium (Stuiver, 1958). When the nasal epithelium is either dry or congested the airflow is abnormal and olfactory function is further diminished. The rate of flow and the temperature of the air are important (Schneider and Wolf, 1960). When exhaled air passes through the mouth it may pick up odorants that affect responses of the olfactory epithelium to inhaled odorants.

2. Olfactory Epithelium

A small area of the mucous membrane at the apex of the nose contains odor-sensitive cells (Figures 1 and 2). This epithelium contains pigments (Takagi, 1969, Moulton, 1971). In animals, some of these pigments are carotenoids. Carotenoids are precursors of vitamin A and losses of smell occur in vitamin A deficiency. But since vitamin A deficiency affects virtually all membranes, and carotenoids are absent from the pigments in human olfactory epithelium, Moulton and Beidler (1967) have concluded that these pigments probably have little to do with olfaction in man.

3. Olfactory Receptor Cells

Estimates of cell numbers vary. Allison and Warwick (1949) estimated that the olfactory nerves of the rabbit contain millions of primary fibers, each presumably connected to a cell body. From electrophysiological responses, Beets (1971) has estimated 10 million cells, each able to conduct 10 impulses/sec, giving a system capacity of 100 million inputs/sec, comparable to the input capacity from the retina of the eye.
Human anatomy of olfaction, showing the right nasal air passage with olfactory area (epithelium) and bulb. Similar structures on the left are not shown. Left and right air passages enter the single air duct at the throat (large arrow). Reproduced from Amoore, Johnston, and Rubin (1964) with permission of the copyright holder, Scientific American, Inc.
Human anatomy of olfaction, showing the structure of the olfactory epithelium. The olfactory receptor cells are nerve cells distributed among the supporting, mucous-producing cells. Not shown are trigeminal nerve endings which occur between the supporting cells and, like other tactile nerve endings, do not reach the surface of the epithelium. Reproduced from Moulton and Beidler (1967) with permission of the American Physiological Society and the authors. For further anatomical detail see Schneider, 1967.
The cilia of the olfactory nerve cells protrude above the epithelial surface (Figure 2). Receptor molecules are believed to be proteins in the outer membranes of the olfactory cells including the cilia. The number of cilia per cell is known for several species (Moulton and Beidler, 1967), but the number of receptor molecules per cell is unknown. Most authorities agree that the receptor cells including their axons are continually replaced; thus, each cell is functional for only part of its life. This turnover might explain the diversity of the estimates of input capacity from the olfactory epithelium.

4. Olfactory Nerve Connections

Fibers from the receptor cells track back to left and right olfactory bulbs (Figures 2 and 3). "Accessory" olfactory bulbs and vomeronasal organs are found in lower animals but are absent or vestigial in man. The role of the bulb may be analogous to that of the horizontal cell layer of the retina. Each bulb contains a large number of glomeruli. Allison and Warwick (1949) have estimated that each glomerulus collects about 26,000 primary nerve fibers, and provides one nerve fiber to the higher brain centers; this is a large input reduction. From each bulb about 2,000 channels go back to the higher centers, some to the same side, others to the opposite, as with the optic nerves (Stone, 1969). Responses evoked by odorants have been detected electrophysiologically in the 1st, 5th, 7th, 9th and 10th cranial nerves.

Trigeminal nerve endings, usually associated with pain or irritation, also are stimulated by impulses arising in the olfactory epithelium; some of these fibers enter the glomeruli, where they interconnect with the olfactory nerves (Amoore et al., 1964).

Channels from the olfactory bulbs are distributed in the general area of the prepyriform cortex (Figure 3). The interconnecting pathways in the brain have not been fully delineated (Stone, 1969), but from psychophysical data there is little doubt that they extend to the reticular cortex, thalamus, hypothalamus (MacLeod, 1971), and other areas in the brainstem and midbrain. These observations suggest that there are interconnections between brainstem pathways and the endocrine system.
Nerve pathways of the rat olfactory system. Primary nerves from the epithelium enter glomeruli in the olfactory bulb, where they synapse with fewer nerves that go deeper into the brain (right side of diagram). The brain sends other nerves ("centrifugal axon") back to the olfactory bulb, and it is thought that by this pathway the brain can modify sensory input from the olfactory bulb. Reproduced from Heimer (1971) with permission of the copyright holder, Scientific American, Inc.
B. TASTE

1. Anatomy of Taste Receptors

The primary organs of taste are the taste buds. The salivary glands contribute to taste by secreting fluid in which solid tastants are dissolved; undisolved molecules cannot be tasted. Locations that exhibit differential sensitivity to specific tastants (e.g., Figure 4) have been demonstrated by experiments in which sensations in parts of the mouth were blocked by local anesthetics (Henkin, 1971, Murray and Murray, 1970). Taste buds contain receptor cells associated with nerve endings (Figure 5); unlike olfactory receptors, these are not nerve cells and do not have fully developed cilia. Taste buds are renewed every 10-10.5 days if innervated; if the nerve supply is severed, the taste bud dies and does not regenerate until the nerve grows back (Beidler, 1970). The number of taste buds varies widely between animal species (Table 1), and cannot be correlated with taste acuity in animals or man (Kare, 1971).

Receptor molecules are thought to be proteins of the receptor cell membranes, because all taste sensations diminish after proteolytic enzymes are held in the mouth (Giroux and Henkin, 1971). It has been suggested that they might be lipoproteins with weak binding capacities. Others believe that the shape of the binding site is more important than the identity of the protein (Amoore et al., 1964, Mazur et al., 1969). However, proteins that bind dissolved tastant molecules and initiate taste sensations have not been identified. Dastoli and Price (1966) have isolated a protein from the sweet-sensitive areas of the tongue. Price and Hogan (1969) reported this protein had dehydrogenase activity, but its structure is not known.

2. Taste Nerve Connections

The taste bud of a rat may contain about 200 nerve fibers, which make contact with most of its cells, but only about 50 fibers enter the base of the bud (Beidler, 1969, 1970). The reduction factor is 4:1; in man the cell numbers may be smaller, but the reduction factor is thought to be of the same order (Pfaffmann, 1959).

The afferent fibers from the taste buds in the anterior two-thirds of the tongue join the lingual nerve, and then are included in the chordatympani nerve, which leaves the lingual nerve, passes through
FIGURE 4

Taste sensitivity of the normal human tongue, palate and pharynx in terms of the "primary" tastes. Each area perceives all four tastes, and differences are relative; capital letters indicate high sensitivity, lower-case letters lower sensitivity. (Redrawn from Henkin, 1970a).
Diagram of a taste bud. The nerves are outside of the cells. Some cells are slender, and others broad, as illustrated in the two cells with detailed nuclei; this difference may or may not be meaningful. Reproduced from Murray and Murray (1970) with permission from the copyright holder, Longman Group, Ltd.
### TABLE 1

**NUMBERS OF TASTE BUDS IN VARIOUS ANIMALS AND MAN**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Taste Buds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snake</td>
<td>0</td>
</tr>
<tr>
<td>Kitten</td>
<td>473</td>
</tr>
<tr>
<td>Chicken</td>
<td>24</td>
</tr>
<tr>
<td>Bat</td>
<td>800</td>
</tr>
<tr>
<td>Pigeon</td>
<td>37</td>
</tr>
<tr>
<td>Human</td>
<td>9,000</td>
</tr>
<tr>
<td>Bullfinch</td>
<td>46</td>
</tr>
<tr>
<td>Pig and Goat</td>
<td>15,000</td>
</tr>
<tr>
<td>Starling</td>
<td>200</td>
</tr>
<tr>
<td>Rabbit</td>
<td>17,000</td>
</tr>
<tr>
<td>Duck</td>
<td>200</td>
</tr>
<tr>
<td>Calf</td>
<td>25,000</td>
</tr>
<tr>
<td>Parrot</td>
<td>350</td>
</tr>
<tr>
<td>Catfish</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Estimates by many investigators published between 1906 and 1961. (Adapted from Kare, 1971).
the middle ear, and enters the brain as part of the 7th cranial nerve (Pfaffmann, 1959, Zotterman, 1971, Sato, 1971). Taste nerves from other parts of the mouth and palate join the 7th, 9th and 10th cranial nerves, which enter the medulla (Pfaffmann, 1959).

Taste areas in the brain are believed to be diffuse, and closely correlated with the somatosensory system (Pfaffmann, 1959). The hindbrain, thalamus and hypothalamus are probably involved (Halpern and Nelson, 1965, Halpern, 1967), but the pathways remain obscure (Burton and Benjamin, 1971).

C. OTHER RELATED SENSORY INPUT

The neuroanatomy of olfaction may be analogous to that of vision; however, the neuroanatomy of taste appears more analogous to that of touch. Both the olfactory and taste-sensitive areas are innervated for transmission of pain sensations, but the innervations differ. Irritation (leading to sneezing) is integrated into the trigeminal system. Touch, leading to texture recognition, is separate from taste but is important in the identification of foods. Although taste fibers pass through the middle ear, there is no anatomical evidence that auditory stimuli interact with taste sensations within the chorda tympani nerve. However, middle ear damage or other closed head injuries often lead to chorda tympani destruction and subsequent abnormal taste responses. Also middle ear surgery often affects taste responses (Benjamin et al., 1965).

It is evident that all senses interact, but the pathways are largely unknown. Brush and Halpern (1970) have noted that efferent nerve impulses are involved. In addition, the associating functions of memory and vivid recall are factors in these interactions.
IV. BASIC MECHANISMS OF OLFACATION AND TASTE

A. OLFACITION

1. Odorants - Substances Perceived by Olfaction

All odorants are volatile, are thought to have molecular weights of 300 or less, and with a few exceptions, contain 1 to 2 functional atomic groups. Aggregates of small molecules or macromolecules may be odorless. Beets (1971) considered that much published information on compounds under 140 molecular weight was unreliable. It is likely that these issues are related to the purity of the compounds tested.

Nonmolecular stimuli such as X-rays and ionizing radiation can be "smelled." The nature of this effect is unknown. Passage of X-rays through air is known to generate ozone and peroxides; several investigators (Smith and Tucker, 1969, Garcia and Koelling, 1971) have suggested that these substances are generated by interactions at the surface of the olfactory epithelium. Cooper (1968) has shown that the surgically exposed nasal epithelium of anesthetized rabbits can be stimulated by soft β-rays. Olfactory bulb neurons responded only when the rays were directed at the olfactory mucosa.

2. Odor Receptor Function

Current theories about how substances interact with chemoreceptors have been reviewed by Moulton and Beidler (1967), and Dravnieks (1967). These theories are based on the principle of a three dimensional "fit" between molecules (Laffort, 1969). A number of pure substances has been found to be consistent with this concept (Table 2). Amoore (1971) has proposed that an odorant initiates impulses when it alights on a specific protein of the receptor cell membrane.

While there is considerable evidence that a single molecule of some odorants can excite one receptor, the probability of a single inhaled molecule reaching a receptor site is quite low. There are other theories of impulse initiation.
### TABLE 2

**FIFTY PURE SUBSTANCES WITH MOLECULAR CHARACTERISTICS THAT HAVE BEEN CORRELATED WITH RESPONSES OF THE OLFACTORY SYSTEMS**

<table>
<thead>
<tr>
<th>Ethane</th>
<th>Formic acid</th>
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<tr>
<td>Butane</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>Pentane</td>
<td>Propionic acid</td>
</tr>
<tr>
<td>Heptane</td>
<td>Butyric acid</td>
</tr>
<tr>
<td>Octane</td>
<td>Pentanoic acid</td>
</tr>
<tr>
<td>Nonane</td>
<td>Hexanoic acid</td>
</tr>
<tr>
<td>Hendecane</td>
<td>Heptanoic acid</td>
</tr>
<tr>
<td>Methanol</td>
<td>Octanoic acid</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Nonanoic acid</td>
</tr>
<tr>
<td>Propanol</td>
<td>Decanoic acid</td>
</tr>
<tr>
<td>Butanol</td>
<td>Dodecanoic acid</td>
</tr>
<tr>
<td>Pentanol</td>
<td>Acetaldehyde</td>
</tr>
<tr>
<td>Hexanol</td>
<td>Acetone</td>
</tr>
<tr>
<td>Heptanol</td>
<td>Allylic alcohol</td>
</tr>
<tr>
<td>Octanol</td>
<td>Ammonia</td>
</tr>
<tr>
<td>Decanol</td>
<td>Bromine</td>
</tr>
<tr>
<td>Dodecanol</td>
<td>Carbon disulfide</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>Chloroform</td>
</tr>
<tr>
<td>Ethyl butyrate</td>
<td>Dichloro-1-2-ethane</td>
</tr>
<tr>
<td>Ethyl hexanoate</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>Ethyl octanoate</td>
<td>Propenal</td>
</tr>
<tr>
<td>Ethyl nonanoate</td>
<td>Pyradian</td>
</tr>
<tr>
<td>Ethyl decanoate</td>
<td>Hydrogen sulfide</td>
</tr>
<tr>
<td>Ethyl hendedecylate</td>
<td>Ethane thiol</td>
</tr>
<tr>
<td></td>
<td>Ethyl sulfide</td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
</tr>
</tbody>
</table>

(Modified from Laffort, 1969).
The "chromatographic" theory was proposed first by Adrian (Moulton and Tucker, 1964) and is being studied by Mozell (1971). Mozell has shown that odorant molecules are repeatedly adsorbed onto the olfactory mucosa and revolatilized, a process that is mimicked by gas-chromatography. The tenacity of the mucosa for an odorant is a major, but not the only determinant of migration rate across the entire mucosa, which can vary from less than 2 to more than 270 seconds. Because most odorants are mixtures, each shows typical "spatial and temporal" migration spectra which, from electrophysiological measurements, are reversed when the air flows in the opposite direction (Figure 6). The absence of quality differences in records of nerve impulses taken from single receptors was a major reason for originally hypothesizing that odorants were somehow separated spatially and temporally.

The arrest mechanism for odorant molecules by receptors is unknown. Beets (1971) suggested that an odorant molecule is held by the receptor molecule until the former is degraded; on the other hand, Davies (1969, 1970) believed that the odorant "penetrates or punctures" the receptor cell, allowing sodium to enter and potassium to escape. The biochemical mechanism by which the nerve impulses are initiated is also unknown, but a recent finding that cyclic AMP (adenosine 3', 5'-monophosphate) is involved (Kurihara and Kayama, 1972) suggests that the mechanism is the same as that by which hormones and other circulatory solutes trigger nerve impulses. Receptor responses have been observed following intravenous injection of some odorants, suggesting also that receptor sites may not be limited to the exposed, ciliated parts of the receptor cells. However, there is evidence that these effects may be due to volatilization of the substances into the alveoli of the lungs and then exhalation through the nose.

To account for the logical inference that specificity resides in the receptor cell membrane, and also for the degrees of specificity observed subjectively, limitations on specificity have been proposed (Cain, 1969, Dravnieks and Laffort, 1972). Thus, theoretically a binding site may attract a range of different odorant molecules, an odorant molecule may bind at a range of different sites, and a receptor cell may contain many different sites and may bind more than one molecule at a time.
Electrophysiological tracings from a frog olfactory nerve: a) Examples of raw data; b) Electronically summated raw data of neural discharges recorded from the lateral (upper tracing of each pair) and medial (lower tracing) branches of the olfactory nerve of the frog. The time differences and relative sizes of the peaks are part of the evidence for the "chromatographic" theory of odor reception. (Supplied by Mozell).
3. Olfactory Nerve Responses

The transmission of olfactory nerve impulses is better understood from both the anatomy and electrophysiological recordings when they are interpreted by electronic summations (Figure 6). Such recordings may be made in animals from single neurons, nerve branches, or the olfactory bulb. Thus it is known that the bulb either summates or to some extent analyzes receptor impulses before transmitting them centrally. The chromatographic theory was inferred from electronic summations of responses recorded simultaneously in the lateral and medial branches of the primary olfactory nerve. Trigeminal nerve responses to odorants differ from olfactory responses and in some cases are more sensitive (e.g., to phenyl ethyl alcohol), but the sensations are difficult to separate subjectively (Moulton and Beidler, 1967).

Although the details of the trigeminal inputs into the olfactory bulb (Smith and Tucker, 1969) and the efferent inputs from the cortex that evidently influence transmissions by the bulb (Moulton and Beidler, 1967) have not been fully elucidated, it is clear that the bulb has selective functions and that bulbar lesions may diminish, distort or prevent the perception of odors.

4. Detection Thresholds

The presence of most odorants is detected at concentrations lower than are needed for their identification. The latter is called the recognition threshold and the former is the detection threshold.

Detection thresholds can be established in animals and man by the electro-olfactogram (EOG) (Figure 7), as revealed by Ottoson in 1956. He defined the EOG as "the monophasic negative potential evoked by odors in the sensory region of the nasal mucosa" as measured by simultaneous recordings from the mucosa under well-controlled conditions of stimulus (Ottoson, 1971). EOG responses vary in amplitude, while "unit" responses (all-or-nothing) are found in the nerves that leave the bulb (Takagi, 1969). Increases of odorant concentrations above certain levels are not detected olfactorily, although some increases may be signaled by the trigeminal nerves; these are perceived as changes in odor quality with increasing concentrations. However, the significance of EOG data in relation to the existence of true thresholds in man is controversial.
Typical human EOG (electro-olfactogram), from the olfactory epithelium. The peak response is very brief. Coffee contains at least 500 different volatile substances, all of which may contribute to the odor (Wick, 1965). Redrawn from Osterhammel et al., 1969.
In man, detection thresholds, estimated by sniffing tests, differ among people and fluctuate over time, so much so that the range of normality is usually expressed in log units of odorant concentration (Amoore, 1968). In a population, the highest normal threshold may be $10^3$ of the lowest, and the range in 95 percent can be 10-fold above and below the mean (Amoore, 1968, Berglund et al., 1971). The direction of an odor source can sometimes be detected within 7-10 degrees (Moulton and Beidler, 1967), especially if the subject is free to move his head or if the odorant stimulates the trigeminal nerves (Schneider, 1967).

5. Odor Recognition Thresholds

The inferred location of recognition mechanisms is the prepyriform cortex (Adey, 1970). Recognition is studied indirectly, by its behavioral effects, which currently are better understood than biochemical or electroencephalographic data. The involvement of memory is implicit (Engen, 1972); however, other sensory input and psychomotor responses are "unwanted variables" that cannot be excluded. Engen (1970) has proposed three forms of mental judgement: discrimination, scaling, and recognition itself. Discrimination, or perception that odors differ, appears to be described by the psychophysical power function (quantum steps) proposed by Stevens (1972). Scaling, or categorization, includes a quantitative element. To the subject, recognition is identification beyond doubt.

Tests comparing odorants are usually more reliable than tests of single odorants alone. Observations suggest that memory generally becomes confused after identification of about 16 single odorants in sequence. Furthermore, behaviorally obtained thresholds were elevated by the addition of thresholds for psychomotor responses, and complicated by "training" effects of repeated test performance. Thus observed recognition thresholds tend to vary more than do detection thresholds. Beets (1971) suggested that, all factors considered, human acuity for odor recognition may be, at its best, no less than canine acuity.

As odorant concentrations increase, there comes a point above which either increases will not be recognized or the odor quality will appear to change. These upper thresholds have been relatively little studied but could be relevant to recognition of dangers, especially when dangerous concentrations are above the upper recognition threshold.
Most odors are generated by mixtures of odorants, and most odorants are hard to obtain in chemically pure form. When this is done, the recognized odor can sometimes be attributed to some impurity or contaminant. Thus, the question of whether all pure odorants are "primary" remains unanswered, and for all of the above reasons it is difficult to utilize any current listing of "primary" odors (Table 3) (Schneider, 1967). The concept of primary odors is derived by analogy from primary tastes and colors. The analogy is in doubt owing to the differences in anatomy and physiology among these three sensory systems.

B. TASTE

1. Taste Receptor Function

All tastants are soluble (Beidler, 1954); even quinine ethylcarbonate has been demonstrated experimentally to be tastable (Faull et al., 1971). This material, originally believed tasteless and insoluble has been shown to be very slightly soluble in saliva. Vastly more fluid bathes the taste areas than the olfactory epithelium, and there is no evidence of "chromatographic" migration of tastants (Davies 1971). Larger molecules can be tasted than can be smelled and there seems to be no grounds for hypothesizing penetration of taste receptor cells. It is emphasized that, unlike olfactory receptors, taste receptor cells are not nerve cells. Support is growing for the proposal that taste receptor molecules are proteins with one or more sites that bind and react with tastant molecules so as to generate nerve impulses (Beidler, 1954, 1971).

Stereochemistry is a guide to taste with some but not all tastants. Sugars and some amino acids can be ranked for sweetness (Tables 4 and 5), and the "glucophore" appears to be some functional group of atoms within the molecule (Kier, 1972).

2. The Primary Tastes

Most workers provisionally accept the theory, formulated by Fick in 1864 (Andersen, 1970), of 4 species of receptors corresponding to 4 "primary" sensations: sweet, bitter, salty, and sour (Figure 8). In 1817, Park had proposed "warm" and "cool" as primary taste sensations; however, these additions are not universally accepted although these 2 sensations are compatible with the 4 primary sensations (Dzendolet, 1969, Sato et al., 1969). The 4 primary sensations are interrelated
TABLE 4

RELATIVE SWEETNESS OF VARIOUS SUGARS IN SOLUTION*

<table>
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<tr>
<th>Sugar</th>
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<tr>
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<td>β-D-Maltose</td>
<td>32-46</td>
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<tr>
<td>β-D-Galactose</td>
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<td>α-D-Lactose</td>
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<td>Raffinose</td>
<td>23</td>
</tr>
<tr>
<td>Stachyose</td>
<td>**</td>
</tr>
<tr>
<td>β-D-Mannose</td>
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</table>

*Compared with arbitrary value of 100 for sucrose.
**Value undetermined.

Table adapted from Shallenberger and Acree (1971).
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Modified from Amoore (1969), who has reduced the 118 proposed odor classifications to 44 "primary" odor descriptions. See Amoore (1969) for a more complete discussion and the original references.
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<td>Valine</td>
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*Data from Shallenberger and Acree (1971), who note that according to Mazur et al. (1969) the dipeptide, or joined pair of amino acids, L-aspartyl-L-phenylalanine methylester is 100-200 times sweeter than sucrose although singly, both amino acids taste bitter.*
Two proposed relationships between the primary tastes in man. Left: the 4-taste system proposed by Henning in 1916, cited by Pfaffmann et al. (1971). Right: the 6-taste system proposed by von Békésy in 1964, cited by Sato (1971), who found nerve responses to all 6 "tastes" in hamsters but somewhat different relationships between them, interpreted as interspecies differences.
(Figure 8), either at the receptor level or, more likely, at a cognitive level in the brain (Frank and Pfaffmann, 1969, Pfaffmann et al., 1971). The opposed pairs, sweet-bitter, salty-sour, warm-cool, were inferred from after-tastes that could not be attributed to breakdown products in the mouth (Pfaffmann et al., 1971). Most workers accept the 4-taste classification as convenient and recognize that the underlying biological systems are more complex.

This theory is supported by some electrophysiological data, but supporting stereochemical data are at best equivocal. Some amino acids taste sweet, but others do not; and not all acids taste sour. Very weak sodium chloride solutions taste sweet. There are electrophysiological indications that some taste buds contain more than one species of receptor, while others do not. Perhaps such tastants are bound at more than one type of site. Some shifts of taste quality indicate merely that a tastant is a mixture. The "taste" of electrical current has been debated since 1754; whether it reflects nerve stimulation, electrolysis of saliva components, or both, is still undecided (Bujas, 1971).

3. Taste Nerve Responses

Chemical mediators are probably involved in the generation of responses, as in other sensory modalities (Kurihara and Kayama, 1972). Responses are monitored electrophysiologically in animals, from single fibers or nerve trunks, and thus detection thresholds are estimated (Doetsch et al., 1969).

Unlike the olfactory system and its paired organ, the olfactory bulb, the innervation of taste appears to have few peripheral neural ganglia for sensory analysis. The taste bud does not seem comparable with the olfactory glomerulus; this suggests two problems for future study. The first is whether the primary taste sensations result from local dominance patterns in the transmission of taste information by the many nerve fibers, rather than from receptor cell differences. The second concerns the possible evolution of taste sense by a localized development of chemoreceptivity in epithelial cells associated with tactile nerve endings. Compared with olfaction, the perception of taste obviously is more restricted by the receptors' microenvironment, cell type, cell turnover, and the need to transfer responses to an associated nerve instead of transmitting them directly.
Human subjective judgments of "pleasant" or "unpleasant" sensations in response to increasing concentrations of cane sugar ("sweet"), tartaric acid ("sour"), sodium chloride ("salty"), and quinine sulfate ("bitter"). The maximum concentrations were: sugar 40%, acid 1.12%, NaCl 10%, quinine 0.004% (weight/volume). The minima were all zero. "Pleasant" and "unpleasant" are separated by a neutral zone. Redrawn from Pfaffmann et al. (1971), who reproduced the figure from Engel.
4. Taste Detection and Recognition Thresholds

Detection thresholds are measured electrophysiologically in animals and there is limited work on their subjective assessment in man. Thresholds in man involve some degree of identification, first in terms of the primary taste, and with increasing intensity, in terms of recognition of the tastant, involving memory and usually other factors as well. It seems likely that chemically pure tastants that stimulate only taste receptors can evoke only recognition of primary tastes (Figure 8). Tactile input, indicating texture, accompanies taste input, but is not integrated peripherally as is trigeminal input.

Recognition is enhanced by practice, and the amount of practice is largely determined by the hedonic effects of tastants (Figure 9). For example, people tend to repeat "pleasant experiences." The mechanism of hedonic effects is important but obscure (Pfaffmann et al., 1971). Enhanced sucrose preference is inducible, and is evident in a vast majority of the U.S. population. The role of taste mechanisms in sugar-seeking appears limited to detection and recognition; thus, sugar preference may have its basis in physiological mechanisms other than taste per se (Gentile, 1969, Nachman and Cole, 1971). Contrary opinions have been expressed (Bartoshuk et al., 1971). This is an area in which basic research is urgently needed.
V. FACTORS INFLUENCING THE CHEMICAL SENSES

A. OLFACTION

The variability of sensory responses to olfactory stimuli reflects a large number of independently varying factors, such as stimulus, receptor, and subjective factors. On the other hand, this variability may have been exaggerated by tests designed for basic research rather than for screening, because observation of the different stages of a response requires the elimination of stabilizing factors normally present, e.g., efferent impulses from the brain to the olfactory bulb.

Olfaction can be altered in various ways, including anosmia (absence), hyposmia (decrease), hyperosmia (enhancement), parosmia (distortion), dysosmia (unpleasant distortion), and phantosmia (hallucination.) Such states may be transient or permanent, and may arise within the subject or be related to his environment.

1. Stimulus Factors

Seldom if ever is the air so pure that only one odorant is present. Odorant concentrations vary, and different odorants have different potencies. An odor may be masked by others present either at the same time or shortly beforehand. If a stimulus is too brief, the odorant is not recognized; if too prolonged, adaptation occurs. The time and intensity factors in recognition of repeated or inconstant stimuli are complex and poorly understood. Odorants, or concentrations of an odorant, that stimulate the trigeminal nerves, add further complications. Similarity between odors may hinder identification, especially when odorants are presented singly or under conditions precluding comparison.

Some odorants and odorless gases may actively distort the perception of others, an effect that is better known in taste and requires study in olfaction. A face mask may affect inhaled air by adding or removing odorants. Intense input from other senses can mask olfactory input (Stone and Pangborn, 1968). Sensory responses are affected by the temperature, pressure, and humidity of the inhaled air, and by its flow rate and turbulence; these factors are partly under the subject's control.
2. Receptor Factors

Other determinants include the condition of the olfactory epithelium, and the amount and pH of the mucus. Factors such as blood endocrine levels and the degree of vasodilation may affect receptor sensitivity. The functional activity of the nasal mucous membranes has an important influence on acuity. Best acuity is seen when the membrane is moderately active (moderately swollen and red), poor acuity is associated with low membrane activity (shrunken and pale) and acuity is lost when the membrane is in a hyperfunctioning state (marked swelling, redness, and wetness) (Schneider and Wolf, 1960).

3. Subjective Factors

A normal, healthy person may associate an odor with particular visual, auditory or tactile sensations, absence of which will modify his detection or recognition threshold for that odor. The presence of other sensations may induce phantosmia, the hallucination that an odor is also present. Other sensations can also distract a person from recognizing an actual odor (Stone and Pangborn, 1968). On the other hand, odor may confirm or deny suspicions raised by other sensory input, or may raise suspicions for other sensory input to confirm or dismiss. Engen (1972) has emphasized that expectation strongly influences judgments of odors.

Odor discrimination can be taught; thus acuity can be enhanced by practice, and self-training can be directed by appetitive or aversive effects of odorants. However, these effects are not uniformly predictable and their mechanisms are obscure. Children are very tolerant of smells (Engen and Moskowitz, 1972), and thus aversive effects may be unique to adult humans. Examples of such aversive odors are onions, smoke and mercaptan. The food and perfume industries capitalize on supposed hedonic effects of odors. Human pheromones (sex attractants) are thought to exist, probably in the apocrine system, though none have yet been identified (Comfort, 1971).

A number of physiological variables influence olfactory acuity. Olfactory response is thought to vary with age and may vary by sex according to some workers (Moulton and Beidler, 1967, Venstrom and Amoore, 1968). Schneider (1967) has reported that females are generally more sensitive, and are most sensitive when ovulating. This has been attributed to cyclical effects of certain hormones, including
an androgen, 5-α-androst-16-en-3-one (Comfort, 1971) and estrogens (Moulton and Beidler, 1967). Circadian fluctuations of acuity can be ten-fold (Stone and Pryor, 1967). Acuity is influenced by exercise (Stone et al., 1967), but may not be affected by smoking (Venstrom and Amoore, 1968) nor by alcohol consumed in moderation. Woods (1968) holds that smoking, alcohol, and diet markedly affect olfactory acuity.

Variations of acuity in naive subjects during preliminary tests should be expected, but the processes of long-term and short-term adaptation differ, and the variations are large. All persons adapt to the constant presence of an odorant (Moncrieff, 1968). Schneider and Costiloe (1969) have shown that the same subject whose pattern of adaptation is determined in the laboratory at intervals, may vary from rapid adaptation to no adaptation, and most often the latter occurs in a setting of psychosocial stress. Food deprivation may be one such stress, but reports that people are more sensitive when hungry are not unanimous (Moulton and Beidler, 1967). Henkin et al. (1972) have reported that olfactory acuity is diminished when tissues are depleted of zinc, copper, or vitamin A. The steroid hormones secreted by the gonads and adrenal cortex are influential. Women who are estrogen deficient have relatively low olfactory acuity which increases when they are given estrogens and decreases when they are given androgens (Schneider et al., 1958). Hyperosmia is associated with Addison's disease (adrenocortical insufficiency) and with cystic fibrosis of the pancreas, and hyposmia with gonadal dysgenesis in females. Many stresses that alter the output of these hormones are believed to affect olfactory acuity directly.

Connective tissue disorders, e.g., Sjogren's syndrome (associated often with rheumatoid arthritis), diminish olfactory acuity (Henkin et al., 1972), as do atrophic rhinitis, and any injuries in the 1st, 5th, 9th, or 10th cranial nerves, such as may result from trauma or surgery to the head (Henkin et al., 1968). Several causes of secondary anosmia or hyposmia have been briefly reviewed by Schneider (1972). Males et al., (1972) have noted evidence for a relationship between olfactory performance and pituitary function. When sensitivity to particular odorants is lost, the symptom may be parosmia (Amoore, 1969, 1971), which is usually noticed when it affects a subject's scale of hedonic values.

General anosmias of various origins are estimated to occur in about 0.2 percent of the U.S. population, and it is believed that they are seldom reported (Amoore, 1968). The view that all albinos are
anosmic has been proved false (Moulton and Beidler, 1967). Anosmias to specific substances (Table 6) are thought to arise by mutations of specific receptor proteins; however, very few such anosmias have been studied in detail. Anosmias or hyposmias for the musky odor typical of urine or sweat are relatively common (Amoore, 1969, Brown et al., 1968).

B. TASTE

1. Stimulus Factors

Temperature influences the potency of tastants, which tends to be greatest at 30-35°C (Pfaffmann et al., 1971). Refrigeration of foods diminishes the potency of most tastants. Dentures that cover the hard palate diminish the acuities for sour and bitter tastes (Henkin and Christiansen, 1967).

A number of substances distort the tastes of other substances, because they do not affect all the receptor types equally. For instance, anesthetics applied to the tongue block taste sensations in the order: bitter > salty > sour > sweet (Kare and Henkin, 1969). Some antibiotics reportedly cause dysgeusia (Henkin, 1970a). Two vegetable extracts have recently attracted attention: "miracle-fruit" and gymnemic acid.

Miracle-fruit (Synsepalum dulcificum) contains a basic glycoprotein of about 44,000 M with L-arabinose and D-xylose. When applied to the mouth, it may cause acids to taste sweet for over three hours without altering thresholds for sour, salty or bitter tastes. It is hypothesized that the glycoprotein binds to the epithelium near the sweet receptors so that acids act on these as well as on their "own" receptors (Kurihara, 1971).

The leaves of Gymnema sylvestre contain gymnemic acids of which one, known as A_1, contains a molecule each of gymnemagenin and glucuronic acid. When gymnemic acid A_1 is applied to the tongue it suppresses sweet taste for up to 30 minutes. Other taste judgments are also modified (Meiselman and Halpern, 1970). The nerve responses are blocked, which could mean merely that the receptors are blocked. However, there are additional biological effects, so that the mechanism of action must be described as unknown at present (Kurihara et al., 1969, Kurihara, 1971).

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### TABLE 6

**REPUTED SPECIFIC ANOSMIAS**

<table>
<thead>
<tr>
<th>Acetic acid</th>
<th>Hibiscolide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamantane</td>
<td>Hydrogen cyanide</td>
</tr>
<tr>
<td>Allicin</td>
<td>Indole</td>
</tr>
<tr>
<td>Allyl isothiocyanate</td>
<td>Idoform</td>
</tr>
<tr>
<td>Δ⁴,Δ⁶-Androstadien-3-one</td>
<td>Ionone</td>
</tr>
<tr>
<td>Δ¹⁶-Androsten-3-ol</td>
<td>Isobutyraldehyde</td>
</tr>
<tr>
<td>Anisic aldehyde</td>
<td>Isobutyric acid</td>
</tr>
<tr>
<td>Anisole</td>
<td>Isovaleric acid</td>
</tr>
<tr>
<td>Benzene</td>
<td>Menthol</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>d,l-Menthone</td>
</tr>
<tr>
<td>Benzyl salicylate</td>
<td>Methional</td>
</tr>
<tr>
<td>t-Butyl carbomol</td>
<td>Methyl cyclopropyl ketone</td>
</tr>
<tr>
<td>n-Butyl mercaptan</td>
<td>Methyl mercaptan</td>
</tr>
<tr>
<td>t-Butyl mercaptan</td>
<td>Musk xylol</td>
</tr>
<tr>
<td>Caproic acid</td>
<td>Naphthalene</td>
</tr>
<tr>
<td>Cedryl acetate</td>
<td>PEME carbinol</td>
</tr>
<tr>
<td>l,8-Cineole</td>
<td>Pentadecanolactone</td>
</tr>
<tr>
<td>Cinnamaldehyde</td>
<td>Phenylacetic acid</td>
</tr>
<tr>
<td>Cyclotene</td>
<td>Phenylethyl alcohol</td>
</tr>
<tr>
<td>p-Dichlorobenzene</td>
<td>Phenyl isocyanide</td>
</tr>
<tr>
<td>Dimethyl disulfide</td>
<td>Phenyl isothiocyanate</td>
</tr>
<tr>
<td>Ethylene brassylate</td>
<td>1-Propenylsulfenic acid</td>
</tr>
<tr>
<td>Ethylenedichloride</td>
<td>Putrescine</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Salicylaldehyde</td>
</tr>
<tr>
<td>Farnesol</td>
<td>Skatole</td>
</tr>
<tr>
<td>Formic acid</td>
<td>Thiophane</td>
</tr>
<tr>
<td>Geranial</td>
<td>Thymol</td>
</tr>
<tr>
<td>Geraniol</td>
<td>Trichloroethylene</td>
</tr>
<tr>
<td>2-Heptanone</td>
<td>γ-Undecalactone</td>
</tr>
<tr>
<td>Δ⁹-Hexadecenolactone</td>
<td>Vanillin</td>
</tr>
<tr>
<td>Hexylamine</td>
<td>Versalide</td>
</tr>
</tbody>
</table>

Substances to which some people are reputedly anosmic as listed by Amoore, 1969.
Other vegetable extracts, e.g., from *Discophyllum cumminsii* and *Thaumatococcus danielli*, have been found to contain proteins that taste very sweet but do not actively distort the reception of other tastes (Morris and Cagan, 1972).

General enhancement of taste acuity is claimed for substances such as monosodium glutamate, the 5'-nucleotides, and maltol (Kermode, 1972). Their mechanisms of action are obscure.

2. **Subjective Factors**

Carbohydrate-active adrenal corticosteroid hormones inhibit taste acuity; when more of them are secreted, acuity diminishes, and *vice versa*. Thus, a progressive taste loss may signify an adrenocortical tumor, or a progressive gain may signify a case of Addison's disease (Henkin, 1970b). By contrast, estrogens promote taste acuity. Stresses that affect secretion of these hormones will influence taste acuity accordingly. It has been noted that acuity increased with rising levels of plasma ascorbic acid, which were influenced by corticosteroid secretion and, in females, by the estrous cycle. Furthermore, the capacity of taste receptors to initiate nerve impulses appears to be governed by blood pressure (Hellekant, 1970).

Dependence of taste acuity on adequate tissue levels of zinc and copper was reported after examination and manipulation of these levels in patients presenting with ageusia (Henkin and Bradley, 1969). However, other workers have found few abnormalities of taste acuity in patients presenting with zinc deficiency. Further studies are needed in which the selection of subjects will be a controlled variable.

Taste thresholds are thought to be influenced by hunger and satiety, but the mechanisms are obscure; nevertheless, taste recognition can directly stimulate processes of digestion (Kare, 1969). Both detection and recognition of tastes are influenced by other sensory input. For instance, the sight and smell of a meal elicits salivation as well as changes in insulin levels not related to modifications in the level of blood glucose (Engen, 1972, Goic et al., 1969).

On the other hand, other sensory input may have masking or distracting effects that diminish taste acuity (Stone and Pangborn, 1968). Many observations are difficult to interpret, because behavioral responses of animals differ between species and tend not to correspond either with electrophysiological responses or with human subjective
judgments of taste. Nevertheless, taste preferences are thought to result from diet selection in man and animals, and to reinforce that selection rather than to determine it in the first place.

A recent preliminary report (Lum et al., 1971) suggests that taste acuities may vary slightly with age and between the sexes, and do vary consistently with the amino acid composition and pH of the saliva. Inherited ageusias have been little studied except for insensitivity to bitter compounds with an \textit{N-C=S} group, such as phenylthiocarbamide (PTC). The incidence of this is correlated with that of goiter (Sunderland and Cartwright, 1968); nevertheless, a Mendelian genetic pattern is accepted (Fischer and Griffin, 1964, Henkin, 1970b, Kalmus, 1971).

Traumatic head injuries, in which some of the taste nerves lose their function, can result in distortions of taste sensations (parageusia, dysgeusia) (Henkin et al., 1971, 1972).
VI. TECHNIQUES FOR STUDIES IN MAN

Both olfaction and taste are tested by methods developed for basic research into the mechanisms of those senses (Engen, 1971). Electro-physiological observations describe stimuli transmitted by the nerves to which electrodes are applied but do not indicate perception of those stimuli by the conscious brain. Perception is estimated subjectively by volunteers. An indirect measure of perception, behavior, includes responses to the sense tested and to other sensory input, as well as variables and thresholds pertaining to the mechanisms of the behavioral response. A subject responds differently before and after he has learned the study techniques (Cain and Engen, 1969).

However, this LSRO study is concerned only with techniques available for practical evaluation of human olfactory and taste acuities by screening populations who are not volunteers, not with tests that are used only in basic research. Methods that can be used for setting and maintaining standards and for interpretation of results of screening tests are of prime importance.

A. OLFACtion

1. Standards and Criteria

Perhaps the most important difficulty has been simultaneous standardization of both background and test stimuli, because it is the difference between these that must be detected and recognized. Odorant-free air probably cannot be achieved or maintained; however, the composition of air can be monitored by analysis.

Methods available for analyzing air for odorants include gas chromatography (GC), mass spectrometry (MS), and plasma chromatography (PC). Each method gives its own pattern of results, that is, it senses some odorants and some odorless gases, fails to sense others, and senses some more acutely than others. Some workers use combinations of these methods, and the relative merits appear to depend on the situation and purposes of the analyses. Many odors are complex; e.g., Wick (1965) showed that coffee contained over 500 volatiles,
and Young et al. (1970) demonstrated the analytical problems by synthesizing a "bourbon" with a gas-liquid chromatogram similar to that of real bourbon but with dissimilar odor and taste.

Analysis of air samples for dilute vapors can sometimes be facilitated by preconcentration methods (Dravnieks et al., 1971). The GC-MS combination is sensitive for detection of traces of contaminants in larger samples of gaseous, liquid, or solid materials. Such techniques would have contributed greatly to a recent study on the social and economic impact of odors in the community (Copley Corp., 1971), where not a single air sample was analyzed. However, the preparation of air samples for analysis by GC or MS may be a problem outside the well-equipped laboratory. Here the PC method has the advantage that air samples do not require preparation.

The PC method is relatively new, and its instrumentation (Franklin GNO Corp., 1972) is still under development. Recent research at the National Bureau of Standards suggests that air from different sources may be simultaneously and continuously monitored by one instrument, and this could be useful for screening situations in the military environment. The degrees of analytical specificity and sensitivity (Cram and Chesler, 1973) seem comparable with those obtainable by GC or MS, and combinations of PC with these methods are currently being explored.

Evaluation of human olfactory acuities by these methods will require the assembly of many standards: identity, quality and intensity of test odors; controlled test conditions; information about subjects; and interpretation of results. Knowledge from basic research will need to be reassessed before application to evaluation of human olfactory acuities (Engen, 1971).

2. Choice of Odors

In selecting odorants for tests, preference should be given to those that are chemically pure and with known olfactory effects (Table 2). When study goals require the use of less well-defined odorants, the limits of the information to be obtained should be recognized. A balance will be struck between the number of odorants and the number of concentrations used. At the present time, approximately 20-30 subjects can be screened per day by double-blind techniques.
3. Threshold Determinations

The utility of threshold studies is highly controversial. One common definition of "threshold" is the lowest concentration detected in 50 percent of responses. There are always many false positive and negative responses; the same applies to recognition thresholds, and to upper thresholds above which concentration increases are not recognized. It may be that studies on lower thresholds are more useful in a training situation than for simple evaluations.

4. Testing of Humans

Techniques rely primarily on subjective responses to odorants delivered to the nasal passages under relatively standard conditions of temperature, pressure, flow rate, and humidity of the air carrying the odorant (Schneider et al., 1963, Amoore, 1968). Though it is difficult to standardize the airflow over the olfactory epithelium, this is desirable for determining differences in olfactory acuity of the two sides of the nose (Schneider and Schmidt, 1966, Schneider, 1972). In practice, subjects tend to determine for themselves the airflow rate that gives them the greatest response. To minimize self-adaptation, some investigators use intervals between successive stimuli of at least 7 seconds, while others find 5 to 10 minutes necessary.

The importance of routinely examining subjects for gross unilateral or bilateral intranasal conditions, such as atrophic rhinitis, or polyps, has been emphasized (Schneider, 1972). Furthermore, it is obvious that valid test results will not be obtained during or immediately after respiratory tract infections, especially influenza.

Behavioral responses and subjective judgments contain extraneous variables that often detract from the validity of olfactory test results (Mozell, 1969). Much of the early work was conducted without emphasis on standardized test conditions. Standardized psychophysical testing techniques are being developed that are said to interfere minimally with the assessment of odor detection and recognition (Cain and Engen, 1969). These include statistical procedures such as factor analysis and "frequency component hypothesis" (Hughes et al., 1969), that may be expected to assist in evaluating the responses of screened subjects who are not research volunteers.
B. TASTE

Acuity in the primary tastes is tested with standard substances: sucrose (sweet), quinine (bitter), sodium chloride (salty), dilute hydrochloric acid (sour) (Sato et al., 1969). Temperature of the tastant is important (Stone et al., 1965). To test the detection and recognition thresholds, prepared solutions are applied to the tongue or are held in the mouth for a set time and then swallowed or ejected (McBurney, 1969). Tongue application avoids unevenness of dilution in saliva, but also neglects the taste areas of the hard palate and pharynx. The perceived intensity of taste is compared with the concentration of tastant. However, perception includes many subjective variables (Powers et al., 1971) and some workers prefer not to use primary taste judgments to evaluate human acuities.

Foods seldom if ever contain only single tastants and their analysis by taste seldom corresponds with instrumental or chemical analysis (Powers, 1970, 1972). Consistent with the relatively minor role of taste in diet selection, panelists in the food industry who judge the potential acceptability of foods before marketing are not screened for acuity in the primary tastes (Hirsh, 1973). Food processing techniques have diminished the usefulness of taste as an indicator of spoilage or contamination, but awareness may still be valuable; often there is an intensity change in only one of the primary sensations. For sensory evaluation of taste acuities, behavioral controls can minimize many errors in volunteer research subjects, and may be effective in the comprehensive screening of nonvolunteers. Such studies are needed; little is known about standardization of screening methodologies for taste acuity.

Electrophysiological studies of taste acuity in man are seldom practical, although in a few cases the results have corresponded well with subjective test data (Zotterman, 1971). The methods tend to interfere with responses, and the results need complex statistical treatment in order to be interpreted (Beets, 1971).
VII. SIGNIFICANT ASPECTS OF HUMAN OLFACITION AND TASTE IN THE MILITARY ENVIRONMENT

A. OLFACITION

The need for acuity in perception of odors is evident from the emphasis that the military has placed on developing sensory devices and biosensors. Yet, the greater part of this need can probably be fulfilled more adequately, reliably, and economically by man. In a recent report to the U.S. Air Force, Gestetland (1972) stated:

"No broad-spectrum detection and identification system for air born chemical substances exists which begins to approach the performance of the vertebrate nose with respect to discriminability, sensitivity, dynamic range and variability of substances detectable."

Instruments do give objective information. However, they require operators and servicing personnel. They have poor directional sensitivity and the ranges of their responses are different from those of man. In addition, there are relatively few substances for which instrumental response spectra have been determined.

Therefore, while instruments and biosensors, such as dogs, will continue to have specialized roles in detection of explosives, illicit drugs, and intruders, and while instruments should become useful in standardization of personnel tests and testing situations, these roles do not substitute for human olfactory performance.

Olfactory acuity seems potentially important in soldiers selected for certain duties, e.g., point duty on patrol. This criterion for selection is seldom used and it seems to be generally unrecognized. Olfactory training is known to enhance aspects of performance and survival of military personnel (Woods, 1968). Enemy weapons, personnel, bivouacs, propellants, arson and chemical agents are examples of odor sources that personnel can be trained to recognize. This training could provide a "vocabulary" of odors and a repertoire of behavioral responses.
It should be noted that man has the ability to mask out many unacceptable odors, particularly those unfamiliar to him and encountered for the first time in foreign lands. Unfortunately, these are the very odors that he should be trained to recognize as they are often peculiar to the enemy. Failure of timely recognition may result in needless casualties.

Though machine-operation odors may mask odors from other sources, machine dysfunctions often give off other odors that can be recognized by the operator before breakdown occurs, e.g., an electrical short circuit or overheating of a power unit. Because sight, hearing, and touch often are fully employed in the operation of military machines, it has been suggested that specific olfactory cues (e.g., amyl acetate) might be built into some machines to give early warning of certain critical dysfunctions.

Personnel who are untrained in the use of their olfactory capabilities will tend to give olfactory information to the enemy and to be unaware that the enemy is using it. Anecdotal information suggests that indigenous military forces may be able to map the deployment of troops by the odors of their personal deodorants and insect repellants. Odors emanating from a work area or a specific military operation may give critical intelligence to a trained enemy agent. The element of surprise in military field operations can be squandered through lack of utilization of the olfactory sense.

Tactical uses of odorants have not been explored to any great extent. Odors typical of certain military preparations might be used to deceive enemy intelligence. An enemy who is trained or experienced might do likewise, and untrained personnel would have little immediate defense.

An improved knowledge of the effects of odors on behavior could be useful to the military. For instance, appetitive or aversive effects of odors on the responses of soldiers to food in mess-halls should be recognized. Specific odor signals could be used judiciously to alert personnel to the presence of hazards, e.g., damage to packaged foods. Personnel with defective olfactory acuity could be allocated to jobs in unavoidably malodorous environments. If personnel were regularly screened for olfactory acuity, options such as these would be available.
Sudden or progressive alterations of olfactory acuity (gains, losses or distortions) can signify hidden trauma or early cases of certain diseases. Examples include the endocrine disorders, anterior fossa tumors, head trauma, the phantosmia of incipient schizophrenia, and exposure to high-intensity X-rays or ionizing radiation. Olfactory testing could result in early referral of such cases for specific medical diagnosis and thus permit early treatment. In contrast, the present practice is to refer a soldier complaining of olfactory or taste loss to either a neurologist or a psychiatrist without ever verifying the original complaint.

A permanent loss of olfaction is rated as a 10% disability for compensation purposes (Veterans Administration, 1964). Claims of this type are being prepared in increasing numbers, especially by personnel who may have had service-connected head trauma. Ideally, claims for service-related olfactory losses should be based on the degree of olfactory competence established at the time of induction.

B. TASTE

Taste is an important guide to recognition of spoiled foods. The use of sauces is thought to have originated in order to mask food spoilage. Kermode (1972) has noted that numerous substances are added to foods to diminish the rate of spoilage and suggested that additives may also diminish the role of taste in recognizing food spoilage. Military personnel abroad have problems of discrimination with unfamiliar foods, in which spoilage may be present. Spoiled foods often result in gastrointestinal casualties which could be minimized by appropriate training in taste recognition and by screening to identify ageusic and hypogeusic individuals.

Taste enhancers, aversants, or distorters might be introduced into an enemy's food supply to induce, respectively, inordinate appetite, rejection, or suspicion. The purpose would be to disrupt the planned use of rations. However, the technical problems may be formidable. Because an enemy might adopt this approach, training of personnel in detection and recognition of tastes may be a desirable protective measure.

Service-related loss of taste is rated like loss of olfaction, as a 10% disability (Veterans Administration, 1964). Claims that such losses are service-related are being prepared in increasing numbers and will be difficult to evaluate in personnel who were not previously tested.
The current techniques of sensory evaluation in olfaction and taste, other than for basic research on their mechanisms, were developed about 35 years ago, and there have been few recent advances (Hirsh, 1973). The methods of personnel training that have evolved from basic research are non-uniform. Industrial corporations with products identified by aroma and taste have of necessity developed techniques of testing and training. Because much of this information is empirical, it is not readily available in the published literature. However, this body of knowledge and experience is applicable to the Army's needs.

In a pilot program for personnel evaluation and training, the following appear to be the initial steps and priorities.

A. OLFACTION

1. Requirements

   A preliminary list of odors that ought to be recognized by trained personnel would be compiled, together with the estimated concentrations at which recognition should become easy. Critical concentrations above which increases should be recognized, will be important in some cases. Situations requiring normal olfactory acuity, e.g., tasks involving "fieldcraft" or machine operation, should be surveyed and subcategorized according to (a) whether or not parallel input would be available from other senses such as vision and audition, and (b) whether recognition of the odors would contribute to assessment of a situation or would demand a specific behavioral response, e.g., to take cover. At this stage feasibility in terms of human olfactory acuity would not be considered.

2. Standards and Criteria

   The next step would be to estimate the extent to which these requirements could be met by both instruments and trained human subjects. These estimates would set provisional standards and
criteria for a pilot program to evaluate and train personnel in odor recognition and discrimination. At this stage the effects of different diets, stresses, and fatigue on odor recognition in the military environment could be assessed.

3. Evaluation of Personnel

Personnel would be screened according to these standards and methods, both before and after training. Primarily screening data would be used to assist in future selection of personnel for specific military duties. In addition these data would be useful: (a) as part of the recruiting process, to assist in detecting disease conditions that might disqualify a recruit, (b) as a component of a soldier's continuing medical record, and (c) for reference in case of a future claim for service-related loss of olfaction. During the pilot program, screening data could be used to evaluate the feasibility of the provisional standards and criteria, and to evaluate the design and the execution of the training program.

B. TASTE

Initially personnel could be screened for acuity in the four accepted primary tastes and for discrimination between compound tastes. As with suggested olfactory studies, screening and training methodologies developed for industrial use might be adopted or adapted to meet Army needs. Screening would be carried out before and after training, and the uses of the screening data would be analogous.
IX. SUGGESTIONS FOR FUTURE EMPHASIS

The following suggestions for future emphasis have been developed during the course of this study. The order of presentation does not imply an order of priority.

1. The olfactory and taste acuities of Army personnel should be assessed and aspects of the military environment in which these acuities are significant should be catalogued. Although techniques for these purposes have been inadequate in the past, this no longer seems to be the case (See Section VI & VII).

2. The usefulness of the chemical senses can be developed in regular personnel training programs. The olfactory component of this training could include recognition of the presence of personnel, recognition by operations and maintenance personnel of various aspects of machine operation and malfunction, and training of combat personnel in detection and security related to field missions (See Section VIII).

3. Self-protection of personnel against environmental hazards from volatile substances can be improved by training in olfactory detection and discrimination. Similarly, hazards from eating unfamiliar or spoiled foods can be minimized by training in taste detection and discrimination. In addition, specific odor producing substances might be used in packaging or in foods to provide olfactory or taste clues to food spoilage (See Section VI & VII).

4. The standards and criteria used for evaluating human sensory performance in civilian environments may not always be appropriate to military situations. Thus the Army will need to determine its own general and special requirements in terms of odors and tastes, their critical
concentrations, and significant thresholds for recognition by personnel. These determinations and the preparation of the standards and criteria could be conducted by the Army utilizing existing research personnel and facilities. (See Section VI).

5. A number of resources are available for the determination of standards and criteria that the Army will need. These include Army laboratories and other government agencies in which instruments or biosensors are being developed to detect military explosives or personnel. For example, the National Bureau of Standards is studying plasma chromatography instrumentation for the chemical analysis of air. Plasma chromatography avoids the need for sample preparation that is inherent in other analyses and has potential for multiple sampling that should be useful for simultaneous monitoring of background and stimulus during Army personnel testing programs (See Section VI, A).

6. In developing techniques for training and evaluation of personnel in the use of their chemical senses, the potential contributions of industrial laboratories should be explored. Industries whose products are identified by aroma and taste have, of necessity, developed evaluation techniques that appear to be directly relevant to many of the Army's needs. Relatively little of this information has been reported compared to the quantity of literature published on basic research (See Section VI, B).

7. There is a need to explore the effects of odors on behavior and the modification of human behavior in the military environment. The Army has an opportunity to investigate and utilize the behavioral consequences of individual variability in detection, discrimination, and responses to odorants and tastants (See Section IV & V).

8. There is a need to explore alterations of sensory performance in personnel exposed to X-rays or
ionizing radiation. Alterations of olfactory and taste sensations may be useful early signs of exposure or of inadequate radiation protection. Human patients undergoing radiation therapy or X-ray diagnosis would be suitable subjects for such observations (See Section IV & VII).

9. There is a need to study the effects of drugs of abuse and therapeutic drugs on the chemical senses. This may be of particular concern to the Army if drug use compromises a man's olfactory or taste acuity and subsequently his performance.

10. The relationships of hyposmias and hypogeusias to nutritional deficiencies of zinc and other trace elements are controversial. Because zinc deficiency might be found in nutritionally deficient inductees and may follow regular heavy consumption of alcohol, these uncertainties should be resolved (See Section V).

11. Because service-related losses of the senses of olfaction and taste are rated as disabilities, testing procedures are required to check the validity of complaints. Evaluation of olfactory and taste acuities at induction would assist in documentation of subsequent claims for service-related losses (See Section VII).

12. While instruments and biosensors have specialized roles in odor detection, these do not substitute for human olfactory capabilities. At present, detection devices and biosensor programs are being developed without reference to the performance potentialities of the man. Increased emphasis on the use of the human olfactory system is required (See Section VII & VIII).

13. When the soldier knows that his full performance capabilities are recognized and used, morale tends to be high. On the other hand, when a soldier's personal capabilities are not fully used, he has less pride in himself. Substitution of detection devices and
biosensors for the chemical senses of man underestimates his capabilities. A program to develop the full capabilities of soldiers to exercise their senses of olfaction and taste in the military environment would tend to enhance their morale and potentially, their performance.

14. This study suggests that there is a need to designate some office or laboratory within the Army research and development community as a center for collation of projects involving the chemical senses and odor-sensing devices.
X. BIBLIOGRAPHY


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XI.GLOSSARY

Ageusia.......................... Lack of a sense of taste, for all
tastants ("general") or for particular
tastants ("specific").

Anosmia ......................... Lack of a sense of smell, for all
odorants ("general") or for particular
odorants ("specific").

Cilia .............................. Hair-like projections of some cells.

Biosensor ........................ An animal trained to signal its re-
sponses to sensory stimuli, e.g.,
a dog trained to communicate to
man the recognition of certain odors.

Dysgeusia......................... Unpleasantly distorted taste sense;
some workers prefer the term "cacogeusia."

Dysosmia ....................... Unpleasantly distorted sense of
smell; some workers prefer the
term "cacosmia."

Glomerulus ...................... A cluster of small structures, tubules
or, in the present context, the nerve
fibers in the olfactory glomerulus.

Hypergeusia ..................... Overly sensitive taste sense; can be
general or specific.

Hyperosmia ...................... Overly sensitive sense of smell;
can be general or specific.

Hypogeusia ...................... Abnormally diminished sense of
taste, general or specific.

Hyposmia ....................... Abnormally diminished sense of
smell, general or specific.
Odorant . . . . . . . . . . Substance perceived by olfaction.

Olfaction . . . . . . . . . . The sense of smell.

Olfactory bulb . . . . . . . A nerve center intermediate between the receptors for olfaction in the nose, and the brain itself.

Parosmia . . . . . . . . . . Altered sense of smell, without implying pleasant or unpleasant. See dysosmia.

Parageusia . . . . . . . . . Altered sense of taste, without implying pleasant or unpleasant. See dysgeusia.

Phantosmia . . . . . . . . . Hallucination that an odor is present when in fact it is not. Phantogeusia means the same for taste.

Tastant . . . . . . . . . . . Substance perceived by taste.
XII. SCIENTIFIC CONSULTANTS

ON

A STUDY OF THE POTENTIAL APPLICATIONS OF OLFACTORY RESEARCH IN MAN

A. ATTENDEES, AD HOC STUDY GROUP MEETING
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**A STUDY OF THE POTENTIAL APPLICATIONS OF OLFACTORY RESEARCH IN MAN**

C. Jelleff Carr, Humphrey F. Sassoon, and Kenneth D. Fisher

This document has been approved for public release; its distribution is unlimited.

This study provides a comprehensive review of the feasibility of developing and utilizing the chemical senses of the soldier. While biosensors and odor-sensing devices can supplement, they cannot replace the potential performance of the normal human olfactory system. Experience in other countries suggests that a soldier trained to recognize olfactory cues is more effective in the field, more responsive to hazards, and less likely to give olfactory information to the enemy than one whose chemical senses are underutilized. Practical testing and training methods suited to that Army's needs have been lacking in the past, and basic knowledge of the mechanisms of olfaction and taste is incomplete. However, elements of a suitable technology have been identified. This technology appears suitable for further development within the Army research and development community. This report concludes that it is feasible for the Army to use these methods in determining classifications of personnel that require normal acuity of the chemical senses and to institute training programs. Regular testing for normal acuity of the chemical senses may uncover cases of some illnesses, indicate extensive exposures to ionizing radiation, and categorize personnel as either suitable or unfit for certain Army duties. If administered at recruitment, these tests can be used later to document disability claims for service-related losses of olfaction and taste.
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