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the Aroma-Chology Review

FOCUSING ON OLFACTORY DEVELOPMENTS AROUND THE WORLD

SOSI IMPLEMENTS MAJOR INTERNET INITIATIVE FOR 2001

The Sense of Smell Institute's (SOSI) web site will be the focus of innovation in 2001 as the organization transforms its site into a leading global resource relating to the sense of smell. In addition to informing the public, new features will make the site a high-value place to visit for scientists and SOSI's financial supporters.

The Institute's Chairman of the Board, Annette Green, observes that, "Many people today look to the Internet as their first source of information and we want our web site to be their gateway to the sense of smell." Many of the site's new features are now publicly available. These include:

- The SOSI Virtual Library is a listing of recent scientific publications in the field of olfaction. Dr. Avery Gilbert, SOSI president, explains, We select recent scientific articles and books that we believe are significant contributions to the field. The listing will include hyperlinks to the National Institutes of Health's online resource PubMed. This means visitors to the SOSI site can save time searching, and go straight to the sources. The SOSI site is the one resource where researchers, students and anyone else with an interest in the chemical senses can get smart fast.
- The Aroma-Chology Review – The complete archive of SOSI's fact-filled bi-annual newsletter will be indexed and available on line. Formerly available only by subscription, back issues will be downloadable for free in PDF format. Current issues will be available to subscribers and corporate sponsors only.
- Booklets – *Living Well with Your Sense of Smell and Aging Well with Your Sense of Smell* will be downloadable for free in PDF format.
- Science Education Bulletin Board provides a list of links to other web sites that provide additional information on the sense of smell. This feature has been designed for teachers and students to provide reliable information on the sense of smell that can be incorporated into lesson plans and science projects. Future plans for this feature include detailed curriculums and lesson plans on the sense of smell for grades 1-12 as well as a "career corner" that will answer frequently asked questions about career opportunities for those with an interest in the chemical senses.

In the coming months, the Sense of Smell Institute's financial supporters will also benefit from new features to be built into the web site that will be housed in a special password restricted area. The **SOSI Abstract Page** will display lay language summaries of new papers selected from the Virtual Library. The abstracts will be particularly useful in identifying potential applications of basic research findings. Sponsors will receive automatic e-mail updates when new abstracts are posted. **continued on page 6**

THE VNO: A VERY NICE ORGAN FOR SMELLING PHEROMONES

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While mammals have only one nose, they actually possess two olfactory systems. The common, or main, olfactory system is the sensor of the environment. It is the primary sense used by animals to find food, detect predators and prey, recognize conspecifics and mark territory. It is noteworthy for both its breadth and discriminatory power, enabling an animal to detect and discriminate many thousands of odors. A second, or accessory, olfactory system has developed for the specific task of finding a receptive mate–undeniably a job of sufficient complexity for all of us that evolution has recognized the need for an independent and dedicated system.
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ALSO IN THIS ISSUE

Female student sniffs boxes containing T-shirts worn by male students and rates performance.

BODY ODORS, PERFUMES, AND THE MAJOR HISTOCOMPATIBILITY COMPLEX

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A typical characteristic of many animals is that they display an enormous olfactory interest in the bodies of their fellows, while our general reaction to natural body odors is that they are unpleasant and distasteful, and, if we can, we put much effort in removing them. Not only do we regularly wash the fatty scented secretions from our skin and clothes, but many of us routinely shave off the tufts of hair that support bacterial action to produce smells in the most scented regions. Today, modern human communication seems to be based on acoustic, visual and tactile cues, not so much on chemical cues, and the consensus of the current literature suggests that humans do not have a working vomeronosal organ of the type found in other mammals (Wysocki & Preti 2000). But then again, humans have a well-developed olfactory system (Wysocki & Preti 2000), and humans in most cultures use perfumes. They often spend fortunes on them, supporting a billion dollar industry (Van Toller & Dodd, 1991; Ohloff, 1992). Humans have batteries of their own scent-producing glands. We have even more scent glands upon our body than any other higher primate (Stoddart 1990), but after we have tried to get rid of our own chemical signals, we use sex attractants of deer, civets and beavers. And even the finest and most expensive perfumes contain notes of a urinary nature, which may unconsciously stir our ancient memory of sex attractant pheromones expelled in urine (Van Toller & Dodd, 1991; Ohloff, 1992).

Even if we were not endowed with scent producing glands, it seems obvious that a living organism of the size of humans cannot avoid producing some smells. Our metabolism inevitably produces volatile chemicals that may be difficult to hide completely. Therefore, it may not be surprising that our body odors reveal some information about our metabolism, for example about the food we ate (e.g., garlic), what we drank (e.g., alcohol), about some metabolic problems or changes (e.g., stress), and possibly about some of the infectious diseases we carry (Penn & Potts, 1998a).

Odors are important components of our emotional life, and although the role of odors in human mate choice and sexual behavior is not as well studied as it is, for example, in rodents, it is clear that such a connection exists and that it may be a complex one. Obviously, the perfume industry would not be that big if there were no connection between odors and sex in our species.

Recent work suggests that a group of genes within the MHC (major histocompatibility complex) is important in the link between odors and mate preferences (reviews in Penn & Potts, 1998b; Penn & Potts, 1999). MHC genes play a central role in controlling immunological self- and non-self recognition (Klein 1986). The MHC is also one of the most polymorphic regions of the genome. This extraordinary diversity is thought to be maintained by pathogen interactions (Apanius et al., 1997).

Human noses can distinguish between two congenic inbred mouse strains that differ only in their MHC (Gilbert et al., 1986), and rodents seem to be able to recognize human MHC-types (Ferstl et al., 1992). When my colleagues and I had asked male students to wear T-shirts and female students to sniff them (Wedekind et al., 1995), we found that womens' preferences for male odors correlated with the degree of similarity of their own and the men's MHC type. T-shirt odors were judged as more pleasant when they were worn by men whose MHC genotype was different from that of the judging woman. This finding is analogous to previous findings in mice (Yamazaki et al., 1976; Penn & Potts, 1999). The difference in odor assessment was reversed when the women were taking oral contraceptives. Furthermore, the odors of MHC-dissimilar men were more frequently reminding the women of their own present or former partners than did the odors of MHC-similar men. These memory associations suggested that the MHC or linked genes influence human mate choice. A second set of experiments (Wedekind & Füri 1997) with new combinations of T-shirt wearer and smellers supported these results. Moreover, when men and women sniffed at male and female odors, there was no significant effect of gender in the correlation between pleasantness and MHC similarity.

Other research groups provided further support for a link between MHC, odors, and the nose. Carol Ober and her colleagues at the University of Chicago found in a large study on American Hutterites that married couples were less likely to share MHC loci than expected by chance, even after incest taboos were statistically controlled for (Ober et al., 1997). And from a completely different angle: a collaboration between groups in Berlin (Germany) and Cambridge (UK), initiated by Andreas Ziegler from the Humboldt University in Berlin, found a gene cluster that contains 36 olfactory receptor genes (OR), of which two belong to the vomeronasal family (Ehlers et al. 2000, Younger et al. 2001). This cluster is located at the telomeric end of the MHC complex. It is the largest sequenced olfactory receptor gene cluster in any organism so far. Thirteen of these genes were tested and found to be polymorphic. Although the physiology of MHC-correlated body odors and odor preferences is not at all clear yet (Penn & Potts 1998b), this polymorphism, and the proximity of such a cluster of olfactory receptor genes to the MHC, suggests that these OR genes could somehow be involved in MHC-related odor preferences.

Not only the physiology, but also the functional, i.e. evolutionary, significance of MHC-correlated body odors and odor preferences is not yet clear. Three non-mutually exclusive hypotheses have been proposed (review in Penn & Potts 1999). First, MHC-correlated mate preference may have evolved because certain MHC combinations or simply heterozygosity confer a strong advantage to resist pathogens, e.g. by providing a larger range of pathogen epitopes that can be signaled to T-lymphocytes. Second, MHC-correlated mate preference may enable hosts to provide a 'moving target' against rapidly evolving parasites that escape immune recognition. Third, MHC-correlated mate preferences may be a sophisticated mechanism to avoid inbreeding. In the latter case, MHC genes would only serve as markers of the degree of relatedness between two individuals.

In his famous book "Perfume. The story of a murderer," Patrick Süskind (1986) is probably wrong in the assumption that there is a perfect body odor, or the perfect composition of odors. Humans do have highly individualistic body odors that are readily detectable by most people, but preferences for body odors vary enormously, too. In general, 'good' body odors tend to be weak, as ratings of intensity correlate negatively with ratings of pleasantness in our studies (Wedekind et al. 1995, Wedekind & Füri 1997). Apart from this, the pleasantness score of six different body odors that were presented to 121 male and female smellers each ranged from very unpleasant to very pleasant (Wedekind & Füri 1997). It seems as if everybody smells nice to someone else, provided that the odor is not too intense. In our laboratory study where we could control for many disturbing variables, we could explain up to 23% of the variance in pleasantness by the degree of similarity on the MHC between T-shirt wearer and smeller (Wedekind & Füri 1997).

All this leads to an hypothesis that could potentially explain another evolutionary puzzle. The puzzle is that there is a great individual variability in preference for fragrances. Manfred Milinski and I therefore tested whether individual preferences for perfume ingredients correlate with a person's MHC-genotype (Milinski & Wedekind 2001). A total of 137 male and female students who had been typed for a part of their MHC scored 36 scents in a first test for use on self ("Would you like to smell like that yourself?") and a subset of 18 scents two years later either for use on self or for a potential partner ("Would you like your partner to smell like that?"). Overall, MHC-genotype and ratings of the scents "for partner" did not seem to correlate. However, there was a statistically significant correlation between the MHC and the scorings of the scents "for self" in both tests. In a detailed analysis, presence or absence of the two most common MHC alleles (HLA-A2 and HLA-A1) appeared to correlate best with the rating of the scents in both tests when evaluated for self. This result suggests that persons who share one of these alleles have a similar preference for any of the perfume ingredients. It should be stressed, however, that this effect is a weak one, i.e., it is probably only detectable with a large sample size. Also, there are obvious further facets of the psychology of fragrance selection besides MHC-correlated odor preferences (Van Toller & Dodd 1991; Ohloff 1992).

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"Humans do have highly individualistic body odors that are readily detectable by most people..."

THE SENSE OF SMELL INSTITUTE 2001: FOUR NEW GRANTS AWARDED

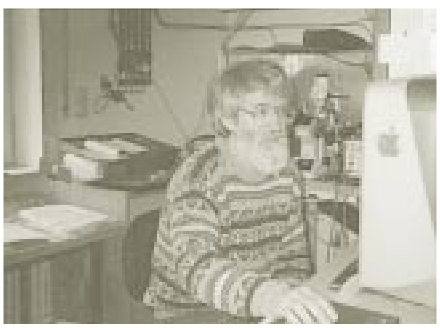
RESEARCH UPDATE

The Sense of Smell Institute has awarded four grants for the 2001 grant period. The Institute's Industry and Scientific Advisory Committees reviewed nineteen applications received in response to its annual call for research proposals. The new projects selected by the committees for funding and the questions they seek to answer are described below. As work progresses, update reports will be included in future issues of The Aroma-Chology Review.

The Effects of Fragrances on Memory and Mental Performance in Schoolchildren

Drs. Elena I. Rodionova and **Alexander V. Minor** of the **Russian Academy of Sciences** will investigate the effects of ambient scent on memory and mental performance of school-children. While the effects of ambient scent on memory and mental performance have been well established in adults, there are few such studies on school-age children, despite the potentially large benefits for learning and achievement.

Drs. Rodionova and Minor will study the question in an elementary school setting with classrooms of 8 to 9 year-olds, 9 to 10 year-olds, and 10 to 11 year-olds. Low levels of pleasant scent (lavender and peppermint) will alternate on a weekly basis with a no-odor condition as pupils work on standardized math and language lessons (two in each subject). In each subject, one task is more attention-dependent (e.g., text copying) and the other more memory-dependent (e.g., spelling). Scores from these tests are already recorded as part of the standard curriculum. At the end of the academic term, statistical analysis will compare performance in the various tasks and under the different odor conditions. Rodionova and Minor anticipate specific odor-by-test interactions.



Dr. Alexander V. Minor

Elucidating Proust Phenomenem

Dr. Simon Chu

Dr. John J. Downs

Although the Proustian phenomenon (the odor-induced recollection of vivid memories) is a widely held cultural belief, experimental analysis of it has been relatively rare. **Drs. Simon Chu** and **John J. Downes** of the **University of Liverpool** will base their exploration of it on Conway's recently developed theory of auto-biographical memory (AM).

Conway proposes that AM is organized at three levels of abstraction, which have consequences for the speed with which memories are retrieved and the level of detail the memories contain. Chu and Downes will leverage these differences in the design of their experiments. They posit that odor-related AM is encoded at a rich level of detail and in a manner closely resembling the original sensory impression.

Conway's theory predicts that odor-related AM will be retrieved more quickly than AM based on visual or verbal cues. This prediction will be tested by having volunteers recall AMs based on visual, verbal and olfactory cues; their verbal responses will be tape-recorded for later analysis of the timing of emotional content and detail.

A second experiment will use a pseudo-naturalistic design in which sensory-based memories are generated during the course of three 15-minute long activities. Some participants will return after an interval (2 day, 3 months or 8 months later) at which time they will be asked to recall details from one of the three original activities. The results will be analyzed to determine whether odor cues yield more additional information than visual cues or no cues; whether the odor cues produce more affect-laden information; and whether the length of delay makes a difference to the amount or content of the retrieved information.

The Shell of Fear: Neurobiological Correlates of Olfaction and Emotion in the Human Brain

Dr. Jay A. Gottfried of the **Hospital of the University of Pennsylvania** will use fMRI to explore the functional relationship between odor and emotion, specifically the emotion of fear. Dr. Gottfried will conduct his research at the **Institute of Neurology, University College London** starting this August.

Functional magnetic resonance imaging (fMRI) has given researchers a means of viewing and quantifying brain activity with a high degree of spatial detail. fMRI reveals brain areas specifically involved in odor perception (olfactory bulb, pyriform cortex, lateral orbitofrontal cortex) as well as areas critical to the processing of emotion and memory (amygdala, perirhinal cortex, hippocampus).

Dr. Jay A. Gottfried

By pairing an odor (e.g., orange) with an aversive stimulus (a half-second of very loud white noise), Dr. Gottfried will create classical fear conditioning in healthy human volunteers. Brains responses to fear-conditioned odors will be compared to non-conditioned odors and

Over 52 research studies, totalling $1.4 million, have been supported by grants from the Sense of Smell Institute. You can see a complete list of grants funded to date on the SOSI website at: www.senseofsmell.org

specific regional activation hypothesis tested statistically. Because emotional responses typically occur faster than cognitive (conscious) ones, Gottfried will conduct a second set of experiments to examine how conscious awareness impacts the regionality of response to fear-conditioned odors. The phenomenon of odor masking (the suppression of perception of one odor by mixture with another) will be used to manipulate level of conscious awareness.

Hedonic Primacy in Human Olfaction: Behavioral FMRI Investigations

Dr. Noam Sobel of the **Wills Neuroscience Institute** at the **University of California, Berkeley,** will examine the categorical perception of odors by applying the idea of hedonic primacy, i.e., the idea that pleasant vs. unpleasant is the main organizing dimension in odor perception.

Many physical stimuli vary in a continuous fashion but are perceived by us in a discontinuous fashion. For example, as the wavelength of a light is continuously varied, we see it change stepwise from red to orange to yellow. This phenomenon is know as categorical perception, and reveals much about how our brain organizes and structures our perception of the world. The categorical perception of odors has been hinted at, but to date not objectively documented. Dr. Sobel's research will address this question.

Dr. Sobel will design mixtures of two odors varying in equal steps of perceived intensity. Some of the component odors will be pleasant, others unpleasant. Volunteers will be tested on their ability to discriminate mixtures as the pleasantness and intensity of odors varies. If hedonic primacy holds true, there should be linear response to odors of similar hedonic value, and discontinuous response to odors of differing hedonic value.

In a second series of experiments, Sobel will record fMRI brain images as subjects make these odor discriminations. He will look for nonlinear brain responses that map onto the categorical judgements made by the volunteers. Specifically, he predicts that activity in the amygdaloid complex, a brain area central to both olfactory and hedonic processing, will correlate best with the psychophysical outcomes.

THE NEUROANATOMY OF MAKING OLFACTORY JUDGMENTS

David H. Zald, Ph.D.
Vanderbilt University

Imagine that you have just entered a room. You smell something. What information can you gain from it? Does it smell familiar or novel? Is it intense or weak? Is it pleasant or unpleasant? Does it smell like something edible? We routinely make all sorts of judgments about an odorant. However, until recently little work has addressed the question of which brain areas participate in these different judgments.

The hedonic (pleasantness-unpleasantness) dimension dominates our ratings of odorants. In the mid 1990s, José Pardo of the Minneapolis VA Medical Center and I began conducting positron emission tomography (PET) to determine what areas of the human brain become active during exposure to different pleasant and unpleasant odorants (Zald and Pardo, 1997; 2000). These studies rapidly made clear that hedonically valenced odorants make excellent probes for activating many areas of the brain involved in aspects of emotional processing. Some of the strongest activations emerged in the orbitofrontal cortex (the bottom most part of the frontal lobe) and the amygdala (an area in the temporal lobe that is thought to play a critical role in emotional processing). Some of the responses appeared valence specific: for instance the left amygdala appeared to selectively respond to more aversive stimuli. We found these results provocative, but as is often the case, they raised more questions than they answered. One particular question that intrigued me was whether there are parts of the brain that are involved in the conscious act of judging whether an odorant is pleasant or unpleasant? Furthermore, are the same areas involved in making these judgments in other sensory modalities?

Luckily for me, an opportunity presented itself to collaborate on some PET studies led by Jean Pierre Royet in Lyon, France. To address the issue of what areas of the brain are involved in making hedonic judgments in different sensory modalities, we exposed subjects to pleasant and unpleasant odorants, sounds, and pictures, and asked the subjects to determine whether each stimulus was pleasant or unpleasant (Royet et al. 2000). To control for the effect of sensory stimulation, each subject received control conditions involving sensory stimulation with hedonically neutral stimuli from the same sensory modality. During the neutral conditions, subjects were instructed to randomly make responses to control for any motor movement during the emotional judgment conditions. Consistent with previous studies using hedonically valenced odorants, bilateral activity emerged in the inferior frontal lobe. Strikingly many of the same areas that became activated during hedonic judgments of odorants, also activated when subjects judged the pleasantness-unpleasantness of pictures and sounds. Performing these judgments consistently induced increased activity in the bilateral inferior frontal lobe, as well as the left temporal pole (anterior extreme of the temporal lobe), and a more superior portion of the left frontal lobe (the superior frontal gyrus). These data demonstrate the existence of a shared neural circuit involved in the conscious determination of hedonic valence across different sensory modalities.

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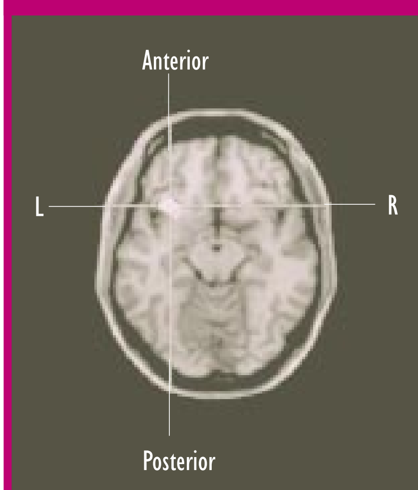
FIGURE 1



The figure displays the portion of the left orbitofrontal cortex that activates when people judge the pleasantness-unpleasantness of olfactory, visual, or auditory stimuli (the area that activation appears in is white and is further marked by the white cross lines that run through it). The activation is overlaid on a horizontal slice of an anatomical MRI.

SOSI IMPLEMENTS MAJOR INTERNET INITIATIVE FOR 2001

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The soon-to-be launched **SOSI Research Exchange** will be of high interest to both smell researchers and Institute sponsors. This innovative service, open to qualified scientists around the world, will allow researchers to post descriptions of experiments for which they seek funding, as well as their availability for public speaking engagements (e.g. sales meeting presentations). The Exchange will also allow Institute sponsors to seek scientists interested in carrying out olfactory research on specific topics. Dr. Gilbert predicts that, "The SOSI Research Exchange will quickly become popular, as it is one of the few web sites to bridge industry and academia, offering scientists a window to private sector funding and industry with the ability to address requests for proposals to a highly relevant and qualified scientific audience." This is a significant added value for SOSI's corporate sponsors.

Summarizing the innovations of the new SOSI web site, Annette Green noted, "The magic of the Internet is that you can have the best brains working for you without leaving your chair."

SOSI Research Exchange

THE NEUROANATOMY OF MAKING OLFACTORY JUDGMENTS

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Interestingly, when comparing the emotionally valenced stimuli to the neutral odorants, we did not observe increased activity in the amygdala. This suggests that consciously making hedonic judgments does not in itself involve increased activity within the amygdala. Scientific reporters and some neuroscientists and psychologists frequently treat the amygdala as if it were the seat of all emotional processing. However, our data (as well as studies of patients with lesions of the amygdala) indicate that it is not necessary for making conscious hedonic judgments.

In the same manner that we asked what areas become active during hedonic judgments, we similarly asked what areas of the brain become active during other types of judgments of odorants. To this end, we conducted another study (again led by Jean Pierre Royet) in which we seperately asked subjects to make dichotomous judgments of the presence or absence of odorants, their intensity, their novelty/ familiarity, their edibility, and their pleasantness-unpleasantness. For each condition odorants were chosen that were relatively easy for all subjects to rate and were balanced for each condition (e.g., for the novelty/ familiarity condition half the odorants were familiar and half were novel). All odorant judgment conditions were contrasted to a non-odorant control condition. In all judgment conditions, the right orbitofrontal cortex showed at least moderate activation. This region of the frontal lobe is frequently described as secondary olfactory cortex, and lesions to this area (especially in the right hemisphere) cause a host of deficits in olfactory processing. Thus, its relatively consistent activation across different odor judgments suggests that it plays a relatively obligatory role in all situations in which we make judgments about odorants. Interestingly, we did not find evidence for a similarly obligatory role for temporal pyriform cortex, which is often referred to as primary olfactory cortex. Indeed, we have frequently failed to observe evidence of pyriform activation of odors and increasing data suggest that this area behaves differently than primary sensory regions in other sensory modalities.

This latest study by Royet et al. (2001) additionally suggests that several areas outside of the traditionally defined olfactory system play a role in several of the different types of olfactory judgments. For instance, portions of the medial and anterior frontal lobe, which are not traditionally thought of as olfactory regions, appear involved during multiple types of olfactory judgments. That is not to say that all olfactory judgments produced identical activations throughout the brain. For instance, a portion of the brain involved in visual processing (the cuneus and lingual gyrus) becomes selectively activated when people make judgments about the pleasantness-unpleasantness or edibility of food. Why do these specific types of judgments engage visual areas? We are not sure, but it appears to be more than just a fluke finding. Indeed, Jean Pierre Royet and colleagues (1999) reported a very similar finding two years ago.

In summary, we have begun to understand the neural architecture involved in processing different aspects of olfaction. The study of olfaction has often focused on the level of olfactory receptors and the olfactory bulb. The present line of research makes clear that we will only fully understand how the brain processes odorants, if we also examine the diverse areas of the brain that appear involved in olfactory judgments.

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FOCUS ON THE FUND

SOSI Names Award in Tribute to Henry G. Walter, Jr.

In a tribute to the late Henry G. Walter, Jr., the Sense of Smell Institute has announced that it will name its annual Sense of Smell Award after the former chairman and chief executive of International Flavors & Fragrances.

SOSI chairman of the board, Annette Green, says "Hank Walter was truly a visionary who brought the realm of sensory and psychological research to our industry when he founded IFF's aromascience program. He was also a key figure in the creation of the Sense of Smell Institute in the early 80s (known then as The Fragrance Foundation Philanthropic Fund)."

The Henry G. Walter, Jr. Sense of Smell Award will be presented each year to a scientist in recognition of his/her achievements in the field of olfactory research. This year, it will be presented at SOSI's annual Night of Honors fund-raising gala scheduled for November 27, 2001 at The Pierre hotel. Members of SOSI's Industry and Scientific Advisory Committees as well as former Sense of Smell Award honorees nominate candidates for the award. The finalist will be selected by a majority vote of the advisory committee members.

For the first time this year, the recipient of the Henry G. Walter, Jr. Sense of Smell Award will receive a $5,000 cash prize in addition to the traditional crystal trophy. International Flavors and Fragrances has generously provided a two-year grant to SOSI to underwrite the cash prize. Pochet of America is providing the unique crystal trophy that will be presented to the winning candidate.

Night of Honors

The Institute will host it annual "Night of Honors" fund-raising gala on Tuesday, November 27, 2001 at The Pierre in New York. The annual event will celebrate the organizations 20th anniversary and will be themed "Night of Honors 2001: A Sensory Odyssey." The reception and dinner will include a myriad of taste and aromatic sensations from around the globe.

Honors to be presented will include the annual Corporate Vision Award, Henry G. Walter, Jr. Sense of Smell Award and Richard B. Salomon Award. The Institute's corporate sponsors will also be recognized. Recipients of this year's awards will be announced later this summer.

In keeping with tradition, the evening will culminate with a sensory door prize drawing and raffle.

National Sense of Smell Day

SOSI celebrated the 8th Annual Sense of Smell Day on April 28, 2001 at sixteen science centers and children's museums across the U.S. A special report, including photos of the activities at each participating location, and a list of corporate sponsors who helped to make the day a huge success, can be found at the Institute's web site (www.senseofsmell.org).

Compendium Supplement

A supplement to the Institute's Compendium of Olfactory Research will be available in August 2001. The supplement containing the full scientific reports on eleven research studies sponsored by the Institute between 1994 and 2000 will be included in the soft-covered publication. The book will be available directly from the publisher Kendall/Hunt Publishing Co. at $39.95. To order your copy, call 1-800-772-9165.

New Board Appointments

The Sense of Smell Institute announced several new appointments to its Board at the start of the year.

■ **Jack Mausner,** Ph.D., scientific consultant, Chanel, Inc. has been appointed honorary chairman. Dr. Mausner previously served as president of the Institute's board from 1988 to 1994 when he was appointed chairman.

■ **Annette Green,** president, The Fragrance Foundation has been named chairman. In 1980 Ms. Green galvanized the fragrance industry to establish the Institute (then known as The Fragrance Foundation Philanthropic Fund) as a charitable organization dedicated to researching the sense of smell and beneficial effects of fragrance. She first served as the organization's executive director and as its president since 1994.

■ **Avery N. Gilbert,** Ph.D., president, Synesthetics, Inc. has been appointed president. Dr.Gilbert joined the Institute's Scientific Advisory Committee in 1986 and became chairman of the Industry Advisory Committee in 1988. He was appointed Scientific Affairs Director in 1995.

■ **Shirley Lord,** vice president of content, ibeauty.com was appointed to the position of secretary of the board. Ms. Lord has served on the Institute's board for over ten years.

■ **Theresa Molnar** was promoted to the position of executive director of the Institute at the start of the year as well. Ms. Molnar joined the Institute as its executive administrator in 1990 and was promoted to director in 1999.

THE VNO: A VERY NICE ORGAN FOR SMELLING PHEROMONES

continued from page 1

Known as the vomeronasal organ (VNO), it specializes in recognizing species-specific olfactory signals produced by one sex and perceived by the other. These signals contain information not only about location but also reproductive state and availability. In fact, many other behaviors are also influenced, if not outright regulated, by the activity of the VNO. It has been implicated in mating, suckling, courtship and other behaviors, and is believed to interact directly with the endocrine system.

Now, everyone wants to know if there is a VNO in humans and if pheromones are effective in human interactions. But you'll have to read to the end of the article to find that out – unless of course you cheat and peek.

For many years, most of what we knew about pheromone reception by the VNO came from behavioral studies. These proved its effectiveness, but were unable to suggest any mechanisms by which it accomplished its work. In the last few years however we have made significant advances. At the April, 2001 meeting of the Association for Chemosensory Sciences in Sarasota, Florida a symposium devoted to the VNO proved that research in this area has come of age. A number of laboratories are now applying the most modern biological techniques to unlock its mysteries. These include genomics, molecular biology, physiology and advanced optical imaging.

The VNO is a small piece of neural tissue hidden inside a bony cigar-shaped capsule attached to the septum in either nasal cavity (Figure 1). It is separate from the tissue that we use for smelling the environment. The cells of the VNO, called vomeronasal sensory cells (or VSNs), have a specialized bipolar shape. Attached to their top end are hair-like projections called microvilli. This is where the sensing of the pheromone molecules takes place. Embedded in the membranes of the microvilli are proteins that act as receptors for pheromones and possibly other molecules. The receptors and pheromones act like a lock and key — if the pheromone fits tightly into the receptor then it will activate it. Once the receptor is activated it turns on a series of proteins in the cell which results in an electrical change across the cell membrane. It is this tiny electrical message (just a few thousandths of a volt) that is sent to the brain where it is interpreted and acted upon.

The most important recent advance in understanding how the VNO works was the identification and cloning of the genes for the receptors. It turns out that there are quite a few of them — more than 200 have been discovered so far. These receptors are closely related to a large class of receptors found in organisms from yeast to humans. They are *G-protein Coupled Receptors* {GPCRs} and are characterized by having a certain shape and by activating a common cellular protein called a G-protein (thus the name). It seems that once evolution happened upon this type of receptor it couldn't get enough of it. There are thousands of GPCRs at work in the body — from the brain to the heart to the lungs, liver, vascular system — virtually everywhere. In fact it was recently estimated that more than 50% of all the drugs on the market or in the pipelines of the major pharmaceutical companies target GPCRs. And olfactory and vomeronasal receptors make up the two largest families of GPCRs.

In the VNO there are two sub-families of these receptors, each with slightly different properties. One sub-family probably selects for volatile compounds that may be similar to normal odors. The other sub-family may be most sensitive to peptides or amino acids that are more likely to be dissolved in solutions. But it must be said that as yet we have not been able to definitively pair up any one receptor with the compounds that best activate it.

Part of the problem is that pheromones are hard to come by. They are typically a minor component of excreted fluids such as urine or sweat, and are therefore difficult to identify, purify and obtain in quantity. In fact, fewer than six chemical compounds have been isolated and identified as possible mammalian pheromones. One of those, a 12 carbon acetate, is a pheromone for both the Asian elephant and the silkworm moth! Presumably they do not have overlapping ranges. It is important to stress that while certain bodily fluids are known to have significant behavioral effects, the specific pheromonal compounds responsible for these effects have yet to be identified in most cases.

There are some interesting contrasts between the VNO and Main Olfactory Epithelium (MOE) that suggest very different strategies for detecting and discriminating odors and pheromones respectively. In both systems an individual sensory cell chooses one particular receptor from the hundreds or thousands in the family and makes only that kind of receptor. Because all the receptors on the membrane of a particular sensory cell are the same, there is a precise correspondence between compounds that activate the receptor and those that activate the cell. This means that any compound that activates a particular cell must be specifically interacting with the receptor being made by that cell. This may seem trivial, but it is an important point because it is much easier to experi-

"The most important recent advance in understanding how the VNO works was the identification and cloning of the genes for the receptors."

"...there appears to be little or no difference in the VNO between males and females."

mentally observe the activity of a cell than a single receptor, which is after all only a single protein molecule. When a scientist applies a pheromone or an odor to a sensory tissue, whether the VNO or the MOE, it is possible to determine which cells are being activated by that compound. And when you do that to the VNO or MOE you get very different results.

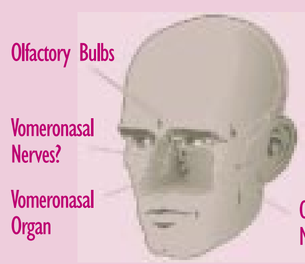
Experiments with mice have shown that only a very few sensory neurons in the VNO respond to a given pheromone substance. Of the 500,000 or so neurons in the VNO only about 0.5% are sensitive to a given pheromone. This seems to imply that a given VNO receptor recognizes only a specific pheromone compound. By contrast, in the main olfactory system many thousands of neurons typically respond to a given odor. Olfactory receptors are apparently rather promiscuous and will interact with many similar odors.

As might be expected from this high degree of selectivity it also appears that VNO receptors are more sensitive than their cousins in the MOE. VSNs respond to pheromone substances at concentrations as low as 0.1 nano-molar – about 20 parts in a trillion in terms of dilution. That is, 20 molecules of pheromone dissolved in a trillion molecules of water could be detected by a cell in the VNO. In the MOE sensitivities are as much as three orders of magnitude lower – typically about 20 parts in a billion. A few notable compounds, like burning odors, can be detected at parts per trillion. Raising the concentration of a pheromone substance does not appear to activate more receptors. This is again in contrast with the main olfactory system, where higher concentrations of the same odor appear to recruit new receptors.

Thus the VNO and main olfactory system use different strategies to detect and discriminate the many compounds they come into contact with. In the main olfacotry system the important thing is to be able to recognize a large number of odors (at least 10,000 and probably many more). This appears to be accomplished by a combinatorial code in which most receptors recognize several odors and most odors are recognized by several receptors – it's up to the brain to sort out one from the other. This bears a superficial similarity to the visual system where different combinations of only three receptors (red, blue and green) are sufficient to produce the perception of thousands of hues. But the VNO, which is interested in far fewer compounds, appears to use a more direct strategy of finely tuned receptors that are very specific for a particular molecule and no other. When that receptor is activated the brain knows that the molecule is nearby.

One curious result from both physiological and molecular genetic experiments is that there appears to be little or no difference in the VNO between males and females. The receptor genes are the same in both males and females, and both sexes respond to many of the same substances. As pheromones are credited with playing a role in sexual behaviors it was anticipated that there would be distinctly male and female receptors and concomitant sensitivities. Rather, it seems that both sexes smell the same substances and the differences in the elicited behaviors are the result of neural processing at higher brain levels. Indeed it may be just as important for a female to know how many other estrous females are in the vicinity, as it for a male to have this information.

FIGURE 1



Are humans sensitive to pheromones? The VNO in humans is vestigial, disappearing prior to birth. In the human genome all putative members of the VR family are "pseudogenes" with one exception. A pseudogene is a genetic sequence that once coded in evolutionary time for a receptor but has somehow become corrupted and is no longer capable of directing production of the receptor protein. In other words, the human genome contains the historical record of the pheromone receptors, but it no longer makes them. The one exception to this is a single V1R gene found to be intact in a comprehensive search of the recently completed human genome. Further, cDNA (a molecule made from RNA and whose presence is diagnostic for an expressed gene) for this gene was recovered from eleven individuals of varying ethnic backgrounds. Thus there is at least one, and probably only one, VR gene found in humans. No ligand is known for this receptor. There are various behavioral studies that implicate putative pheromones in regulating endocrine dependent behaviors such as menstruation, but the precise site of action is unknown.

This really shouldn't be too surprising. With the development of the human brain and in particular the expansion of the neocortex, an area devoted to synthesizing input from many sources, it would be astonishing if any one set of sensory cues unleashed a pre-patterned behavior. We are certainly sensitive to odors, and they certainly have an impact on our behavior (we still talk about the "chemistry" between two people), but only in concert with visual, aural, tactile and cognitive stimuli. As the advertising says "It's the whole package."

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CAN ODOR IDENTIFICATION DEFICITS BE USED TO MAKE AN EARLY DIAGNOSIS OF AD?

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Introduction

The hallmark neuropathological changes associated with Alzheimer's disease (AD), β-amyloid plaques and neurofibillary tangles, are detected only by brain biopsy or autopsy. This fact makes the clinical diagnosis of AD difficult. An important goal is to identify early diagnostic behavioral and biological markers for AD. Identifying early markers has very important clinical and potential therapeutic implications for individuals at risk for AD in that it facilitates early diagnosis and possible intervention that could halt or slow disease progression.

Our research group is funded by the NIH to systematically evaluate the predictive utility of potential markers of AD in patients with mild cognitive impairment (MCI), defined broadly as the category between "normal" and "dementia," as compared with healthy elderly individuals. While epidemiologic data suggest that 20-50% of elderly people experience cognitive impairment (Coria et al, 1993), only some of these patients progress to AD (Devanand et al., 1997). Important demographic risk factors for AD include age, family history of dementia (Amaducci et al, 1986), female gender (Gao et al, 1998), and education (Stern et al, 1994). Recent findings by our group (and other research groups) have identified a number of neurobiological markers of AD. These include: structural and functional changes in specific brain regions (i.e., atrophy and reduced blood flow) as seen with brain imaging techniques, and the presence of the apolipoprotein E4 genotype. However, it has been difficult to demonstrate that the predictive utility of these markers significantly adds to that of known risk factors such as increased age, low education, and poor cognitive test performance.

A potential cost-effective marker of AD is the impaired ability to identify common odors. Research has consistently demonstrated that patients with AD identify odors less accurately than do healthy elderly individuals (Doty et al., 1987). This finding is not surprising, since amyloid plaques and neurofibrillary tangles appear first in brain areas that are critical for the processing of odors, particularly olfactory bulbs and the entorhinal cortex. Interestingly, Nordin and Murphy (1996) demonstrated that patients with mild cognitive impairment performed more poorly on tasks requiring subjects to identify different odors than did healthy individuals. Impaired olfactory identification has also been observed in first-degree relatives of AD patients (Serby et al., 1996). Building on these findings, the main goal of this study was to evaluate the extent to which smell identification deficits in MCI patients can add to our current ability to predict a future diagnosis of AD.

Here we present a brief overview of initial findings from our study on the predictive utility of olfactory identification deficits in MCI patients (and normal controls) followed systematically in a clinical setting.

Methods

Subjects: Ninety outpatients who presented with mild cognitive impairment to our Memory Disorders Center were recruited for the study. Patients were followed at 6-month intervals. Forty-five normal controls, group-matched to the MCI patients on age, sex, and education, were also recruited and followed annually. All patients met rigorous inclusion/exclusion criteria (see Devanand et al., 2000, for a detailed description).

Procedures: Based on information obtained from medical history and a general physical, neurological, and psychiatric examination, as well as neuropsychological (comprehensive testing of memory and other intellectual functions) assessment, a team of expert raters made a consensus diagnosis. At follow-up visits, similar evaluations were conducted. The diagnosis of dementia was based on DSM-IV criteria, and the diagnosis of possible or probable AD was based on the standard NINCDS-ADRDA criteria (McKhann et al., 1984).

Test of olfaction: The University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1985) was administered at baseline evaluation to all participants. This is a forty-item scratch-and-sniff test that takes about 15-20 minutes to complete. Each of 40 common odorants is embedded in a microcapsule on a separate page, and the subject has to select one of four written multiple-choice alternatives for each odorant (total score range 0-40).

To assess subjective awareness of smell difficulties, participants were also asked whether or not they suffered from smell problems.

Results: At initial evaluation, the MCI patients had a mean age of 66.7 years (SD 10.7) and mean education of 15.0 (SD 3.9) years. In normal controls, the mean age was 64.0 (SD 10.0) years and the mean education was 15.6 (SD 2.6) years. The mean Mini Mental State (MMS; Folstein et al., 1975) score (range 0-30) was significantly lower in patients (mean 27.4, SD 2.1) compared to controls (mean 29.4, SD 0.8; $t=4.5$, $df=133$, $p < .001$). The baseline olfaction score (range 0-40) was also lower for the 90

MCI patients (mean 31.0, SD 7.4) compared to the 45 normal controls (mean 35.2, SD 3.9; t=3.6, df=133, $p < .001$). Of the 90 patients, 77 were followed (13 recently recruited patients have not yet returned for follow-up) for a mean duration of 20 months (SD 12.0). Of these 77 patients, all 19 patients who met consensus diagnostic criteria for dementia also met criteria for probable AD (McKhann et al., 1984).

Olfaction scores were lower in patients who developed AD compared to those who did not (t=3.4, df=75, $p < .001$). Patients with low olfaction scores (≤ 34 out of 40) were more likely to develop AD than the rest of the clinical sample ($\chi^2=16.1$, df=1, $p < .001$). However, low olfaction scores (or olfaction scores dichotomized as ≤ 34 versus > 34) were not significantly predictive after controlling for the effects of age, sex, MMS scores and education.

Patients with low olfaction scores who reported no subjective smell problems were classified as "low olfaction-lack of awareness." This group of subjects was more likely to develop AD than the rest of the sample ($\chi^2=13.2$, df=1, $p < .001$) even after controlling for the effects of age, sex, MMS scores and years of education (relative risk 7.3, 95% CI 1.7 to 23.1, $p < .01$). This effect remained when measures of attention or memory replaced Mini Mental State scores in the model. After restricting the clinical sample to only high functioning patients (MMS scores ≥ 27 out of 30), low olfaction-lack of awareness remained a significant predictor of AD.

Discussion: In this clinical sample of MCI patients, low olfactory identification test scores at baseline predicted the diagnosis of AD on follow-up, particularly in patients who in addition to low scores on the smell identification test also lacked awareness of their smell problems. This effect remained significant even after controlling for age, sex, education, and cognitive scores (MMS, attention or memory measures), indicating that the results could not be explained by lack of attention or poor memory.

In patients with high baseline scores on the MMS score (≥ 27 out of 30), low olfaction-lack of awareness remained a significant predictor of AD even after controlling for demographic and clinical predictors. This suggests possible predictive utility for olfactory deficits in patients with minimal cognitive deficits who are often difficult to diagnose and in whom the prognosis is very unclear.

From a theoretical perspective, lack of awareness (or anosognosia) is thought to be mediated primarily by the parietal lobe (Lopez et al., 1994), though the frontal lobe may also be involved (Starkstein et al., 1995). In Anton's syndrome, unawareness of visual deficit is due to damage to visual association cortex that is in close proximity to the primary visual cortex (Ramachandran, 1995). Using this analogy, we speculate that awareness of the loss of sense of smell, for which the brain center remains to be identified, may be localized to medial temporal lobe structures that are known to be affected early in AD and are associated with olfactory identification deficits (Martzke et al., 1997). This could explain why low olfaction scores accompanied by lack of awareness of olfactory deficit in MCI patients strongly predicted AD on follow-up.

The strength of the findings reported here suggest that odor identification deficits, particularly when accompanied by a lack of awareness of smell difficulties, have the potential to be an effective early diagnostic marker of AD. This is particularly true since a scratch and sniff test of olfaction can easily be administered in a clinical setting in a very time and cost effective manner. However, longer follow-up and independent replication in larger clinical samples are needed to establish clinical utility. To improve our scientific understanding of the role of olfaction in AD, brain imaging studies need to be conducted to further examine the underlying mechanisms mediating the olfactory deficits observed in MCI and AD patients.

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"...odor identification deficits, particularly when accompanied by a lack of awareness of smell difficulties, have the potential to be an effective early diagnostic marker of AD."

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