Physiological and Neurological Approaches to Fututre Olfactory Research

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Authored by:

Michael A. McGinley
McGinley Associates, P.A.

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St. Croix Sensory Inc. / McGinley Associates, P.A.
13701 - 30th Street Circle North
Stillwater, MN 55082 U.S.A.
800-879-9231
stcroix@fivesenses.com

While communities worldwide continue to grapple with the odor nuisance issue, a smaller subset of citizens from this population are introducing a new topic which has yet to be fully defined. These citizens are experiencing non-specific symptoms (e.g. headache, itchy nose and/or eyes, dizziness, etc.) which are being attributed to chemical odors.

These concerns and complaints are very similar to those expressed in individuals with "Multiple Chemical Sensitivity" and those associated with "Sick Building Syndrome." Currently, these environmental problems are thought to be at least partially linked to olfactory response, however, clinical ecologists have not determined an etiology for these illnesses.

The increasing prevalence of these community concerns makes it an imperative research topic of the future. While odor nuisance research has been based on environmental analyses, these new issues will require research based in physiology and neuroscience. However, both depend heavily on personal sensory perception of the individuals involved. Current theories and definitions related to these fields will be outlined and explained and alternative research will be proposed.

INTRODUCTION

Over the last ten years there has been a plethora of technical research, case studies. and organization position papers referring to and discussing the issues of environmental illnesses and the possible relationship of the olfactory system. While most of these articles, papers, and books have provided a forum for medical experts to present current findings and to debate controversial issues, it is difficult to find a reference which concisely summarizes the basics of the issues. This paper was developed in order to present this issue to a professional organization which should be interested in the progress of this research as it's implications could have a severe impact on regulations, community relations, and legal actions beyond nuisance suits.

While not a medical expert in areas of physiology, neurology, etc., I am an environmental health professional who sees a need to continually develop and transfer knowledge pertaining to current issues to other professionals who may be directly affected. This paper will conclude with an extensive, but by no means complete, literature list for those who are interested in investigating the issues further and learning more from the experts.

OLFACTORY ANATOMY

Of the five senses, the sense of smell is the most complex and unique in structure and organization. While human olfaction supplies 80% of flavor sensations during eating, the olfactory system plays a major role as a defense mechanism by creating an aversion response to malodors and irritants. This is accomplished with two main nerves. The olfactory nerve (first cranial nerve) processes perception of the chemical odors. The second nerve, the trigeminal nerve (fifth cranial nerve) processes the irritation or pungency of a chemical odor.

During normal nose breathing only 10% of inhaled air passes by the olfactory receptors in the top, back of the nasal cavity. When a sniffing action is produced, more than 20% of inhaled air is distributed to the area near the olfactory receptors due to the turbulent action in front of the turbinates (Shusterman 1992). These receptors are ten to twenty-five million olfactory cells making up the olfactory epithelium. Cilia on the surface of this epithelium have a receptor contact surface area of approximately five square centimeters due to the presence of many micro-villi on their surface. Supporting cells surrounding these cilia secrete a mucus which acts as a trap for chemical odors.

Chemical odors pass by the olfactory epithelium and are dissolved into the mucus depending on their water solubility. The more water soluble the chemical, the more easily it is dissolved into the mucus layer. The chemical odor is then received by a "matching" site on the olfactory cells much like enzymes bind with a substrate. The response created by the reception of a chemical odor depends on the mass concentration or the number of molecules present. Each reception creates an electrical response in the olfactory nerves. A summation of these electrical signals leads to an action potential. If this action potential has a high enough amplitude (threshold potential), then the signal is propagated along the nerve, through the ethmoidal bone between the nasal cavity and brain compartment where it synapses with the olfactory bulb.

All olfactory signals meet in the olfactory bulb where the information is distributed to different parts of the brain. One major pathway of information is to the limbic system which processes emotion and memory response of the body. This area also influences the signals of the hypothalamus and the pituitary gland, the two main hormone control centers of the human body. It is thought that this pathway can cause mood and behavioral changes without entering conscious awareness. The second major information pathway is to the frontal cortex. This is where conscious sensations take place as the information is processed with other sensations and are compared with cumulated life experiences to possibly recognize the odors.

The location of the olfactory system and the direct connection of the nerves with the brain create a unique pathway for environmental pollutants to potentially cause adverse health effects. This pathway is thought to be at least partially responsible for symptoms experienced in Sick Building Syndrome, Multiple Chemical Sensitivity, and other named and unnamed syndromes.

SICK BUILDING SYNDROME

The changing attitudes towards energy conservation in the late 1960's and the world oil crisis of 1973 influenced the way buildings have been constructed and have been managed over the last two decades. Buildings have been built tighter in order to conserve energy, and heating, air-conditioning, and ventilation (HVAC) systems have been designed to operate efficiently by limiting the number of air exchanges between the indoor and outdoor environments.

Since these changes in construction and operation took place, there has been an ever growing concern for the adequacy of indoor air quality. In the mid to late 1970's employees of general office buildings began to express concerns about their indoor environment. The employees were reporting symptoms such as headaches, fatigue, difficulty concentrating, skin irritations, eye irritations, and respiratory irritations. Originally, these concerns were considered to be mass psychogenic illness. These concerns, illnesses, and symptoms the employees were reporting were being attributed to either job function stresses, job dissatisfaction, or administrative related problems. The actual quality of indoor air was not thought to be a "real" concern.

In the 1980's the increasing number of general office buildings faced with large numbers of employees suffering from non-specific symptoms and the lack of proven causes for these symptoms created the need to define the phenomenon universally. The terms "tight building syndrome" and "sick building syndrome" were both introduced to designate the problem buildings. Over the last decade a building has been determined to have sick building syndrome if there is a significant percentage of employees reporting various non-specific symptoms, there is no source or recognizable reason for reported symptoms, and the symptoms generally improve after leaving the building.

Through the 1980's, increased research and more extensive investigations led to the identification of causes for the symptoms in many buildings. Once a cause for the symptoms experienced by employees is identified and proven, the employees are then said to be suffering from a "building related illness" (BRI). However, quite often the building related illness is classified by a specific diagnosis. For instance, Legionnaire's Disease is an illness caused by the legionella bacteria. Still many cause-effect relationships are never determined and the designation of sick building syndrome continues to be used as a general classification for the symptoms.

MULTIPLE CHEMICAL SENSITIVITY

In the early 1980's, another phenomenon began to develop surrounding environmental exposures. Industrial workers and average citizens were experiencing symptoms including headaches, dizziness, fatigue, respiratory irritations, eye irritations, cognitive disfunction, etc. whenever exposed to chemical odors. This syndrome has been called Environmental Illness (EI), Ecologic Illness (EI), 20th Century Disease, Chemical AIDS, and Total Allergy Syndrome. The most widely used and accepted title for the symptoms has been Multiple Chemical Sensitivity (MCS). MCS was defined by Cullen (1987) as a syndrome which manifests itself as general symptoms effecting multiple systems of the human body when a patient is challenged with many unrelated chemicals odors at concentrations well below accepted standards, guidelines, and documented exposures known to cause adverse health effects. The syndrome is thought to start after either an acute dose of a high concentration of a chemical odor or long term exposure to low levels of chemical odors.

Throughout the last fifteen years the number of cases of MCS have been increasing at an alarming rate. However, very little epidemiological data has been collected and this increase could be due to improved reporting. As with Sick Building Syndrome, the initial cases of MCS were blamed on psychological problems. Unfortunately, while some causes of Sick Building Syndrome have been found (BRI), thus justifying the symptoms, no universally agreed upon cause has been found for MCS, and the majority of diagnoses of MCS continue to be associated with psychological disorders.

SICK COMMUNITIES

Throughout this same time period, this phenomenon of non-specific, multi-system symptoms has been experienced in communities near industrial sites, waste water treatment plants, agricultural sites, and hazardous waste sites (Shusterman 1992). Citizens report that chemical odors are making them sick. In a survey near a waste treatment plant in 1983, one in nine respondents reported that odors had made them sick (Bruvold 1983). A 1991 study of health effects from pesticides used on a potato field showed that while health effects were not related to proximity of citizens to the fields, odor perception was strongly related to the number of symptoms reported, the length of occurrence of the symptoms, and the severity of the symptoms (Ames and Stratton 1991). More recently, these odor related symptoms are being reported by large groups of citizens near agribusiness feedlots around the country and near other industrial sites.

Even with these and other studies reporting a relationship between odors and health, citizens are still told that the problem is all "in their head." It is thought that the citizens are suffering from "environmental fear" or "environmental worry" (Shusterman 1992). These terms refer to the idea that concerns over unknown and misinterpreted information lead the citizens to fear different facilities near their homes. This fear leads to symptoms through psychological processes.

POSSIBLE HEALTH EFFECT MECHANISMS

This theory that the psychologic health of the patients is to blame has also been applied to those experiencing Sick Building Syndrome, Multiple Chemical Sensitivity, and most recently Gulf War Syndrome. The feeling is that family, job, or environmentally related stresses in the patients' lives lead to psychological disorders such as anxiety, depression, distress, etc. One study explains how many patients with Environmental Illnesses have a long history of unexplained illnesses and high utilization of health care systems (Simon, et. al. 1990). Many other studies show that along with the non-specific symptoms patients also have a diagnosed psychological disorder. Shy children who express symptoms with Environmental Illness are more often diagnosed with a psychological disorder while also expressing a lower than average odor threshold (Bell, et.al. 1992).

Those who believe that the symptoms could not be caused by toxicological mechanisms are assuming that currently accepted standards and guidelines are sound and robust. However, there is little scientific research surrounding long term, low level exposure to chemicals. Furthermore, any extrapolations from studies which use high level exposures to actual low level exposures does not take into consider those who are most sensitive or most susceptible. As Ziem and Davidoff (1992) explain it is an axiom of medicine that physiological causes must be ruled out before assigning psychologic etiologies. This has failed to happen in almost all Environmental Illnesses over the last two decades. Today's managed care health systems make it a disadvantage

for physicians to investigate complex cases. When a doctor is unable to identify a disease in his/her medical "cookbook," it is much easier to prescribe a psychiatric evaluation than to investigate the cause.

Doctors have not yet realized that these psychological disorders are also present simultaneously with many legitimate chronic medical disorders (Ziem and Davidoff 1992). In other words, they may be a secondary effect to physiological problems. Further, these psychological problems could be a sign of susceptibility to physiological mechanisms. Regardless of the true reason for the coexistence of symptoms and psychological problems, even if psychological disorders are to blame, it is still a problem. Facilities must still deal with this issue through risk communication and community involvement.

One group of doctors who are investigating alternative cause-effect relationships are clinical ecologists. Clinical ecologists have been defined as physicians who believe that exposure to low levels of environmental substances present in the air or ingested in food or liquids cause a variety of symptoms affecting nearly every organ system in susceptible individuals (AMA 1992). These physicians feel that where there is smoke there is fire and the symptoms cannot be passed off as purely psychological, yet they do not have all the answers. They hear the duck and smell the duck, but they cannot find the duck. Clinical ecologists have begun to search for answers by putting away the cookbook and beginning to use non-traditional theories and practices not well accepted by traditional doctors.. Most of these research based theories and practices have not been scientifically proven, yet they have shown some success. Traditionalists feel that they are seeing false improvements because they are "supporting" the plight of the patients (Brodsky 1987). Clinical ecologists feel that they are just performing the job of the physician. Their research has lead to several theories for mechanisms of environmental illnesses.

The California EPA summarized the issue by stating that their investigations have led them to believe that the apparent health effects of chemical odors defy explanation by classical toxicological terms (Shusterman 1992). It is believed that non-traditional, odor related toxicological mechanisms likely prevail.

One theory is that at some point the total body burden of a person's exposure to physical, chemical, antigenic, and psychosocial stressors is exceeded (Terr 1987). When this occurs, the body reacts by the immune system eliciting a response. These changes in the immune system lead to the various symptoms. Other research has shown that moods are negatively affected by unpleasant odors (Schiffman, et. al. 1995a,b). Further, negative moods have been shown to affect the immune system function. Those who oppose the immune system theories feel the immune system is often blamed because of its complexity and unknowns related to mechanisms and how functional changes manifest themselves (Brodsky 1987).

A second theory is the conditioning theory. It was first thought that the responses were initiated by a traumatic exposure to a chemical odor, however, the majority of patients experienced exposures over months and years. After this initial exposure or after a certain duration of exposure, the body becomes conditioned to respond to stimuli through symptoms (Sparks, et. al. 1994a). This could be solely an effect or it could be the body's way of warning of possible unknown future effects. It is thought that this conditioning is rooted in the powerful relationship of the olfactory system and memory.

Still another theory is that the symptoms are due to an electrochemical response. This could be related to the transmission pathways of nerve signals or to the action of different neurotransmitters. One researcher has termed this response "olfactory dementia" (Duehring 1996), which relates this theory to the large number of patients who report symptoms related to decreased cognitive function. The olfactory system sends signals to the brain where signals are processed and sent out throughout the body. These signals may be incorrectly sent leading to symptoms or signals sent to the hypothalamus and pituitary adversely effect the endocrine system and thus hormone balance. These adverse effects are then thought to cause the immune system to elicit a response, thus leading to further symptoms.

Other theories exist and are being developed currently. One relatively new theory is that a microorganism imbalance in the body makes some people susceptible. With this theory it is still necessary to look upon other theories to draw a complete picture. It is most likely that there is not one theory which will explain all the symptoms. The three major physiological theories discussed have many similarities, and many concepts cross over between them. In the end, the different environmental illnesses may be caused by very different mechanisms which are all presenting as the same symptoms. Furthermore, different individuals may be showing the same symptoms through different mechanisms caused by the same exposure. The complexity of the situation and the need for additional research is quite obvious without even mentioning added considerations of confounding factors such as age, gender, occupation, life style (diet, smoking, etc.), medications, and other unrelated illnesses just to name a few.

FUTURE OLFACTORY RESEARCH

The success of future research will depend heavily on three main topics: who will conduct the research, what methods will be accepted, and who will fund the research. It will be imperative for input between many disciplines and fields of study including, but not exclusively, neurologists, toxicologists, physiologists, psychologists, physicians, immunologists, and microbiologists.

One area which requires improvement deals with the logistics of conducting research in order to develop consistency. First, universally accepted operational definitions of the various environmental illnesses must be created. Further, it is necessary to develop objective methods for diagnosing subjective symptoms. For instance, in one study blinking rate was used to quantify eye irritation. Also, new and current methods must be developed for research techniques, instrumentation, and recording and documentation.

The validity of research will be strengthened with well designed studies. Careful selection of control groups is necessary. Currently, most studies look at the patients specifically and few studies include control groups. Further, the studies must include all age groups, both genders and different susceptible individuals. Current studies, which haven't looked at patients specifically, have used young, healthy adult males who are generally the least susceptible group in the general population. Finally, almost all studies currently conducted are retrospective. It is imperative that persons with environmental illnesses or citizens next to a new facility keep symptom logs for analysis on a prospective basis.

The articles and books reviewed for this paper suggested a long list of research possibilities. The majority of these possibilities are in some way related to the olfactory system. Some of the most prominent possible topics are listed:

- Nose versus mouth breathing and the effect on symptom response;
- Neurophysiology and neuropsychology effects of olfaction including:
    - Detected versus undetected odors
    - Hedonic tone quality of odors
    - Intensity of odors
    - Temporal effects of odors;
- Emotional impact of odors;
- Neurological brain mapping during chemical odor challenges;
- Function and effects of neurotransmitters;
- Stress and it's effects on the immune system;
- How chemical odors effect the endocrine system and hormone balance;
- How the endocrine system and hormone balance effect odor perception;
- How the endocrine system changes can lead to symptoms; and
- Microbiological mechanisms both in the systems of the human body and in the environment.

Is all this research really possible? It is possible that the need for the involvement of so many disciplines and fields of study make organization of combined research very difficult. One researcher has stated that not even the National Institute of Health (NIH) is organized enough to handle a well designed combined study (Jewett 1992). Further, nothing will ever be completed without funding.

Ziem and Davidoff (1992) explain how grants centered around environmental illnesses have been found to be funded less frequently compared to environmental research in other areas (OMB Review of CDC Research 1986). Standards and guidelines have been funded by those who would be economically affected by them. The most economically affected parties, besides the patients themselves, are insurance agencies and various industries. However, insurance agencies and industries have been found to fund psychology oriented health based studies more frequently than physiology based studies (Swaen and Meijers 1988). Funding needs to be secured from organizations beyond these interested parties. The possibility of government funding is unlikely until the mechanisms of the disorders are better defined.

Regardless of the cause of these non-specific, multi-system symptoms, the problem is real and is happening now. I could not end this paper better than by quoting two researchers from The Johns Hopkins University School of Hygiene and Public Health. Drs. Ziem and Davidoff (1992) wrote:

> 'Odor-related' complaints cannot ethically be dismissed as nontoxicologic curiosities. Of all nerves, the olfactory nerve has perhaps the closest and most intense contact with the chemical environment. Olfaction helps to protect us from chemical dangers. Alteration in olfactory function...may well represent a valuable indication of toxicity - perhaps an early warning sign of neurotoxicity... Whenever there are chemical odors, chemicals are present, and their toxicologic potential should be investigated seriously.

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