Capstone Project: Overview

Truly Man's Best Friend: Cancer Detection By Means Of Canine Olfaction

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When I was first considering my topic for this capstone project, I contemplated choosing the subject of chemistry. Most of my previous education had involved the study of biology; however, I struggled with the chemistry classes I was required to take. This was unsettling to me, since I knew that biology had its basis in chemistry. Therefore, I decided to pick a topic that dealt with biochemistry to challenge myself to better comprehend chemistry, yet still appeal to my interest in biology.

Having always enjoyed dogs and wanting to learn more about them, I narrowed my concentration in biochemistry to canines. One of my professors suggested that I research their olfactory system, specifically their use in detection of various materials. After investigating all the fields in which dogs are utilized for detection purposes, I decided that the most current and interesting would be cancer. As a dog-lover, I enjoyed learning about how “man’s best friend” was able to help us in the realm of medicine. I am confident that this same reasoning will be appealing to my students, since many of them have dogs as pets.

Studying canine detection required me to examine how the sense of smell worked in mammals. It was surprising to me that so little concrete information had been established prior to 1991 and that the functioning of the olfactory system is still not fully understood. I had always wondered why my students’ textbooks did not delve into this sense as much as the others and I look forward to sharing the reasoning for this omission with my pupils. This reaffirms one of the enduring understandings I have gained during this program: Science is constantly changing based on new discoveries.

The articles that I read explaining the ability of canines to detect cancer were fascinating. I was amazed that these animals were overwhelmingly successful at targeting the disease, especially in the cases where an individual that had volunteered as a healthy subject was confirmed as having cancer after a dog had indicated this. Reviewing scientific articles was also useful in reminding me to teach students the importance of clearly explaining scientific results and reaffirming the fact that the experiment processes used in middle school science are similar to those used by working scientists. This allows students to understand that science is a subject driven by questioning and can take place by anyone, at any time and location.

For my pedagogy piece, I decided to focus on having students hypothesize why dogs are able to smell odors that humans cannot. This is achieved through a unit on evolution that uses the development of a domesticated canine from a wolf as an example of how new species are formed. The topic of canine detection can also be referred to when teaching the concepts of olfaction, cancer, or genetics.

This capstone project gave me the opportunity to take a very current science topic, research it, and develop a unit that will demonstrate to students a number of valuable points. Aside from the actual science content, I will be able to share with my pupils the importance of non-human species on Earth, the fact that scientists do not have all the answers, the idea that there are constantly new advances and understandings in science, and the enthusiasm that they can become part of the discovery process by investigating the world around them.

Capstone Project: Science Content Component

Truly Man's Best Friend: Cancer Detection By Means Of Canine Olfaction

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August 26, 2007

Introduction

There is a new way to detect cancer, and it was right under our noses for years…well, not really our noses, but our favorite pets'. Throughout history, humans have utilized the talents of dogs. Though they may have originally been helpful in various stages of hunting prey, canines have now found themselves working to help humans herd other animals, locate people, drugs or explosive materials, or perform many other tasks. Now, a new niche for this species has been established in the medical field.

Dogs have already been trained to recognize chemical triggers that are emitted by people prior to their having seizures, as described in Nature ("Medical Dogs", n.d.). They are now being trained to detect cancer in humans because they have formerly been shown to do this on their own. This is yet another example of how the incredible olfactory system of *Canis familiaris* is being used to help us.

Physiology of Smell in Mammals

To understand how a canine has the ability to smell the chemicals involved in cancer, it is important to be able to follow an odorant molecule from its introduction to the body to its effect on the animal. This path was not explained until Axel & Buck's pivotal work described it in 1991, opening the doorway to this unexplored sense (Nobel Foundation, 2007). By applying knowledge of the working of the human and other mammals' sense of smell to canines, researchers have learned a great deal about the exceptional canine olfactory system. However, a complete picture of the complexities of smell in either organism has still not been determined. Therefore, although the current understanding of mammalian olfactory physiology will be included in this paper, research in this field has yet to provide total physiological details of the operation of this sense.

Basic Anatomy of the Olfactory System

Within the mammal's nose, there is a layer on the outer part of the nasal septum and specialized outcroppings (turbinates) within the nasal cavity called the olfactory epithelium, which contains millions of olfactory receptor neurons, or nerve cells (Nobel Foundation, 2007). Each olfactory neuron expresses only one of the olfactory receptor genes found in the genome. There are many of these genes. Indeed, an incredible three percent of all the genes in mammals are members of the olfactory receptor gene family

(Nobel Foundation, 2007). These genes are distributed across a large number of chromosomes, which points to the complexity of the sense of smell (Hatt, 2004). Even a simple sperm cell seems to have all the components of an olfactory neuron and has been shown to alter its behavior in the presence of certain odorants (Hatt, 2004). The existence of olfactory components in this "pre-development" cell indicates the importance of smell in all mammals.

There are three types of cells in the olfactory epithelium. First is the olfactory neuron, or nerve cell, which is responsible for receiving odorant molecules and sending information about them to the brain where this information is interpreted (Figure 1). Second, there are supporting cells surrounding the neuron. Finally, there are stem cells which can generate either neurons or support cells. These stem cells are unique in that they constantly reproduce, creating 30 million new olfactory neurons in less than a month in humans (Hatt, 2004), compared to other neurons which typically are not replaced throughout life.

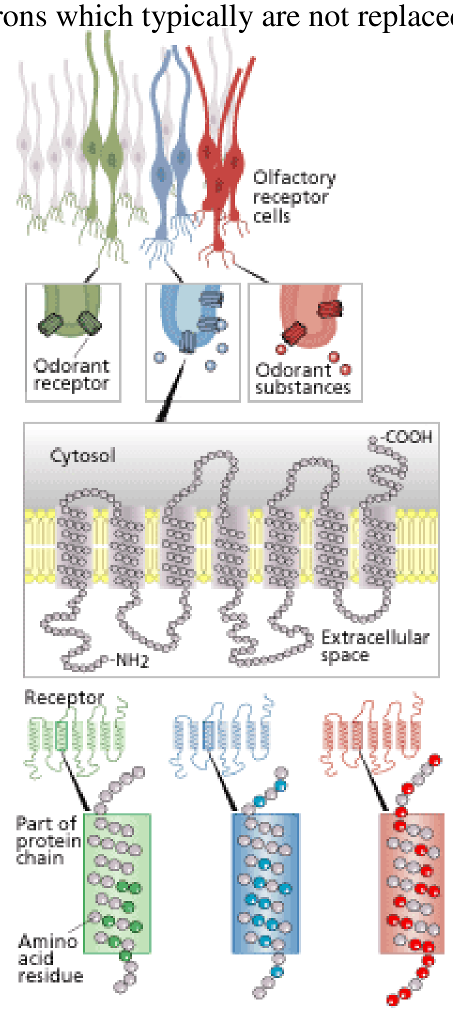
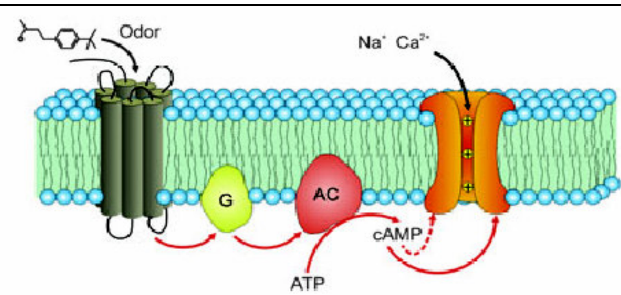


Figure 1: from Nobel Foundation, 2007. Shows each level of organization from cell to protein chain of receptor.

How an Odorant Molecule is Detected in the Nose

A specific type of odorant molecule is recognized by multiple neurons, which may be spread out across a large area of the epithelium. At one end of the cell is an apical dendrite, or neuron extension, that has hair-like cilia protruding into the nasal mucus. These cilia contain the olfactory receptor proteins and are bathed in mucus (Hatt, 2004). When an odor molecule that is capable of activating the sensory cell comes in contact with the protein, it sets off a sequence of events in a G-protein-coupled receptor that traverses the cell 7 times (Nobel Foundation, 2007). This type of receptor works in a system by binding molecules and activating, through a series of steps, a messenger molecule (Kimball, 2002). In this reaction, the messenger in the cell's cytoplasm is cAMP, or cyclic adenosine monophosphate. The cAMP molecule changes the shape of a protein channel in the cell membrane so that it can allow ions to pass through it (Hatt, 2004). When the channel is opened, calcium cations, or charged atoms, rush into the cell and depolarize it (Hatt, 2004) (Figure 2). When a cell is depolarized, it has taken in positively charged atoms, which reduces its resting potential (Kimball, 2003). Eventually, as more and more positively charged atoms enter the cell, the cell reaches its depolarization threshold, and an action potential is created. This action potential, or impulse, is fired through to the end of the olfactory neuron that is opposite of the dendrites, which is know as the axon. In summary, this is how the odorant molecule changes the cell's chemistry to create a message carrying the odorant's identity.

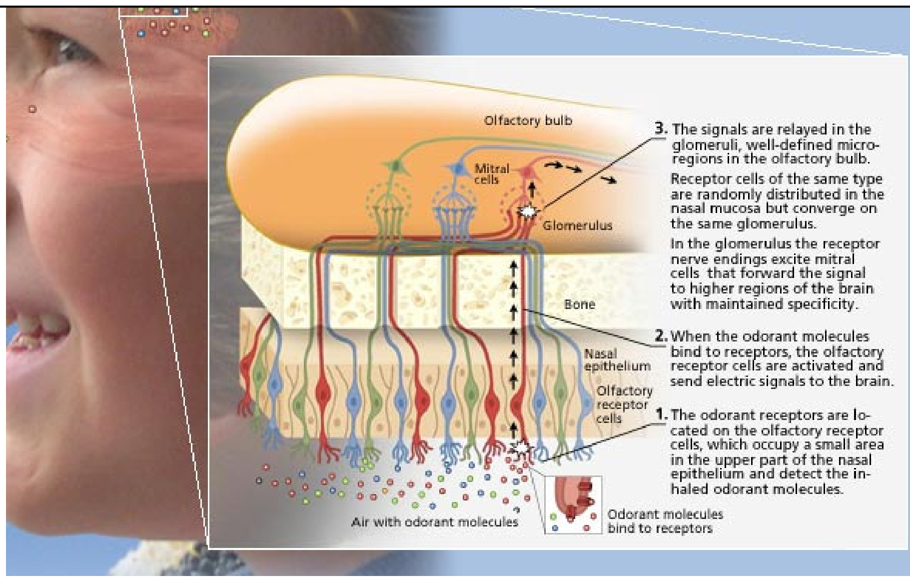
Figure 2: from Hatt, 2004. Shows how an odorant activated the G-protein-coupled receptor embedded in the cell membrane, leading to the depolarization of the cell



Schematic representation of the cAMP-mediated transduction pathway operating in the sensory cilia of olfactory-receptor neurons

Opposite the end containing the dendrites is the axon of the cell. The axons of the neurons of these sensory cells stretch up out of the olfactory epithelium, through the nasal bone, and into the olfactory bulb (Nobel Foundation, 2007). All of the axons of cells that express the same molecular receptor gene meet within the same glomerulus, which is a specific site in the olfactory bulb. After the impulse reaches the glomerulus, it crosses a synapse, or space, to stimulate the dendrite of a mitral cell. This cell sends the message to the cerebrum of the brain to be interpreted (Figure 3). Because of this direct communication with the evolutionarily-advanced cerebrum, the sense of smell is unique, since all other sensory impulses must be regulated by the thalamus, a separate part of the brain responsible for relaying information to the cerebrum to be processed. This may be due to the fact that olfactory responses in animals known as macrosmatic animals, such as dogs, are heavily relied upon in processing information about the environment.

Figure 3: from Nobel Foundation, 2007. Shows the process of smell from odorants to mitral cells.



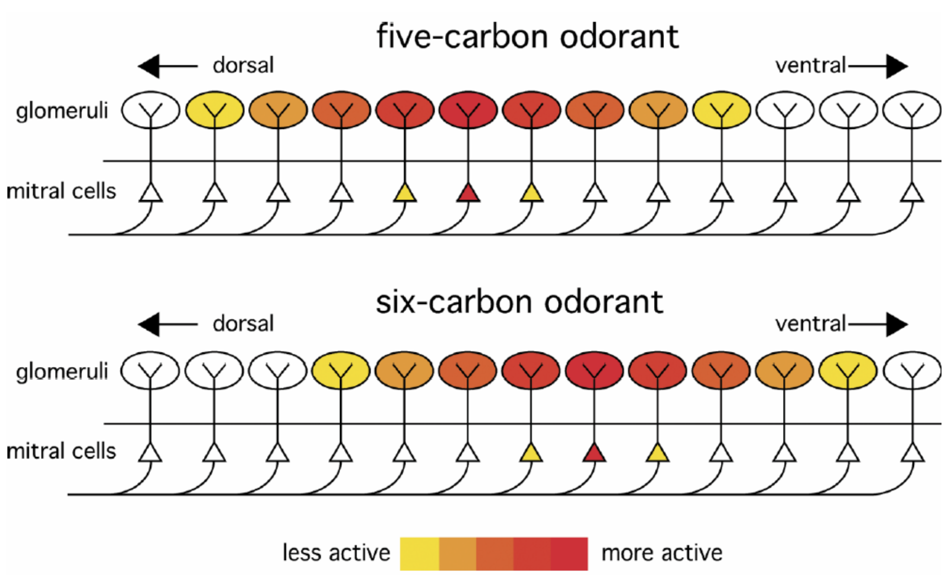
Smell is complicated because an odorant molecule could stimulate any one of many different types of receptor cells, and the receiving proteins on the cells can be activated by a number of different odors. This generates the belief that there is a code by which specific odors are identified, based on which receptors were activated (Nobel Foundation, 2007). While the codes may be similar in all members of a species, it is not yet known whether the actual pattern is genetic or learned, or a combination of both.

However, researchers are currently attempting to determine a pattern in the body through which smells are interpreted.

How Impulses are Interpreted in the Brain

Through imaging, scientists have observed that the part of the olfactory bulb that is stimulated depends on which odorant is present. These sections of the bulb are the same in many animals exposed to the same odorant (Johnson & Leon, 2007). Glomeruli have been shown to become activated based on structural features of the odorant molecule or its physical properties (Johnson & Leon, 2007). Molecules that are more flexible, meaning they have more conformations, activate multiple areas of the glomeruli, whereas smaller molecules only stimulate a limited number of a glomeruli (Johnson & Leon, 2007). Molecules that have similar functional groups or properties, such as water solubility, stimulate the same region of glomeruli, but still maintain a unique position within the group of glomeruli (Johnson & Leon, 2007). Also, sequential patterns can be observed, such as the shifting path throughout the glomeruli that would occur as odorant molecules that have an increasing number of carbon atoms within them were presented to an animal to smell (Figure 4).

Figure 4: from Johnson & Leon, 2007. Shows difference between mitral cells and glomeruli activated by a five-carbon odorant and a six-carbon odorant.



There are two ideas for how similar odorants activate glomeruli. One is that more water-soluble odorant molecules are absorbed by the mucus soon after inhalation, which initiate impulses that are sent to the dorsal olfactory bulb, while less water-soluble molecules, which are more difficult to absorb, diffuse to the back of the olfactory epithelium and trigger impulses that connect to the ventral olfactory bulb. Another explanation is that shorter molecules are sent to the dorsal areas while longer molecules stimulate areas in the ventral part of the bulb (Johnson & Leon, 2007). Regardless of how these maps of olfactory regions are formed, epithelial chromatography, a process that involves the separation of various chemicals, has shown that the molecules that are absorbed in specific areas of the nose correspond to where the impulse from the neuron will be sent, and where the molecule is absorbed depends on some aspect of its chemistry.

The reasoning for the patterns observed in glomerular activation is not yet known. However, some suggestions for the purpose of these patterns are that the responses of "nearby glomeruli can be 'compared'…to produce a pattern of mitral cell output that is more distinct with respect to these similar odorants" (Johnson & Leon, 2007, p. 10).

Different concentrations of a substance seem to have an effect on the activity in a glomerulus. However, the observations of this activity may not be a result of the input from the neurons, but rather the responses that are coming out of the olfactory bulb. It is hypothesized that there are regulatory cells that can detect the activation of glomeruli throughout the olfactory bulb, and adjust which mitral cells to fire based on the number of glomeruli that are receiving information (Johnson & Leon, 2007). Therefore, the olfactory system recognizes increases in odor concentration, but this may not be reflected in how the brain perceives the information. More research in this area can be useful in discovering the effectiveness of canine cancer detection during different stages of the disease.

Based on evidence of both mammals and other animals, it seems that there is a way that odor mixtures are evaluated. It is thought that odorants must compete for receptors and this has an effect on the reaction to the smell (Johnson & Leon, 2007). The importance of this in cancer detection studies is crucial, since odors from this disease are found in combination with others, such as those found in breath or urine.

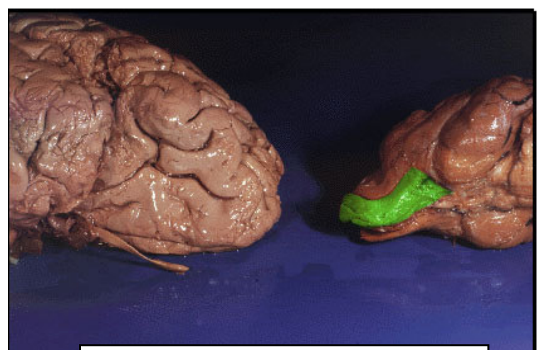
In summary, there seems to be patterns among which odorant molecules are recognized by various glomeruli, which glomeruli stimulate certain mitral cells, and how these mitral cells distribute impulses to create responses to smells. However, unlike most other senses, there is not yet a definitive map of how this complex, evolutionarily constructed process occurs.

The Olfactory System of a Dog

Dogs have a large surface of olfactory epithelium, almost twenty times greater than humans, which suggests that they have more olfactory neurons also (Rouquier & Giorgi, 2006). The olfactory bulb is larger in dogs than humans, since dogs are macrosmatic. Humans are known as microsmatic (having a poor sense of smell) animals, which suggests that they rely on other senses more heavily to interpret the world around them. The physical appearance of the brains of humans and dogs clearly shows the difference in their ability to use smell as an indicator of their environment (Figure 5).

Figure 5: from "Comparisons:olfactory systems," n.d. Shows difference between the size of the olfactory bulbs of humans and dogs.

Human olfactory bulb – highlighted in green



Dog olfactory bulb – highlighted in green

The number of functional genes responsible for smell is larger in dogs. A dog has 80% working olfactory receptor genes and 20% pseudogenes, which are non-functioning (Quignon *et al*., 2005). Humans have a similar number of olfactory receptor genes, but approximately two-thirds of them are non-functional (C. Wysocki, personal communication, August 2, 2007). Also, dogs utilize sniffing to maximize the air that is breathed into the nose. A nasal pocket is created that holds odorant molecules within it. By taking short, rapid breaths, more air accumulates in the olfactory epithelium, allowing odorant molecules to be more thoroughly absorbed into the olfactory system (Correa, 2005).

There is not yet conclusive evidence for the idea that pheromones play a role in the process of detection in canines. However, new research on the vomeronasal organ, or Jacobson's organ, may prove to be useful in the understanding of how canines detect cancer. The vomeronasal organ, which is located above the roof of the mouth, is an additional sense organ in many animals that is used to detect chemicals used in such events as pregnancy, mammalian nursing, territorial marking, etc (Wysocki & Preti, in press). Some of these chemicals, known as modulator pheromones, adjust behavior according to a stimulus. These were first investigated in humans, but it is thought that other mammals may have the same pheromones. For example, it has been shown that mice that are placed in stressful situations, such as a being trapped in a cage that sends electrical shocks to them, emit an altered body odor which can be transmitted to other mice. These mice, in turn, will avoid that cage (Wysocki & Preti, in press). These pheromones may be involved in a dog's ability to detect the body's stress in response to cancer. However, some research indicates that the canine vomeronasal organ is not well-developed, since it is thin and not as complex as the olfactory system (Rouquier & Giorgi, 2006). Therefore, the possibility of the use of this organ in canine detection is still questionable.

Though the sense of smell remains an important one in humans, it is not as complex as that which is found in dogs. Early humans realized the potential of using dogs to their advantage when they began rewarding them during different stages of hunting. This produced many different breeds of working dogs with different advantageous characteristics (Tyson, 2004). More recently, dogs have been trained to detect not only devices and chemicals, but also injured humans in search-and-rescue operations, as described by NOVA ("Working Dogs," 2004). This ability to pick up on the scent of a sick human may be part of dog evolution that we may be able to use for medical purposes.

Training Canines to Detect Cancer in Humans

When early humans began domesticating dogs and developing breeds, one of the groups of dogs became today's retrievers, which are able to smell and locate an injured animal, as Nature explored ("Hard-wired behaviors," n.d.). This ability to detect illness may be an evolutionary adaptation that has been carried in dog DNA since dogs were more closely related to wolves. The reason for this is that wolf packs tend to sense and hunt the more sick or weak members of a herd (Zoological Society of San Diego, 2007). Therefore, it may be assumed that a dog is genetically programmed to detect illness in other animals.

Using this advanced olfactory system to our advantage, a new frontier in medicine is being explored. Canine detection of cancer and other diseases is being evaluated for its effectiveness, early detection of the disease, financial savings, and specific methods of olfactory analysis for possible mechanical or chemical analogs.

First reports of detection

In 1989, Hywel Williams and Andres Pembroke reported a case of a woman whose dog, a mix of a Border collie and Doberman, continually sniffed a lesion on her thigh. After months of obsessing over this one of many moles on the owner's body, the dog eventually tried to bite off the mark on a day when the woman was wearing shorts. This concerned the woman enough to have her doctor evaluate the area, which led to a biopsy and diagnosis of melanoma. Williams & Pembroke (1989) hypothesized that dogs may possess the ability to smell cancer. This seems to be the first reported suggestion of the use of canines in a cancer clinic.

A similar story was reported involving a man who had a patch of irritated skin for over 18 years (Church & Williams, 2001). Until his new Labrador began to show increasing interest in that particular section of his body, the patient was not overly concerned with it. However, upon medical review of the area following the man's suspicion about the dog's behavior, it was discovered that the man had basal cell carcinoma. Once the lesion was removed, the pet no longer sniffed at that area.

Based on incidences such as these, researchers began to develop scientifically-designed studies to determine the potential of using canines in cancer detection. This idea was supported by the history of this species' training and utilization in the detection of drugs, explosives, missing persons, hunted prey, and even forewarning the onset of a seizure. Scientists, recognizing the complexity of the canine olfactory system, decided to test dogs' abilities to smell varying types of cancer at different stages of the disease. Many successful attempts have shown promise in the future of cancer diagnosis by dogs or analogous instrumentation.

Bladder cancer: Proof of principle study

One of the first benchmark studies in this field was reported by Willis et al in 2004. The objective of their research was to "determine whether dogs can be trained to identify people with bladder cancer on the basis of urine odour more successfully than would be expected by chance alone" (Willis *et al*, 2004, p. 712). Participants in this study included a number of healthy individuals, those with varying stages of previously-diagnosed bladder cancer, and others with various non-cancerous urinary conditions.

In this experiment, samples of both healthy and diseased participants' urine were pipetted on filter paper in Petri dishes (Willis *et al*, 2004). Six dogs were trained to lie beside the one of seven samples that contained urine from a person with bladder cancer, ignoring the other six that were from undiagnosed people. Some of the dogs were exposed to dry urine and some to wet, but those that sniffed the wet samples performed better. This was believed to have occurred because the wet samples had not lost as many of the volatile organic chemicals (VOCs). VOCs are chemicals that will evaporate when they come in contact with air.

Training dogs to recognize the chemicals in cancer was more difficult than previously done with other substances because the single cause of the odor is unknown (Willis *et al*, 2004). Therefore, it was important for the researchers to include participants with different stages of cancer so that the dogs might be able to detect a similar odor in all of the urine samples collected from cancerous patients. The only previous evidence of a "cancer odor signature" from mechanical methods was an increase in formaldehyde, alkanes, and benzene derivatives in some previously researched cancers (Willis *et al*, 2004, p. 715).

The overall results showed that trained canines were able to successfully detect the dish containing the urine from a patient with cancer 41% of the time. The two most successful dogs in this experiment were both working strain Cocker Spaniels tested with wet samples, one a two-year-old female, and one a one-and-a-half-year-old male.

This study generated scientific confidence in the idea that canines can be trained to recognize some chemical(s) that is present in the bodies of cancer sufferers. It provided other scientists a platform on which to base future investigations in this field.

Melanoma detection

Around the same time as the previously mentioned study, another group of scientists was approaching the idea of canine detection of cancer in a different way. This study focused on melanoma instead of bladder cancer, which was a more direct association with the original Williams and Pembroke report (Pickel, Manucy, Walker, Hall, & Walker, 2004). Two experienced detection dogs were used in this experiment, a Schnauzer and a Golden Retriever. These dogs achieved such great successes with the original series of tests that three subsequent modifications to the original technique were also performed.

At first, the dogs were trained to retrieve a perforated piece of PVC tube that contained a mixture of cancerous skin tissue. The pipe was thrown into a grassy area containing a number of other tubes and the dog was to return with the one containing the diseased specimen. Though these initials results were not recorded, the dogs proved successful enough to be tested in a more challenging way. Next, the trained animals were exposed to melanoma tissue wrapped in gauze, which was placed in a compartmentalized box. In the ten sections of the box, one section had the sample and a varying number contained distracting items that might be found in a hospital setting, such as gauze or latex gloves. Each dog was trained to give a response to the compartment with the cancer sample, either by pawing at it or mouthing at the opening, depending on the dog. Again, both canines performed very well in this test (Pickel *et al*., 2004).

Once successes were demonstrated in these trials, the researchers began a new phase of study that involved planting melanoma tissue samples on healthy volunteers. After training, the dogs were led by a trainer to a volunteer laying on his/her back whom had a number of adhesive bandages placed on him/her. One of these bandages had a previously frozen and thawed melanoma sample beneath it, and anywhere from three to thirty-four other bandages with only gauze inside them. The trainer was unaware of whether or not a sample was actually present. Both dogs correctly identified all cancerous tissues in these tests.

Finally, the most medically-useful test was executed. Patients from a clinic who were suspected of having melanoma were immediately brought to the testing site. The body-sites in question along with seven to twenty-nine "healthy" sites were covered in adhesive bandages. The dogs were led into the room where the participants were lying, and used the previously mentioned recognition signals to indicate the spot at which the cancer was located. In most of these trials, the dogs were able to find the bandage covering the suspected cancer.

This research project provided evidence to support the hypothesis that canines can detect cancer in various ways. It also indicates that cancer has a scent associated with it that is different than that of a healthy person.

Breast and lung cancer detection

A more recent study in 2006 involved the detection of breast and lung cancers. McCulloch *et al.* (2006) attempted to rapidly train dogs that had no prior scent detection experience to distinguish breath samples of lung and breast cancer patients from those of healthy volunteers to determine if a dog's abilities were hindered by other factors, such as age, smoking, or most recent meal.

Recruited patients had not yet undergone chemotherapy, since the researchers presumed that this might alter the exhaled breath in a different way than simply the cancer alone would. Also, participants with varying stages of the disease were enlisted to ensure that dogs would be able to detect any progression of the disease because it was suspected that the longer a person had the illness, the larger the tumors would be, causing more chemicals to be emitted.

For this investigation, McCulloch *et al.* gathered breath samples in a cylindrical polypropylene organic vapor sampling tube. This equipment contained fibers that would capture organic compounds during exhalation. Patients were instructed to breathe into the tube as long and deeply as possible and a number of samples were collected from each subject.

Five dogs with only basic obedience training were selected, three of which were Labrador retrievers and two of which were Portuguese water dogs. A reward-based approach was used to encourage dogs to locate the one station among five in a room that contained a cancerous sample. The correct response indicator was sitting or lying down in front of the station, and sniffing but not responding to the sample was considered a true negative reaction. After training was completed, a similar approach was taken using either four blank, control, or a combination of other samples in addition to the one containing breaths from a cancer victim. First, the dog's handler was blind to the placement of the target sample, and then both the trainer and experimenter were ignorant of the location in the double-blind portion of the experiment.

The results of this research showed that the sensitivity of the detection was 99% for lung cancer and 88% for breast cancer. The stage of the disease did not have an effect on the results. It was determined that the indication of the presence of cancer was not learned in a systematic way, but rather was a pure identification of it by the dog. Age, past smoking, and most recent meal ingested showed no statistically significant effect on the outcomes of the trials.

McCulloch *et al.* suggested that the promising results of this study show that other dogs would provide the same outcomes, if they were properly trained. They also stated that "breath analysis may provide a substantial reduction in the uncertainty currently seen in cancer diagnosis" (McCulloch *et al*., 2006, p. 38). However, the authors do note that dogs may have detected "odors associated with cancer, such as inflammation, infection, or necrosis rather than…cancer specifically" (Mc Culloch *et al*., 2006, p. 37).

Summary of Canine Cancer Detection Studies

The success of canine cancer detection in multiple types and stages of the disease, regardless of the methods used in training, provides a basis for the understanding of the sense smell in mammals as well as the potential for the use of canines in future illness detection. Canines have shown to be either as or more correct as other non-invasive strategies in finding cancer.

It is interesting to note that in each of the research projects, there was at least one instance of a dog correctly identifying cancer in a victim that was unaware of the presence of the disease in his/her body. These were participants whom had volunteered to be healthy subjects at the start of the experiment, but were eventually diagnosed with cancer by a doctor following the dog's behavior during the tests. This provides strong evidence that canines are able to sense a difference in the smell of a person who is unhealthy even in the early stages of the disease, when other methods of detection are not successful. It also shows that the Clever Hans effect, where a human is unknowingly cueing the appropriate response to an animal through certain actions, it not a factor in these instances.

Canine cancer detection would be an inexpensive and non-invasive method that may prove to be useful in early diagnosis or in the development of similar technology that can be utilized in the same way. However, unless the specific compounds that are produced in a sick person can be isolated, it will be difficult to create equipment that will target the smell of cancer. There have been chemicals that were suggested to be the possible volatile ones that are emitted by people with cancer. One of these is butane, an alkane with four carbon atoms, which may not be a molecule from the tumor itself, but rather from the stress in a cell that cancer causes (Phillips *et al*., 2003). This uncertainty is creating difficulty in pinpointing the exact difference in smell between a healthy and unhealthy person.

Humans have benefited from dogs' incredible olfactory systems for thousands of years, from the very first trained hunting dogs to the drug and explosive detection canines of today. The medical field is one of the newest frontiers in canine detection, and promises to be useful in early diagnosis of various diseases in the future. What we have lost in the evolution of our nervous and sensory systems we compensate for in the ability to harness the power of other organisms' adaptations. In this way, we provide a mutually beneficial relationship between both humans and dogs.

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