The Scent of Nobel Prize Success

"The sense of smell long remained the most enigmatic of our senses", noted the Nobel Assembly in Sweden, announcing the winners of the 2004 Nobel Prize in Physiology or Medicine. Richard Axel, 58, of the Howard Hughes Medical Institute at New York's Columbia University and Linda Buck, 57, of the Fred Hutchinson Cancer Research Center in Seattle share the $1.36 million prize in recognition of their "pioneering" solution to the neurochemical riddle of how people discern individual smells.

Smell is one of our two chemical senses – the other being taste –, so called because smells are, of course, chemicals. With these senses we probe our environment for information. We are continuously testing the quality of the air we breathe – this can alert us to potential dangers, such as smoke – as well as using our sense of smell to acquire other important information, for example, the proximity of food or of another individual. The chemicals detected by our sensory systems need to have certain properties. For instance, odorant molecules must be small enough to be volatile (less than 300-400 relative molecular mass) so that they can vaporise, reach the nose and dissolve in the mucus. Hence, smell, unlike taste, is a sense that picks up signals over long distances (thereby serving as an early warning device). We appear to have an innate ability to detect bad or unpleasant smells.

As the Nobel Assembly pointed out, until now the basic principles for recognizing and remembering about 10,000 different odours were not understood. This year's Nobel Laureates in Physiology or Medicine have solved this problem and in a series of pioneering studies clarified how our olfactory system works. They discovered a large gene family, comprised of some 1,000 different genes (three per cent of our genes) that give rise to an equivalent number of olfactory receptor types. These receptors are located on the olfactory receptor cells, which occupy a small area in the upper part of the nasal epithelium and detect the inhaled odorant molecules.

It was in a 1991 paper in the journal Cell, that the pair first revealed that an extensive family of genes produced by olfactory cells are capable of differentiating at least 10,000 separate smells. It was a landmark in the understanding of our sense of smell. Later studies showed that about 350 smell sensors, or "olfactory receptors", embedded in olfactory cells are derived from the gene family identified by Buck and Axel. In their subsequent, separate research, Buck and Axel showed how the olfactory cells are organized and how the brain weaves individual signals from these cells into patterns that we recognize as distinct smells. Buck compared the system to the alphabet, in which 26 letters can combine to form countless words.

Our olfactory system does more than just give us warnings. It also serves a recognition function. Smell and memory are closely linked. Smell evokes memories. Damage to the temporal cortical region of the brain does not affect the ability to detect a smell, but, rather, the ability to identify it. We have to be able to remember a smell before we can identify it. Particular smells can trigger distinct memories from our childhood and evoke emotions – positive and negative – experienced later in life. A single clam that was not fresh and made us ill will leave a memory that stays with us for years, and make us unable to partake of any dish, however delicious, that has clams in it. To lose the sense of smell is a serious handicap: with it, we lose our ability to perceive the quality of food, for example, or to pick up warning signals, such as the smoke from a fire.

In the literary field, Marcel Proust is associated with the phenomenon of memory recall in response to specific smells. Whole memories, complete with all the attendant emotions, can be triggered by a smell, a process that is entirely unconscious and that cannot necessarily be induced voluntarily. That said, countless studies have shown that recall can be enhanced if learning was done in the presence of a particular smell and if that same smell is used to prompt recall. As we age, our sense of smell diminishes. The same applies to our sense of taste: indeed, food seems to lose its flavour as we get older. Eighty per cent of 80-year-olds have some major smell dysfunction and 50% are "anosmic" by the standards of young people. Not only do we lose our sense of smell, we also lose our ability to discriminate between smells. Women, whose sensitivity to smell also diminishes with age, perform better than men at all ages. Patients with neurodegenerative diseases, such as Alzheimer's disease, suffer olfactory losses – in
Olfaction is an evolutionarily conserved sense

We can recognize 10,000 different odours

deed, even very early stage Alzheimer’s patients show a loss of sensitivity to smell – and, according to the United States’ National Institute on Deafness and Other Communication Disorders, about 200,000 Americans report some loss of their sense of smell every year, usually due to head trauma, sinus ailments or infection. These people are around twice as likely as those with a normal sense of smell, to have some kind of accident, such as eating spoiled food or not smelling leaking gas.

All living organisms can detect and identify chemical substances in their environment. It is obviously of great survival value to be able to identify suitable food and avoid that which is putrid or unfit. Smell is what enables a newborn mammalian pup to find the teats of its mother and obtain milk – without olfaction the pup cannot survive unaffected. Olfaction is also of paramount importance for many adult animals, since they observe and interpret their environment largely through the sense of smell. For example, the area of the olfactory epithelium in dogs is some forty times greater than in humans. Studies of the smell receptor genes in fish and mice underlined their relative importance to different species. Mice possess far more than people, about 1,000 genes, and fish possess far fewer. In more recent work, Buck has found that receptors may underlie the sense of taste, identifying sweetness and bitterness receptors. Axel has pioneered a mouse model of the sense of smell in insects.

The olfactory system is the first of our sensory systems to be deciphered primarily using molecular techniques. When an odorant receptor is activated by an odorant substance, an electric signal is triggered in the olfactory receptor cell and sent to the brain via nerve processes. Each odorant receptor first activates a G protein, to which it is coupled. The G protein in turn stimulates the formation of cAMP (cyclic AMP). This messenger molecule activates ion channels, which are opened and the cell is activated. Axell and Buck showed that the large family of odorant receptors belongs to the G protein-coupled receptors (GPCR). All the odorant receptors are related proteins but differ in certain details, which explains why they are triggered by different odorant molecules. Each receptor consists of a chain of amino acids that is anchored into the cell membrane and traverses it seven times. The chain creates a binding pocket where the odorant can attach. When that happens, the shape of the receptor protein is altered, leading to G protein activation.

Independently, Axel and Buck showed that every single olfactory receptor cell expresses one and only one of the odorant receptor genes. Thus, there are as many types of olfactory receptor cell as there are odorant receptors. It was shown, by registering the electrical signals coming from single olfactory receptor cells, that each cell does not act only to one odorant substance, but to several related molecules – albeit with varying intensity.

Buck’s research group examined the sensitivity of individual olfactory receptor cells to specific odors. By means of a pipette, they emptied the contents of each cell and showed exactly which odorant receptor gene was expressed in that cell. In this way, they were able to correlate the response to a specific odorant with the particular type of receptor carried by that cell. Most smells are composed of multiple odorant molecules, and each odorant molecule activates several odorant receptors. This leads to a combinatorial code forming an “odorant pattern”, rather like the pattern of a patchwork quilt or a mosaic. This is the basis of our ability to recognize and form memories of approximately 10,000 different smells.

The finding that each olfactory receptor cell only expresses one single odorant receptor gene was highly unexpected. Axel and Buck went on to clarify the organization of the first relay station in the brain. The olfactory receptor cell sends its nerve processes to the olfactory bulb, where there are some 2,000 well-defined microregions, glomeruli. There are thus about twice as many glomeruli as there are types of olfactory receptor cell. Axel and Buck independently showed that the processes of receptor cells carrying the same type of receptor converge into the same glomerulus, and Axel’s research group used sophisticated genetic technology to demonstrate, in mice, the role of the receptor in this process. The convergence of information from cells with the same receptor into the same glomerulus demonstrated that the glomeruli, too, exhibit remarkable specificity.

In the glomeruli we find not only the nerve processes from the olfactory receptor cells but also their contacts with the next level of nerve cells, the mitral cells. Each mitral cell is activated by only one glomerulus, and the specificity in the information flow is thereby maintained. Via long nerve processes, the mitral cells send the information to several parts of the brain. Buck showed that these nerve signals in turn reach defined microregions in the brain cortex. Here, the information from several types of odorant receptor is combined into a pattern characteristic for each smell. This is interpreted and leads to the conscious experience of a recognizable smell.