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The Nobel Prize for mapping the sense of smell (the olfactory sense)

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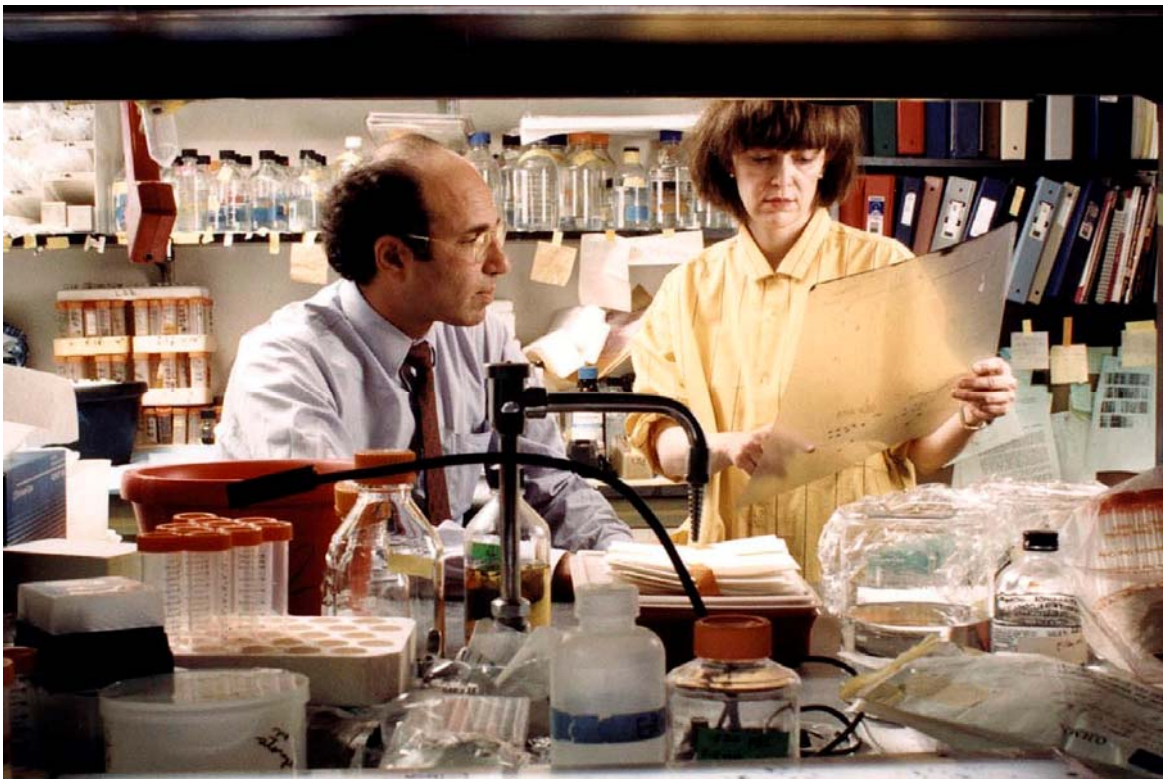
The Nobel Prize in physiology or medicine for the year 2004 honours the discovery of smell receptors and the organisation of the olfactory sense. The laureates, Richard Axel and Linda Buck, both work in USA.

It was only when molecular genetics became sophisticated enough, among other things enabling mass production of DNA thanks to the PCR technique, that one of our most complicated senses, the olfactory sense, could be mapped in detail. The basic discovery for which Richard Axel and Linda Buck now are being honoured was published in the journal The Cell in April 1991. In there they described the family of smell receptor genes that code for the receptors in the nasal olfactoy epithelium which enable the ability to discern about 10 000 different odours.

The researchers Buck and Axel used mice in their studies. Their results, in combination with later findings, have shown that 3 percent of the genes in mammals form up to about 1 000 different scent receptors. In humans it is estimated that there are about 600-700. Since most odours comprise several scents, and each one of them activates different receptors, a “scent pat-



It was the collaboration between Richard Axel and Linda Buck between 1982 och 1991 in the research group of Axel in New York that led to the discoveries that are rewarded by the Nobel Prize in physiology or medicine this year.

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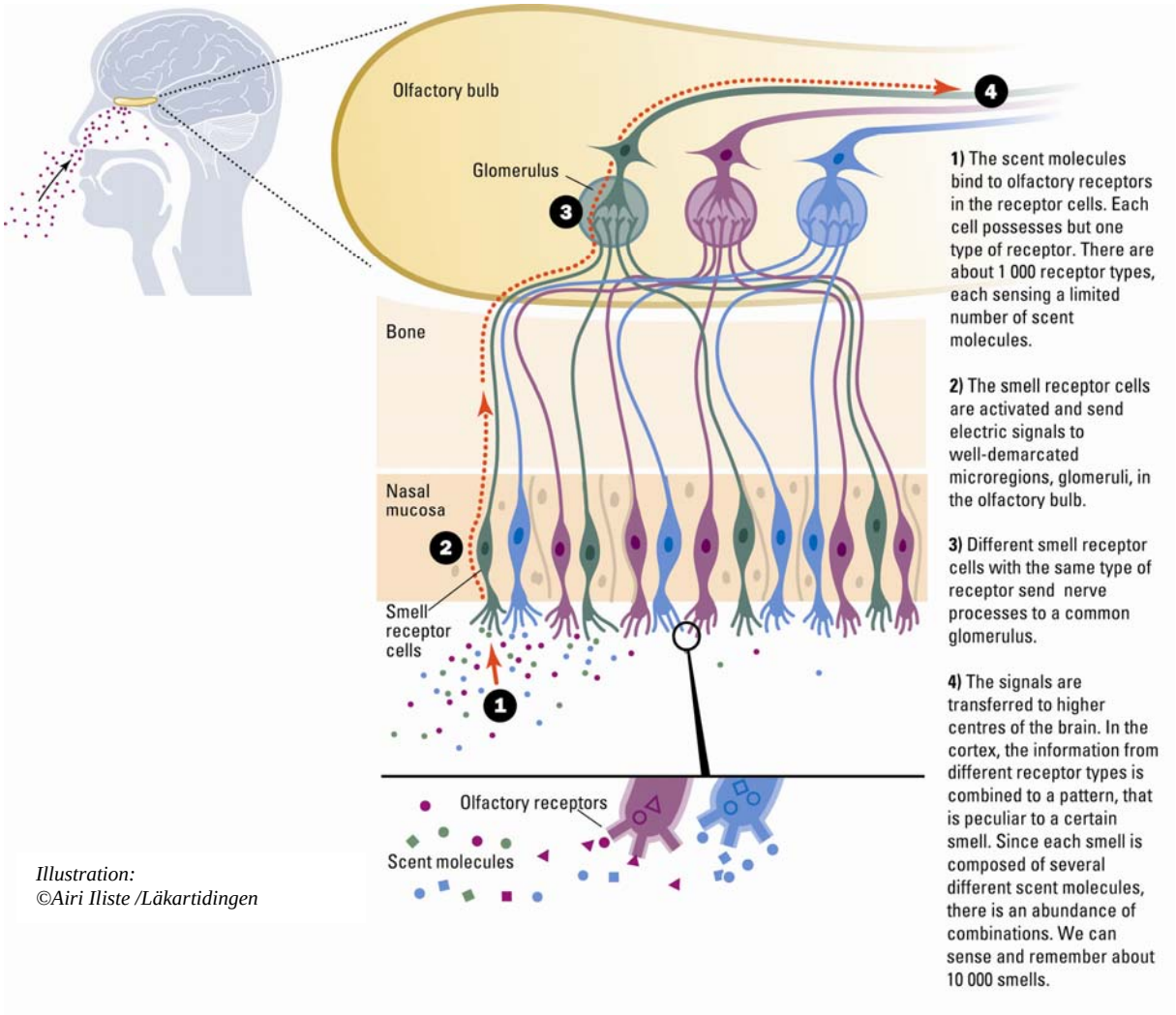
tern" is created that we recognise – remember – as a special odour.

— Before Buck and Axel presented their studies the sense of smell was a mystery. Already 100 years ago we knew that there were olfactory receptor cells in the nasal epithelium but besides that there were only speculations, Professor Sten Grillner, a member of the Nobel committee, explained when this year's Nobel laureates were presented.



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1 000 different kinds of olfactory receptors

Richard Axel and Linda Buck have shown in their research that the olfactory receptors belong to the group of receptors, which are combined with so called G-proteins. G-proteins activate the formation of a messenger molecule in the cell when the receptors are stimulated by an odour. The messenger molecule, cAMP, influences the ion channels of the cell to open up and the cell can be activated. The discovery of G-proteins was awarded with the Nobel prize in physiology or medicine in 1994, when Martin Rodbell and Alfred G. Gilman in the USA received it.

Richard Axel and Linda Buck have also shown that each

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single olfactory receptor cell only expresses one of the approximately 1 000 different scent receptors in the animal model. This means that there are as many types of olfactory receptor cells as there are types of scent receptors.

By recording electric signals (impulses) from single olfactory receptor cells, Axel and Buck have been able to show how a single cell reacts not only to one molecule but to several similar molecules, but with varying sensitivity. Small differences in the structure of the receptor molecule will determine with which scent the cell will react. In order to decide which gene that is expressed, and which single receptor molecule that is activated by a special odour, each of these cells was drained of their contents when they had been stimulated by a scent.

In their further research the couple has also studied how the olfactory receptor cells send their signals via nerve fibres to the olfactory bulb, where about 2 000 micro-regions, glomeruli, register the signals. Olfactory receptor cells that express the same scent receptor, send their nerve fibres so they unite in one and the same of these micro-regions. In this way the results showed that each one of these regions is highly specialized in receiving signals from the olfactory receptor cells.

The signals from the olfactory receptor cells finally reach the cortex of the brain via the mitral cells of the olfactory bulb. Each single micro-region of the bulb activates one mitral cell via the processes of this cell. These signals reach different regions of the cerebral cortex, where the information from different types of olfactory receptors is combined into a pattern, which is special for each smell(odour). What we then identify as a smell, after the mixing from different activated regions in the cortex, is built on our earlier learning.

Valid also for other senses

When Richard Axel and Linda Buck published their results in 1991 they had been cooperating since 1982, when Linda Buck joined Richard Axel's research group as a postdoc at Howard Hughes Medical Institute, Columbia University in New York. They started their research on the olfactory sense in 1988.

After 1991 Linda Buck left New York and is now working at Fred Hutchinson Cancer Research Center in Seattle. Richard Axel is still at Columbia University. They have both continued their research on the olfactory sense and have each separately published several scientific articles.

Both researchers have independently of each other, shown that many of the principles of the olfactory sense are also relevant for other senses, *e.g.*, pheromones which are molecules which have an influence on different kinds of behaviour in animals. Axel and Buck have shown in different studies that these molecules can affect other families of receptors on the cell, recep-

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tors that like the olfactory ones are coupled to G-proteins, but that are located in a quite different part of the nasal epithelium. Yet another family of receptors coupled to G-proteins have been found on the taste buds of the tongue.

Fewer scent receptors in humans

Nobody knows exactly how many types of scent receptors there are in the human nasal epithelium. The estimate of 600-700 genes is made from animal models where about 3 per cent of the genome expresses specific scent receptors. In fact no studies have been made on primates to find out the number of scent receptor genes. Most likely man has lost some genes for scent receptors during evolution.

In zebra fishes the corresponding number is 100 genes. The very sensitive olfactory sense in dogs is most likely explained by the epithelial surface being about 40 times larger than in man, not because the number of different types of scent receptors would be much higher.

The olfactory sense and the mapping of its structure is regarded as a very important scientific step forward – not least because of its role in our experience of security - it gives us memories from long ago and warns us of dangerous matters or unsafe food. The olfactory sense plays a major role also for our survival, and people who have lost part of this sense can testify about a impaired quality of life. In addition, a damaged olfactory sense is also irrevocably lost.

Will these findings, for which Richard Axel and Linda Buck are being honoured, help in diagnostic or terapeutic applications on humans?

— This is primarily a prize in physiology. All our senses are used a lot more than we think and in contrast to, *e.g.*, vision the olfactory sense is used subconsciously and affects us in a way we do not always are aware of, says Professor Hans Jörnvall, secretary of the Nobel Committee for physiology or medicine.

It is unclear how our knowledge about scent receptors and how the olfactory sense is organised can be used in the future, for instance in pharmacology. Presently there is no commercial application coupled to that knowledge.

— But the whole research field concerning receptors coupled to G-proteins is very big, Hans Jörnvall concludes.

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