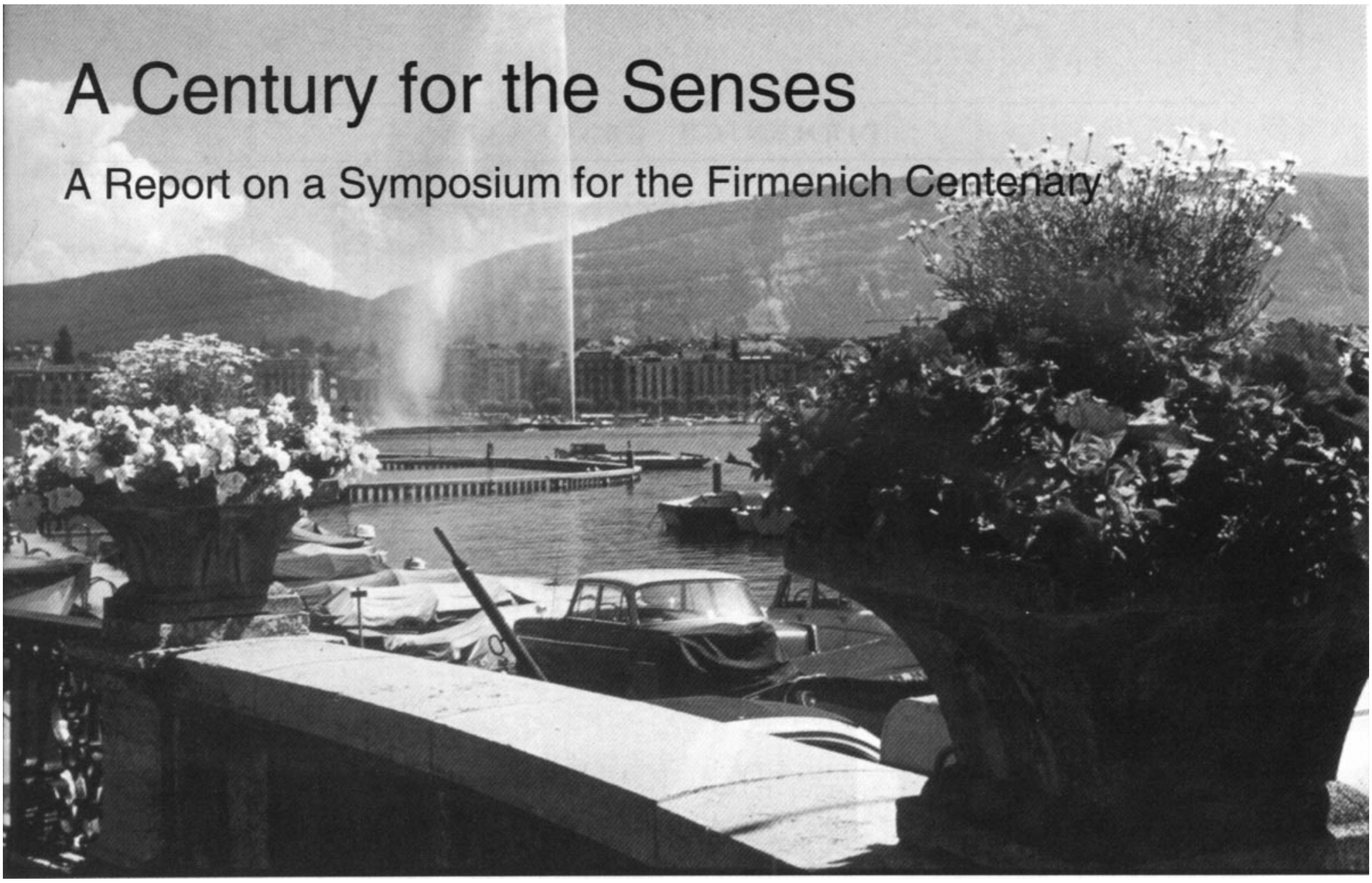
A Century for the Senses

A Report on a Symposium for the Firmenich Centenary



The setting in Geneva for Firmenich's Century for the Senses symposium, September 4-5, 1995

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A friend of ours once observed that natural catastrophes and anniversaries are both unavoidable; however, the latter have the advantage that they can be planned in advance. And indeed, the Firmenich Scientific Jubilee Symposium called "A Century for the Senses" was a carefully planned event.

The Anniversary

Firmenich is not only the name of a company. It is the name of a family personally committed to the industry for one hundred years.

As pointed out by CEO **Pierre-Yves Firmenich**, "The more we understand about the basic science of smell and taste, the more effective our flavors and fragrances will be." And he added, "Our company invests around 10% of its annual turnover in basic and applied research, far more than the industry average. The new molecules discovered in our laboratories represent a relentless source of innovation for our perfumers and flavorists, adding quality and originality to their creations."

There is no doubt that throughout its history, Firmenich has shown that dedication to research is the key to success.

This confession of faith found a tangible expression in the organization of an international symposium on olfaction and gustation, an event with which the company wished to associate prominent personalities coming from different scientific horizons.

During two days, on September 4 and 5, 1995, nearly two hundred scientists gathered in Geneva to discuss the latest research developments related to understanding the perception of odor and taste.

The nature of odor and taste perception has remained an elusive mystery until recent years. However, tremendous progress has been made in the last decade.

The profound changes occurring in physical and biological sciences and the importance of international scientific collaboration, together with a genuine desire to associate academic scientists in this undertaking, constituted the motivation for Firmenich's symposium.

Of course, this meeting also was a part of the company's one hundred years' anniversary celebration and a respectful tribute to a century of scientific endeavor in olfaction and gustation. We prefer to see it, however, as the beginning of a new exciting adventure along the avenue of knowledge.

It is fitting that we remember the remark of **Fred-Henri Firmenich**, Chairman of the Board: "Success does not just come along, you have to make it happen!" The company will strive for success, and for the future of the industry. It's a bright future because, according to an old Jewish saying, the only sense that has remained really intact after the expulsion from Paradise is the sense of smell.

Protection of Intellectual Property

The international character of Firmenich was clearly

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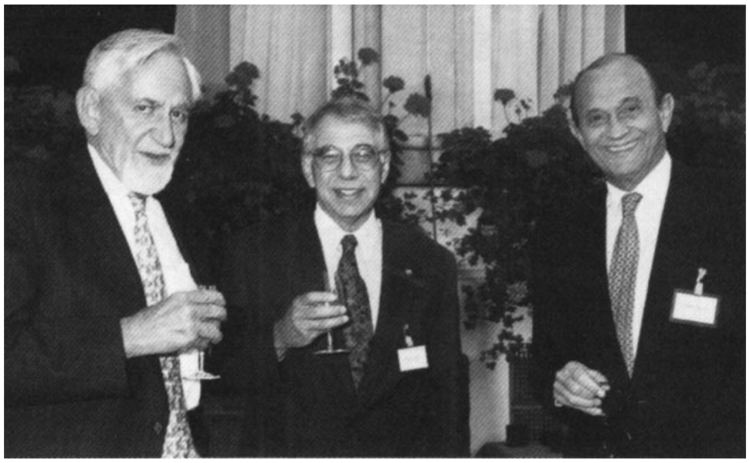
Professor Albert Eschenmoser addressing a question. Seated at the first table, from left to right, Professor George W. Whitesides, Professor Albert Eschenmoser, Dr. Fred W. Stone and Dr. Günther Ohloff

Professor Patrick MacLeod, Chairman of the Symposium



From left to right, Dr. Fred W. Stone (Firmenich Inc.), Dr. Robert H. Cagan (Colgate-Palmolive Co.), Fred-Henri Firmenich (Chairman of the Board, Firmenich International)

apparent by listening to the introductory remarks of **Arthur Dunkel**, former Secretary General of GATT (General Agreement on Tariff and Trade) and a close friend of the company, who observed that, following the implementation of the Uruguay Round, the world community would greatly benefit from improved cross fertilization in the scientific world. This would result from a progressively harmonized commercial legislation, concerning in particular the protection of intellectual property.

The Role of Organic Chemistry

One of the leading pioneers of modern natural products chemistry, **George H. Büchi** (M.I.T.) concentrated on the natural flavor and fragrance stimuli. During his talk entitled *The Chemistry of Perfumes and Flavors. Its Evolution over the Last 100 Years,"* he emphasized the contribution of organic chemistry both in the elucidation and synthetic reconstitution of natural fragrance and aroma chemicals.

As the formidable task of identifying the most characteristic chemicals in highly complex mixtures has been solved in the course of lengthy investigations, such indispensable materials as the macrocyclic musks, Ambrox* and p-menth-1-en-8-thiol have been revealed to perfumers and flavorists. These chemicals have become accessible following elegant synthetic work, highlighted by Büchi with witty anecdotes.

Converting Odor Information

The detection of odor stimuli requires the conversion of information from airborne chemicals into signals that can be perceived and analyzed by the brain.

In his lecture *Primary Events in Olfaction: Odorant Receptors and Signal Transduction*, **Randall R. Reed** (Johns Hopkins University School of Medicine) took us on a tour of the biochemical components involved in that conversion. From the ciliated olfactory neurons to the gene sequences encoding our olfaction, he zoomed with an ever increasing magnification into the transduction elements that provide the extraordinary discrimination and sensitivity of the sense of smell.

The difficulties encountered in the identification of the preferred ligands of the famous putative olfactory receptors prompted Reed to try another approach to elucidate the molecular recognition of the odor molecules themselves. Recent evidence has shown that animals may also have specific anosmias, a genetically determined trait, and the availability of mice libraries convinced Reed to search for the genes responsible for isovaleric acid detection. Successive breeding experiments producing osmic and

* Ambrox is a registered trade name of Firmenich

anosmic animals allowed his group to progressively restrict the genetic differences. Presently a 200,000 base pair segment of chromosome 4 appears very likely to encode the elements responsible for isovaleric acid detection.

So, what about the putative olfactory receptors of Linda Buck and Richard Axel? As Reed says, "Presently, nothing can be excluded. They might recognize odorants or be involved in that process, but they might also do something very different, for example provide the axonal guidance to connect the new, continuously regenerating olfactory receptor neurons to their target in the olfactory bulb."

Olfactory and Immune Systems

Gary K. Beauchamp (Monell Chemical Senses Center) discussed the connections existing between the olfactory and the immune systems in *Diversity: Olfactory and Immunological."*

Using two strains of mice differing only by their MHC complex of genes (0.5% of their genome), he demonstrated how Lewis Thomas was right when he remarked upon the parallels between olfactory and immune recognition: whereas both systems are able to recognize a vast array of chemical structures, the immune system evolved to discriminate self from non-self, and olfaction became the detector of external chemical signals.

The Monell Center team showed that the immune system genes determine the characteristic odor of every mouse. The functions for that odor include the regulation of mating preferences (favoring outbreeding), maintenance of pregnancy and modulation of parent-infant interactions. Thus, while immune system genes are intimately involved in odor production, the question of a modulation of odorant recognition remains an intriguing possibility.

Biological Odorant Receptors

The very initial event of odor detection is the molecular recognition of the odorant molecules by the corresponding receptor proteins. **W. Clark Still** (Columbia University) addressed the issue in *Modeling of Biological Receptors*.

One of the key features of biological receptors is the extraordinary selective binding of their preferred substrates. To circumvent the difficult task of characterizing the operation of these very large and complex receptors, Still described new ways to design and prepare receptor-like, simple molecules that bind organic molecules with high selectivities.

In addition, the new technique of combinatorial chemistry allows the rapid preparation of huge libraries of different molecules. "Fifty thousand different molecules is not unusual," says Still, who developed his own strategy to produce such libraries and used them to identify very efficiently, by a single screening, some preferred ligands for his artificial receptors. With the help of molecular modeling, these synthetic receptors provide new cues for determining the essential nature of receptor-substrate interactions.

Signals From Receptors to the Brain

After molecular recognition by the odorant receptors, transduction of the chemical message produces an electrical signal sent to the brain. **Gordon M. Shepherd** (Yale University School of Medicine) followed the fate of an odor signal from the receptor protein on the ciliated cell membrane to higher brain areas in *Primary Information Processing: From Odor Molecules to Odor Images.*

The response of each olfactory neuron is conditioned by the responsive range of its expressed receptor(s), and the cumulated responses from these neurons are processed at the first relay on the way up to higher brain levels: the olfactory bulb. The subsets of receptor cells expressing a given receptor type project to single or small groups of modules called glomeruli in the olfactory bulb. Each of these glomeruli is thus the convergence of receptor neurons with similar receptive ranges.

Together, the glomeruli activated by a given odor form an odor map coding all the odor information. The shape of this map is further modulated by intra- and inter-glomerular interactions, as well as feedback interactions, and it is believed that this primary processing level offers opportunities for inhibitory and excitatory processes.

Olfactory Images In the Brain

The most recent progress in imaging technology allows the visualization of the areas of the brain receiving the olfactory information. **Gerd Kobal** and **B. Kettenmann** (University of Erlangen) presented *Magnetic Source Imaging (MSI) of Olfactory Cortical Activity in Man."*

Potentials caused by specific odors were recorded in humans with an array of electrodes attached to the surface of the skull. Topographical analysis of these potentials allowed the distinction of trigeminal and olfactory responses, since different areas of the brain appeared to be responsive.

New recordings of the event-related magnetic fields within the skull (by magneto-encephalography) then allowed identification of the precise location of the areas of the brain responsible for the skull potentials visible in EEG recordings of olfactory related events.

Olfaction and Behavior

Eric B. Keverne (University of Cambridge) addressed the hot theme *Olfaction and Behavior* with a cool scientific approach.

Chemical communication has variable importance in mammals. Whereas it is a major determinant of the social life of mice (a mouse identifies the sex of another mouse by its odor, and its physiological reproductive state is largely determined by pheromonal cues), within primates it is integrated with other sensory information. However, primates possess the ability to focus on whatever sensory channel is most relevant at the time.

How does the odor imprinting work that allows olfactory recognition to play an integral part in the establishment of normal behavioral relationships such as mother-offspring, consort interactions and kin recognition? For example, lamb recognition by its mother relies on memory formation at parturition. This memory formation is noradrenalin dependent, and noradrenalin production is partly regulated by oxytocin. Pre-partum, most neurons in the main olfactory bulb are responsive to food; post-partum, there is a dramatic shift in sensitivity and most neurons are responsive to the odor of the mother's own lamb, and these changes are correlated with a change in neurotransmitter releases.

Thus, Keverne discovered that certain olfactory experiences cause a modification of the synaptic connections in the olfactory bulb through a subtle interplay of hormones and neurotransmitters. The olfactory bulb not only acts as the first relay of information between the olfactory receptor neurons and the brain, it also synthesizes its own message depending on previous experience with the present odor.

Human Axillary Organ

One of the most important anatomical sites of human odor production is the axillary organ lying at the top of the armpit. Although a number of studies have been conducted which suggest a role for armpit secretions similar to that played by sex pheromones in a wide range of animals, **D. Michael Stoddart** (University of New England) views the armpit as a relic.

In his lecture *The Human Axillary Organ: Evolution of an Olfactory Adornment*, Stoddart postulated that the organ functioned in the ancestral past to give olfactory information about the state of sexual development of both sexes, but that olfactory desensitization occurred when our ancestors became gregarious.

Upon consideration of paintings from Renaissance to present day, Stoddart suggested with some humor that the visual signals of the bare axillary adornment seem to be more important than the olfactory cues.

Neurobiology of Taste

For a long time, taste perception was considered to be relatively simple and relied on the classical four basic modalities. In *The Neurobiology of Taste: New Dimensions and New Directions*, **Stephen Roper** (University of Miami School of Medicine) addressed the aspect of taste transduction, revealing a striking complexity.

Multiple pathways exist to convert the chemical information of the tastant into an electrical message sent to the brain. Namely, certain stimuli interact with membrane-bound receptors and open ion channels, whereas some ions, especially sodium and potassium, pass directly through ion channels, leading to a depolarization of the cell. Finally, certain stimuli like sugars and monosodium glutamate activate receptors, triggering a second messenger cascade analogous to that involved in olfaction.

Reckoning that glutamate receptors are among the most abundant neurotransmitter receptors in the brain, Roper investigated their occurrence in tongue tissue. Using the tools of molecular biology, he found that only some taste papillae express a single glutamate receptor ($mGlu_4$). Taste aversion experiments using lithium chloride showed that rats trained to avoid monosodium glutamate will also avoid structurally different glutamate receptor agonists, demonstrating the role of the glutamate receptor in taste perception.

Chemical Structure and Sweet Taste

Concentrating on the compounds that elicit sweet taste, **Dr. Grant E. DuBois** (The Coca-Cola Co.) discussed the relationships existing between chemical structure and taste in *New Insights on the Coding of the Sweet Taste Message in Chemical Structure*. Following a tour of the wide variety of chemicals eliciting sweet taste, DuBois discouraged the audience from trying to rationalize structure-taste relationships for all sweet compounds with a single model.

Systematic investigations, both chemical and psychophysical, lead DuBois to the conclusion that sweet-tasting compounds activate taste bud cells through a variety of biochemical mechanisms. Polyol sweeteners, like glucose and the other polyhydroxycyclic organic molecules, activate taste receptor cells by a common mechanism, where cyclic AMP is involved as the transduction secondary messenger. This mechanism is distinct from the perception pathways of high potency sweeteners, such as saccharin and aspartame, where IP3 appears to mediate the transduction as the secondary messenger.

Since all neutral polyols are sweet with an equivalent maximum efficiency, and since sensory tests show no differences between enantiomers, DuBois proposes that sensitivity to these polyols is mediated either by an osmoreceptor, or by changes in the solvent environment of the sweetener, shifting the receptor equilibrium to its activated state.

Taste and Olfactory Stimuli in Monkey Brains

Looking at how olfactory and taste stimuli can modulate behavior in another way, **Edmund T. Rolls** (University of Oxford) investigated the destination of these sensations in the brain, using monkeys. His report was in a paper entitled *The Representation of Olfactory and Taste Stimuli in the Primate Orbitofrontal Cortex*.

The neuronal response of the primary taste cortex, recipient of the taste receptor information via the thalamus, shows no shift before and after satiety; it does not attribute a quality to the stimuli. In contrast, the orbitofrontal (secondary) cortex neurons may be tuned quite finely to gustatory stimuli. It is known that the activity of these neurons, which receive input from the primary taste cortex in addition to the olfactory bulb and the visual cortex, is related to reward, providing an incentive to continue the source of this pleasurable stimulation. For example, some neurons categorize odors depending on whether they are associated with glucose or saline. Thus, their activity is dependent on the association with taste reward. The response of some neurons is also modulated by hunger, in that those responding to the taste of food do so only if the monkey is hungry.

Rolls concluded that some functions of this olfactory representation may be related to the control of feeding, as well as other types of reward-related behavior.

Artificial Noses

Evolution has provided many living organisms with senses of astonishing sensitivity, and scientists have devoted much effort to develop optical, thermal and acoustic sensors which may rival or, in some cases, surpass natural capabilities.

With a lecture entitled *Chemical Sensors in Olfaction*, **Cyril Hilsum** and **Mark P. Byfield** (The General Electric Co.) covered the more recent attempts to develop artificial noses for volatile compounds. These devices are based on electrochemical, optical and microbalance sensors, or made of conducting polymers.

Since discrete sensors cannot provide sufficient discrimination for most purposes, modern instruments are based on arrays. Recent work with arrays of differently coated quartz crystal microbalances shows a very promising potential for these instruments in quality or process control. Looking to the future, Hilsum even envisaged the use of these sensor tools in fragrance creation. Is it any surprise that perfumers in the audience expressed mild dissent?

Reference

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