IAPO-Interamerican Association of
Pediatric Otorhinolaryngology

Electronic Nose

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Doctors may soon have a new diagnostic tool in their kit bags

Since time immemorial—or at least as far back as Hippocrates—novice physicians have been taught to smell patients' breath for signs of illness. Though unpleasant for the doctor, it is a useful trick. The sweet smell of rotten apples, for instance, indicates diabetes. Liver disease, by contrast, often causes the breath to smell fishy. But the human nose cannot detect all the chemical changes brought about by disease. Science, therefore, seeks to smell what human doctors cannot. The aim is to create a diagnostic nose as discriminating as those of perfume mixers or wine buyers. Such a nose would, however, be sensitive not to life's pleasures, but to its pains.

The idea of creating a diagnostic nose goes back to the 1970s. In that decade Linus Pauling, a Nobel-prize-winning chemist and some collaborators, performed the first serious scientific analysis of human breath [1]. They used a technique called gas chromatography, which enables complex mixtures to be separated into their components, to detect some 250 volatile organic compounds in the air exhaled from lungs. Gas chromatography by itself, however, does not allow you to identify each component—it is merely a way of separating them. To make the identifications, you need to add a second step, called mass spectrometry. This, as its name suggests, works out the weight of the molecules in each component. Often, weight is enough by itself to identify a molecule. But if two molecules happen to have the same weight, they can be analysed by breaking them up into smaller, daughter molecules. These are almost certain to differ in weight.

Using gas chromatography and mass spectrometry, researchers have, over the years, identified more than 3,000 compounds that are regularly exhaled, excreted or exuded from the body. The search, now, is to understand how changes in the mixture of these compounds may indicate disease, and to find ways of recognising such changes routinely and robustly.

Exhaustive analysis

One of the first practitioners of the field of olfactory diagnosis, Carolyn Willis and cols of Amersham Hospital in Britain, decided to contract the job out to dogs [2]. The dogs have the necessary nasal apparatus to sniff out illness, and there was already some anecdotal evidence that they could, indeed, smell people with cancer. It worked. For the past four years her sniffer dogs have been diagnosing

bladder cancer. They are now training them to detect prostate cancer and skin cancer as well.

But training dogs is probably not the best solution. It takes time and needs special skills, so mass-producing sniffer dogs would be hard. Moreover, a dog can give you only a yes-or-no answer. It cannot describe nuances, even if it detects them. Ewa Klodzinska and Boguslaw Buszewski of Nicolaus Copernicus University in Torun, Poland, compare this approach to checking for fever by touching a patient's forehead [3]. That tells you he is ill. However, it is only by measuring his temperature with a thermometer that you can discover how serious his condition is. In Klodzinska & Buszewski's view the breath-analysis equivalent of the thermometer is the mass spectrometer, and that is where effort should be concentrated.

Other researchers agree. In August 2008 Michelle Gallagher and George Preti, of the Monell Chemical Senses Centre in Philadelphia, announced the results of a study that uses this approach [4]. They confirmed that the early stages of basal-cell carcinoma, a type of skin cancer, can be detected by analysing the odour of a person's skin using gas chromatography and mass spectrometry. To do so, they sampled the air immediately above the tumours and compared its composition with that of air from the same sites in healthy individuals. They also checked the composition of the air in the room when nobody was present, as an extra control. They found that although air collected from both groups contained the same chemical substances, there was a difference in the amounts of some of them. This finding allowed them to produce what is known as a biomarker profile for the illness. That means it can be diagnosed reliably and—crucially—early on.

Preti and cols. have expanded the study into parallel areas and are examining volatile organic compounds emanating from melanoma (in vivo from patients and in vitro, using cell cultures) as well as in vitro ovarian carcinoma. Cell systems can be more cheaply and efficiently examined and have provided considerable data.

Alan Gelperin at Monell Chemical Senses Centre and Charlie Johnson at the University of Pennsylvania are presently developing DNA-coated carbon nanotube sensor-based electronic nose that is proposed to be used for translation to clinical application.

The combination of gas chromatography and mass spectrometry thus works. It can, nevertheless, take up to two days to run the tests. Klodzinska & Buszewski hope to refine and speed up the process so that it can be carried out within an hour.

To do this, he has developed a device that can be tuned to pick up and concentrate the most relevant molecules. With patents still pending, he is cagey about the details, but the principle is to trap relevant molecules using columns made of metal or silica that are the width of a human hair. Each column is coated with special polymers tweaked so that they bind preferentially to particular compounds found in the breath. Pass a sample through a forest of these columns and the molecules of interest will be sucked out. They can then be flushed into the analytical machinery and a result quickly emerges.

Klodzinska & Buszewski are now tweaking their device so that it works with the biomarker profiles of a range of diseases. If they can do this successfully, olfactory diagnosis could become mainstream without a wagging tail in sight [5].

Electronic Nose Technology

One potential drawback of gas chromatography/mass spectometry is that, while it may be refined to identify particular compounds through breath analysis, it is difficult and expensive to bring to the bedside. An alternative technology, the electronic nose or e-nose, may be able to bring these compact and inexpensive features to diagnostic medicine. While there is variability in technology, the general principles of the e-nose are similar to biologic olfaction. E-noses comprise an array of non-specific, chemical sensors that reversibly bind to volatile chemicals. This binding produces a quantifiable change in the sensor array (for example, by changing conformation of the sensors and thus a current carried across those sensors), in a pattern which is unique to the particular set of volatile chemicals. When such patterns cluster together in multidimensional space, the e-nose can be trained to identify unknowns that have the same response pattern.

A variety of e-noses have been studied in the quest for an instrument which can replace the human nose in medical diagnosis. Investigators have shown them to be capable of distinguishing: cerebrospinal fluid from serum[6]; a variety of bacterial species, as distinct from controls and each other[7]; several strains of lung cancer cell types, as distinct from each other; the presence of lung cancer in patients with active disease versus controls [8]; the presence of ventilator acquired pneumonia in intensive care unit patients versus controls [9]; and the presence of sinusitis in patients with active infection versus controls[10]. While these studies lack the sensitivity to be brought to the clinical arena, continued progress in development of e-noses specific for medical application is likely to produce a device which can function as a diagnostic aid in the office or at the bedside.

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