specialist at the IBM Thomas J. Watson Research Center. But like others intrigued by the prototype lenses, Spiller questions whether they can be assembled with precision, particularly for the stringent requirements of X-ray lithography. The lenses comprise from several thousand to several million carefully aligned glass capillaries. Adds Jerome Hastings of National Synchrotron Light Source at Brookhaven National Laboratory: "You can have a nice idea, but if you can't execute it, it remains a nice idea."

And then there are those who have become concerned not so much by the soundness of the basic science as by the selling of that science. Some researchers, such as Denis McWhan, chairman of the National Synchrotron Light Source, have been put off by the door-knocking tactics of Gibson and Kumakhov and the scarcity of published experiments using the lenses. "He [Walter Gibson] came down with his son. That put me off a little bit," he says. But that didn't prevent McWhan from saying, "It would be fun to try one of these lenses."

Gibson defends the meetings as providing a valid means for peer review and a forum for identifying potential applications for the lenses, which he says can be tailor-made for specific uses. And they are proving effective in whipping up interest. Researchers consistently express a desire to get hold of prototype Kumakhov lenses, direct some X-rays through them, and see if the technology can deliver as much as the pitch promises. For Gibson and Kumakhov that means getting lenses out to the trenches. Gibson cautions that it will take some time to do this.

The machinery to realize this goal has been set in motion, however. Last year, soon after Kumakhov contacted Gibson and suggested forming a collaboration to develop, market, and manufacture Kumakhov lenses, Gibson founded a company called X-ray Optical Systems, Inc. His son David, who is president of the company, says they expect to offer high-end lenses custom made for synchrotrons as well as "mass-produced" versions that might add on to standard X-ray sources. It's too early to put an exact cost on the lenses, but David Gibson speculates that they could run about $20,000 to $100,000.

Gibson has put his hard-earned scientific reputation behind the success of the new technology and X-ray Optical Systems. And his son David, who has three degrees from MIT, including one in business management, may have gone even further, leaving a high-paying position at McKinsey & Co, a top-notch management consulting firm, to become the company president. "I put my career, and the financial security of my five children and my wife on the line for this technology," he says. ■ IVAN AMATO

How the Nose Knows: Olfactory Receptor Cloned

The abundant variety of receptors has powerful implications for the brain's processing of smells

HERE'S A BRAIN TEASER THAT HAS PUZZLED neuroscientists for decades: How does the mammalian nervous system distinguish among 10,000 different odor molecules?

To most investigators it didn't seem possible that the nose could have a specific receptor for each odor. Indeed, many neuroscientists thought the likeliest solution was that there are a mere handful of receptor types, each detecting a wide range of odors; the specific pattern of receptors responding to any one smell would then produce a signature that the brain could decode. But what was needed to settle the question was the receptor molecule itself and, despite years of looking, no one had been able to identify the receptors. Now that seems to have changed.

Olfaction faction. *Linda Buck and Richard Axel.*

In a report in the current issue of *Cell,* Linda Buck and Richard Axel of the Howard Hughes Medical Institute of Columbia University describe a family of genes that seem to code for the long-sought odor-receptor proteins. One surprise is that the family appears to be huge—including many more receptors than most researchers would have predicted, raising the possibility that much of the discrimination between odors is done at the level of the receptor and not in the brain. And one of the beauties of Buck and Axel's work is that it provides the tools needed to find out whether that hypothesis is correct.

Most olfaction researchers agree that smells are detected when "odorants" (small, volatile, lipid-soluble molecules) bind to receptor proteins on the surface of nerve cells in the nose's olfactory epithelium, triggering electrical signals to the brain. Beyond that general agreement, however, lie some tough questions: How many types of receptors are there? And how is the job of discriminating between odors apportioned between the sensory cells and the brain? The fewer the receptors, the more complex the decoding job that would fall to the brain.

If, for example, there were a receptor type for each odorant, and each olfactory neuron had just one type of receptor "then [the brain] would simply have to ask which cells respond [to a particular smell]," says olfaction researcher Randall Reed of Johns Hopkins University. Alternatively, he says, the brain could discriminate among 10,000 odors using just 10 receptors, but "you would have this very diffuse signal, which you would have to process [in the brain] at a very sophisticated level."

What the brain actually does, however, needn't correspond to either of these extreme scenarios. An in-between view that has been held for some time by Yale neurobiologist Gordon Shepherd and others holds that the signal is not diffuse, but follows "labeled lines," corresponding to different components of a smell, making the signal easier for the brain to decode. This hypothesis proposes that sensory neurons having a particular receptor type all send their projections to the same place in the brain. In this view, the small and unique subset of receptors activated by any particular odor will produce a characteristic "fingerprint" of neuronal activity in the brain.

For many years it has been impossible to declare either the labeled-line or the diffuse-signal hypothesis a winner, because while there are data that could be taken to support each hypothesis, many questions could not be addressed directly without the receptors in hand. But efforts to identify the receptors were foiled—apparently because of the scarcity of the receptor proteins in the sensory epithelium and the difficulty of working with the lipid-soluble odorants they recognize.

In the early 1980s, neuroscientist Solomon Snyder and his co-workers at Johns Hopkins tried a strategy that had been used to purify receptors for a variety of neurotransmitters. They mixed radioactively labeled odorants with proteins from olfactory epithelium and

purified the protein to which the odor molecules bound. Unfortunately, the protein they fished out in this way wasn't the long-sought receptor—instead it was an abundant mucous protein that binds odorants of all types and may help deliver poorly soluble odor molecules to the receptors themselves. But those receptors remained at large.

Though Snyder's group had come up empty-handed, their work helped spur the recent research by Buck and Axel that may have provided the actual solution. Buck, a postdoc in Axel's Columbia lab, read about Snyder's work and got interested in the search for the olfactory receptor. "My interest in the system came from having studied immunology," she recalls. "I was fascinated by another system in which there is this tremendous diversity of ligands [molecules that bind to receptors] being recognized."

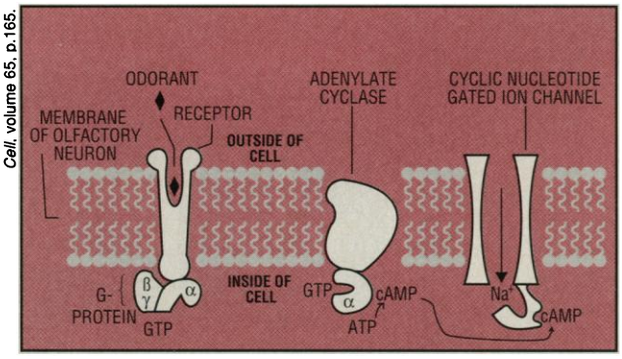
Buck decided to bypass the pitfalls of protein purification and fish out DNA clones corresponding to the genes for the receptors. She didn't know exactly what she was looking for, but she did have some general ideas: "The one thing I thought would probably be required was that there be a multigene family, although it might be very small or very large," she recalls. She designed a search for families of genes expressed specifically in the olfactory epithelium of rats.

This approach didn't produce instant success. Indeed, the first couple of attempts failed. So Buck refined her search, taking advantage of new information about the biochemistry of the odorant receptor. Work from a number of laboratories had shown that odorants cause olfactory neurons to produce the intracellular messenger, cyclic AMP (cAMP), and, furthermore, that the cAMP production depends on the presence of guanosine triphosphate (GTP).

That finding suggested the odorant receptors, when found, would turn out to be members of a large family of proteins that transmit signals inside the cell by interacting with special GTP-binding proteins called G-proteins. All the G-protein-linked receptors (a group including the light-responsive rhodopsin molecules of the retina along with many hormone and neurotransmitter receptors) are similar in amino acid sequence and structure, their most prominent feature being that they thread back and forth through the cell membrane seven times.

Armed with the insight that the olfactory receptor could well belong to the large super-family of G-protein-coupled receptors, Buck designed DNA probes that would hybridize to any of the 40 or so known receptors in the group. She then began using those probes to look for olfactory-specific genes.

Her strategy was a good one: She found a large family of genes for proteins that seem to be G-protein-linked receptors and are expressed exclusively in the olfactory epithelium. So far Buck and Axel have identified 18 different genes that are members of this family. The proteins they produce are similar but not identical in amino acid sequence—differing most in what Axel and Buck guess is the part of the protein that binds the odor molecule.



Cell, volume 65, p.165.

Smelly business. *When an "odorant" (odor molecule) binds to its receptor, it may trigger the G-protein to activate adenylate cyclase, producing cAMP, which in turn opens ion channels in the membrane of the sensory neuron.*

The discovery has the olfaction community buzzing, although even Axel and Buck quickly point out that the definitive evidence is not in yet that these are in fact the odorant receptors. "Although nobody has shown yet that these things bind odor molecules...it would be hard to imagine what else [they] could be doing," says Stuart Firestein, a neurophysiologist who studies olfaction at Yale. Hopkins' Snyder agrees: "Most people would say it sounds like a good bet they are odorant receptors."

And if that bet is right, it could have dramatic implications for understanding how smells are processed. For one thing, there seem to be far more receptors than many researchers were predicting. The newly discovered proteins can be grouped into at least seven subfamilies, each of which seems to contain 5 to 20 members. Axel won't venture a guess at the upper limit on family size because, he says, there is no way to tell how many more subfamilies there may be that they haven't found yet. "One hundred to 300 [genes] may be a reasonable estimate," he says, "but on the other hand it is conceivable that we are just looking at the tip of the iceberg, and [the number] could be considerably larger."

"The notion that there are large numbers of them is striking," Snyder adds. "It's not what a lot of people would have predicted, but it's reasonable." Indeed, most olfactory researchers familiar with the data are now talking in ball-park terms of 1000 receptors—an order of magnitude lower than the number of odor molecules we can smell, but nevertheless a number that opens the way for some exciting possibilities.

If there really are that many odorant receptors, it seems likely that there is enough specificity at the level of the receptor that the brain doesn't have to do any heavy computation, says Reed of Johns Hopkins. Even if the number of receptors were no higher than the 100 or so that Buck and Axel already have solid evidence for, neurons would only need to express those receptors in mixed pairs—two receptor types per cell—to produce 10,000 different unique combinations. And if both receptor types on a given cell needed to be triggered for the cell to fire an impulse to the brain, that would produce a diversity on the level of one neuron-type per smell.

But that is only one conceivable scenario, says Reed—it remains possible that the brain must still do a fair amount of processing or computation. Indeed, the data so far are too preliminary to rule out either the labeled-line or diffuse-signal hypothesis. "All the same questions still exist," says Yale's Firestein, adding that the only difference is that the Buck and Axel work provides at least a rough approximation of the number of receptors. It also provides a means of doing away with some of the guesswork that has dominated the field for so long.

The first order of business is to confirm that the receptors do indeed bind odorants, something Buck and Axel plan to do by putting the genes into non-neuronal cells and checking to see whether the cells gain the ability to respond to odors. If those experiments work out, the tools of molecular biology could then be used to ask more detailed questions about how the sense of smell works. Cultured cells expressing just one receptor type will be useful to address the selectivity of the receptor-odorant interaction, says Axel; antibodies against specific receptors can be used to look at the distribution of the receptors in olfactory tissue.

Beyond that, researchers will be able to turn to wiring questions: whether, for example, sensory cells with the same receptor send projections to specific parts of the olfactory bulb, the brain region where odors are processed. And with that information in hand, researchers will be able to close in on the question that's been tantalizing them for so long: how the brain knows what the nose smells. ■ MARCIA BARINAGA