familial Alzheimer's cases can be traced to a mutant APP gene.

Other research has shown that in normal brain cells most of the APP is transported by vesicles to the cell's plasma membrane, where it is clipped right in the middle of the β-amyloid sequence. That might explain why the β-amyloid fragment doesn't accumulate in normal brains. But even in normal cells, some APP winds up in other vesicles called lysosomes, where it is chopped up in a way that releases β-amyloid. Supporters of the amyloid hypothesis argue that a mutation in APP, or a change in how it travels through the cell, may tip the balance toward that second reaction, increasing β-amyloid deposition and touching off the disease (*Science*, 22 January 1993, p. 457).

If the S182 protein is indeed a player in protein transport, says Tanzi, it may be "involved with the packaging of APP in a vesicle and its delivery to portions of the neuron where it ... is going to be processed normally." Defects in the *S182* gene, he speculates, may cause a snag in APP's travel through the cell, possibly detaining it in a spot where it is more likely to be cleaved to β-amyloid.

But there are also other hypotheses about the development of Alzheimer's that view amyloid deposition as an effect, not a cause, of the disease. Selkoe, who studies amyloid, agrees that it is appealing to take a clue from SPE-4 and propose that mutations in *S182* disrupt APP transport in the cell. But he says that is "pure speculation" at this point and does not constitute further support for the amyloid hypothesis. "The [S182] finding is neutral as regards the amyloid hypothesis at this moment," he says.

Still, Selkoe notes that his lab and Steven Younkin's at Case Western Reserve University School of Medicine have found signs of increased β-amyloid secretion in cells from some chromosome-14 family members. "If this gene product turned out to have nothing to do with APP and [β-amyloid], then we would still have to find the reason why these patients have terrible amyloid deposition," he says.

That puzzle and others will spur the next phase of the research, as labs around the world pounce on the *S182* gene and begin racing to put it into cell lines, make knockout mice lacking the gene, and do anything else that may hint at its function. "There is a lot more work in figuring out what this gene is doing and what the relation is to Alzheimer's disease pathophysiology," says Van Broeckhoven. "Finding a gene is a good beginning, but it is definitely not the end." Although one heat of the Alzheimer's gene race is done, the starting gun for the next leg just went off.

–Marcia Barinaga

CHEMISTRY

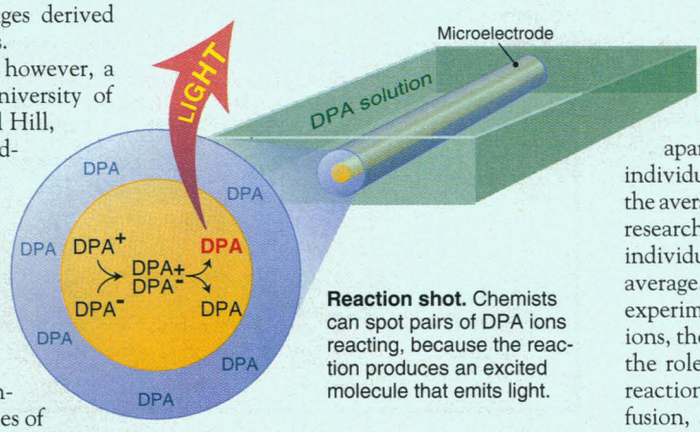
Getting a Reaction in Close-up

Chemists have long been curious about the time it takes for two molecules to react to produce a product. That timing varies, even among pairs of the same molecules in a solution, and researchers don't really know why. The difficulty of tracking individual molecules in solution has forced scientists to content themselves with averages derived from large numbers of molecules.

On page 1883 of this issue, however, a group of researchers at the University of North Carolina (UNC), Chapel Hill, report catching a series of individual reactions in the act, by narrowing their viewing window to a tiny volume of solution—thus narrowing down the number of molecules observed—and detecting faint flashes of light given off when pairs of reacting molecules collide. Although they were still unable to measure the reaction times of these pairs directly, the scientists were able to clock the interval between light pulses and statistically crunch these numbers to show how individual reaction rates were distributed about the average.

"It's really wonderful work," says Jonathan Sweedler, a chemist at the University of Illinois, Urbana, as the ability to see the distribution of individual reaction times adds a new level of sensitivity in monitoring chemical reactions. That, adds UNC team leader R. Mark Wightman, may eventually help researchers refine their knowledge of reaction dynamics, such how different rates of electron transfer between colliding molecules can slow or speed up reactions between pairs of the same type of molecule.

Wightman and Maryanne Collinson studied a reaction between oppositely charged ions of 9,10-diphenylanthracene, or DPA. When these ions collide and react, one of the partners briefly jumps into an excited state, then gives off a photon of light. To track these flashes, the researchers began by placing DPA molecules in an organic solvent and then rapidly reversing a potential in an electrode to first create a burst of positive ions followed by another of negative ions in the solution. The electrode had to be extremely small, a mere 10 microns in diameter. A device this small ionizes far fewer DPA molecules than would a larger variety, reducing the likelihood of overlapping photon bursts that would make it hard to discern the finishing times of the reactions.



Reaction shot. Chemists can spot pairs of DPA ions reacting, because the reaction produces an excited molecule that emits light.

ILLUSTRATION: K. SUTLIFF

It's even harder, however, to discern the starting times. Because the electrode generates ions continuously when charged at one potential, it was impossible to gauge the starting time for any particular ion. Nevertheless, from previous electrochemical experiments, the researchers knew that the positive ions were being added to the solution at a constant average rate, which the scientists used to derive an average start time for the reactions.

The key to the work was determining a series of specific finishing times. The UNC team was able to use a sensitive photon detector to clock the precise time each photon emerged. When the researchers looked at the finishing times of these photons, "we found that some occurred very close together in time and others occurred much farther apart in time," says Wightman. These individual photo finishes were compared to the average reaction time, and for the first time researchers were able to get a sense of how far individual reaction times departed from the average. By manipulating variables in future experiments, such as the concentration of ions, the researchers hope to get a handle on the role that diffusion plays in varying the reaction times. And after accounting for diffusion, the remaining variation can be ascribed to changes in electron transfer rates at the moment of molecular interaction.

This technique may also find a practical use, such as detecting trace numbers of molecules such as antibodies, says Allen Bard, a chemist at the University of Texas, Austin. Techniques already exist for tracking antibodies by tagging them with one ion of an electrochemiluminescent pair and then adding a batch of oppositely charged ions to the solution, triggering a photon burst that reveals the tagged molecule. But they require hundreds of luminescent molecules to generate a signal. If the UNC technique can do more with less, says Bard, it would also be an above-average achievement.

–Robert F. Service