She designed theoretical "super strong" polymers that are supposed to hold their alignment with side chains that "interdigitate" like teeth of a zipper. She predicts her super strongs will give twice the tensile strength and 25 times the compressive strength of the best available oriented polymers.

Other researchers consider her vision a long shot. Indeed, most doubt anyone will be able to synthesize the stuff. But the proof is still in the polymer rather than in the speculation—and Jack Preston of Research Triangle Institute is now attempting to synthesize a version of Dowel's super strong oriented polymers.

"Part of the problem is no one really understands all the math in Dowel's theories and computer models," says Preston. "But even if the theory is all wet, these materials will show some interesting properties," he adds.

For the companies that want to make the new polymers for a market, processing isn't the only problem; cost is another key factor. The high price of producing materials sometimes outweighs the advantages conferred by their material properties. And, as a result, even the strongest oriented polymers are now largely confined to specialized applications—sporting goods, protective armor, cut-resistant surgeon's gloves, kite strings, and fishing nets—because of the cost of making them.

But oriented plastics are now on the verge of breaking into higher volume markets, particularly in the aerospace industry. Don MacLemore, a lab director at Dow Chemical, expects plastics to make a splash in the aerospace market as ingredients in molecular composites. In this new class of materials, individual rods of super-rigid polymers intersperse through a matrix to bolster its strength—much as glass and carbon fibers do in traditional composites, but with more strength and less weight. MacLemore and his Dow colleagues are exploring a rigid polymer known as polybenzobisoxazole (PBO) to fill the role. "This is one of our biggest projects," he says.

PBO is stiffer than existing rigid rods, and prototype materials made from PBO boast twice the stiffness and equal strength of its nearest competitor, says MacLemore. "It's tough as nails."

Because of the significance of molecular composites for aircraft, U.S. Air Force scientists are eagerly collaborating on producing them. Thaddeus Helminiak of Patterson Air Force Base explains that molecular composites escape some of the weakness that comes from the interfaces between different materials in traditional composites. He is now helping work out remaining kinks, such as the tendency of PBO rods to clump together. "In the Air Force the important words are higher, faster, farther, cheaper, and invisible," he says, adding that PBO composites promise to fill those goals.

Most aircraft applications so far have centered on strength, but those who are working on conductive polymers also hope that the aircraft industry will provide an outlet. Some see conductive polymers in shields that would protect equipment from static electricity or make planes invisible to radar. Others envision lightweight coatings that would protect planes from lightning and save ships from corrosion.

The first commercial conductive polymer, however, didn't appear in the aircraft market, but in a much humbler product: rechargeable batteries. These have had some commercial success, although industrial researchers have much more powerful successors already on the drawing board.

Other applications for the conductive properties of oriented polymers are even more intriguing, because they are less closely tied to existing products such as batteries or aircraft. Scientists hope to exploit the sensitivity of conductive polymers, which react to small changes in temperature, chemistry, or radiation by switching from the conductive to a nonconductive state and often changing color. These polymers may someday go into the detectors used to measure environmental pollutants.

In addition, Mercouri Kanatzidis of Michigan State University and others are trying to harness the same switching ability to make conductive polymers into "smart" windows that let in just enough sunlight on hot days and insulate rooms on cold nights. To do that requires a polymer that can alter its opacity, by changing from colored to transparent and back. A transparent conductive polymer could also convert sunlight to electricity in solar energy collectors without blocking any of the light. "Transparency is sort of a holy grail in our field," says Kanatzidis.

Kanatzidis and others in the field get excited about the variety of possibilities new polymer materials open up. "We will see major commercialization within the next few years," predicts Heeger. "The really exciting thing is we are seeing a full range of applications—things from low-cost commodities to high-priced, high-technology products," he adds. Kanatzidis compares the prospects for today's new polymer materials to the bright future of ordinary plastics around the time Dustin Hoffman's graduate came home from college. "Our work has the potential to start a revolution like the first one," agrees Heeger. "We just have to see how far it will go."

■ FAYE FLAM

Faye Flam is the Washington correspondent for Chemical Week.

Mutation Identified

In the annals of medical research, few ideas have seen such rapid ups and downs as the notion that mutations in the gene encoding a protein called amyloid precursor protein (APP) might cause the hereditary form of Alzheimer's disease. In 1987, when the gene was first isolated, researchers thought it might be *the* Alzheimer's gene. Barely a year later, new studies seemed to rule out the possibility that a defect in the gene could be the primary cause of the brain disease. Now comes yet another study—and the APP gene's stock is shooting up again.

In work described in the 21 February issue of *Nature*, a team of nineteen researchers, led by neurogeneticist John Hardy of St. Mary's Hospital Medical School in London, reports that it has discovered a mutation in the APP gene that may cause some—but definitely not all—cases of hereditary Alzheimer's disease. If that is the case—and Hardy emphasizes that this is still a big if—it would be the first time that researchers have been able to pin down a biochemical event leading to the brain degeneration that characterizes Alzheimer's.

And that would certainly be reason for celebration. Any clue that could result in a better understanding of the biochemical basis of Alzheimer's pathology is sorely wanted by researchers who have been studying the baffling and devastating disease. Such an understanding might help researchers devise effective therapies for Alzheimer's—which is currently incurable. Moreover, if the disease should turn out to be caused by one or more mutations that can be picked up by genetic screening, then early detection of the condition should be possible.

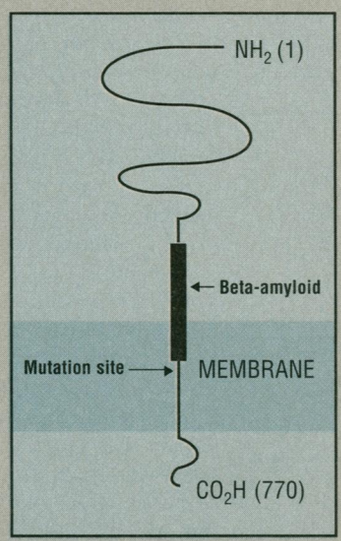
What Hardy and his colleagues have done in the current study is determine the nucleotide sequence of one segment of the APP gene in members of a family with hereditary Alzheimer's disease, which is characterized by early onset of symptoms, usually when the patients are in their forties or fifties. (There is also a late-developing form of the disease, which generally comes on after 70 years of age, that may not be of genetic origin.) The researchers chose the family they did, Hardy says, because earlier genetic analysis had indicated that the gene causing Alzheimer's in its members is on chromosome 21, the same chromosome that carries the APP gene.

When the researchers sequenced the APP gene segment, they found that all the family members with Alzheimer's had a specific mutation not seen in unaffected members. The result: amino acid 717 in the 770-amino

as a Possible Cause of Alzheimer's Desease

acid amyloid precursor protein is changed from valine to isoleucine. They did not find the mutation in normal controls or in people with the late-onset form of the disease. The St. Mary's group got a further indication that the mutation might be important in Alzheimer's when they found it in affected members of a second, and apparently unrelated, Alzheimer's family that is being tracked by Allen Roses of Duke University Medical Center in Durham, North Carolina.

The big question, of course, is does this mutation actually cause the disease in those two families? That answer just isn't in yet. "It's exciting that [the mutation] only occurs in affecteds, but not in unaffecteds," says Rudi Tanzi of Massachusetts General Hospital, who heads another group studying Alzheimer's genetics. Nevertheless, he continues, "the amino acid change caused by the mutation is not compelling enough by itself to say that it causes Alzheimer's." The valine to isoleucine change is "conservative," meaning that the two amino acids are structurally related—and so it is possible that the substitution does not alter APP function or handling in the cell.



Altered protein. *The amino acid change in APP is in sensitive site where it might disrupt APP handling by the cell.*

Hardy agrees with the need for caution. "I'm wary about going over the top and saying that this is it," he says, citing the checkered history of the efforts to pin hereditary Alzheimer's disease on the APP gene as one reason for his wariness.

Those efforts reached their peak about 4 years ago. At that time, the APP gene had just been cloned and mapped to chromosome 21—very close to and perhaps at the site where genetic linkage studies indicated the Alzheimer's gene was located. That was exciting, because there was already a biochemical reason for thinking APP might be involved in Alzheimer's.

The reason is that APP gives rise to a smaller protein, beta amyloid, which is a major component of the abnormal plaques that are one of the features of Alzheimer's pathology. The plaques consist of degenerating nerve endings surrounding a beta amyloid core, and neurobiologists have long argued about whether the beta amyloid deposition is the cause or the consequence of the neuronal deterioration. Proof that the APP gene really was the Alzheimer's gene would have gone a long way toward resolving that argument. But further work seemed to show that it was not the Alzheimer's gene.

Indeed, genetic linkage studies by Tanzi's group and that of Christine van Broeckhoven at the University of Antwerp, Belgium, indicated that the APP gene and the gene for Alzheimer's disease are not always inherited together. Yet some neurobiologists refused to give up on the notion that beta amyloid—and APP—had a key role in the origins of Alzheimer's disease (also see *Science*, 31 August 1990, p. 984). And now the Hardy group's new findings may be proving them right—at least for some inherited cases. "In general, this is good for APP," Tanzi says.

But while the APP gene may be an Alzheimer's gene, it is apparently not the only Alzheimer's gene. About 2 years ago, a group at the University of Washington in Seattle reported that they could not find an association between chromosome 21 where the APP gene is located and Alzheimer's in the families they were studying. That suggested that hereditary Alzheimer's is a heterogeneous disease, caused by a chromosome 21 gene in some families, but by another gene, located elsewhere in the genome, in others.

That conclusion has since been confirmed by a much larger genetic linkage analysis, performed by the Familial Alzheimer's Disease Collaborative Study Group, under the leadership of Peter St. George-Hyslop, who has recently moved from Massachusetts General to the Tanz Institute in Toronto. The genetic heterogeneity of Alzheimer's may account, Hardy says, for the failure to find a tight linkage between the APP gene and the disease in the earlier studies.

In any event, the Hardy group's new findings are consistent with the idea that familial Alzheimer's is genetically heterogeneous. The researchers failed to find the APP mutation in the majority of the early-onset families they screened, although they didn't sequence the entire gene and therefore can't rule out the possibility that other mutations in it might contribute to Alzheimer's in some of the families.

The work also suggests that the mutation is rare. Not only was it not present in most of the families the Hardy group screened, but Tanzi and his colleagues didn't find it in any of their 21 Alzheimer families.

But even if the mutation is rare, it may still be very important as a clue to the biochemical basis of Alzheimer's disease. If the APP gene mutation is the primary cause of the disease in even a few patients, then it may mean, Hardy suggests, that other genes and even environmental factors all work through APP and amyloid deposition.

The next step, everyone agrees, is to begin lab studies to try to see whether the mutation has biochemical or physiological effects that might lead to Alzheimer's pathology. According to Donald Price of Johns Hopkins University Medical School, who is an APP expert, an important question to ask is whether the mutation fosters beta amyloid deposition by altering the processing of APP by the cell.

Although the amino acid change caused by the mutation is conservative, it is in a critical part of APP. In normal neurons, the protein is apparently embedded in the cell membrane where it may play a role in neuronal communication. The mutation is within the membrane segment, just two amino acids away from the end of the beta amyloid portion of the molecule. In that location, it might interfere with normal APP function, causing membrane degeneration and enhancing beta amyloid release. That possibility can be tested, Price says, by putting an APP gene with the mutation into cultured cells to see how they handle it.

Another approach would be to create transgenic mice carrying the mutated APP gene to see if their brains develop plaques and other characteristic Alzheimer's lesions. If they did, it would buttress the case for the APP mutation as a cause of human Alzheimer's. More than that, it would also mean that Alzheimer's experts would for the first time have a good animal model for the disease. And that would be a major boon both for studying the mechanisms of Alzheimer's development and for testing therapies aimed at halting that development.

■ JEAN MARX