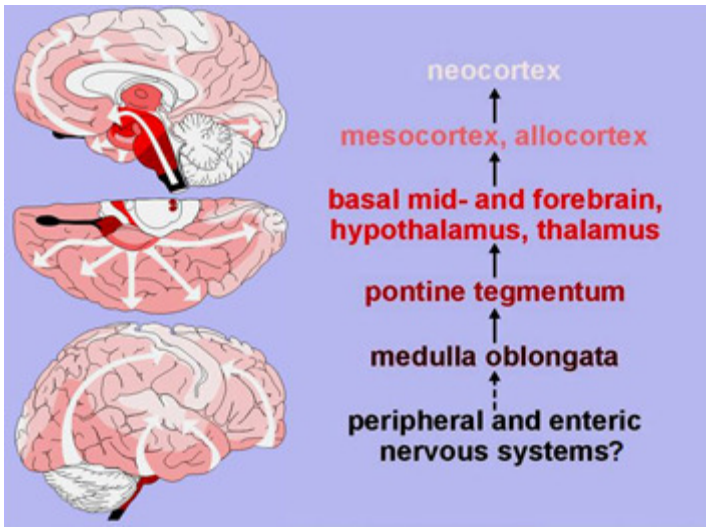
Parkinson's: Thinking Outside the Brain's Black Box

8 July 2011. When a German anatomist first proposed in 2003 that Parkinson's disease (PD) begins in the gut, then slowly makes its way to the brain and spreads to different regions, his idea might have sounded like fiction. But when he and a collaborator then added that a pathogen, possibly a virus, sneaks its way into the nervous system simultaneously from the nose and gut to set off the disease process, the hypothesis became downright fantastic. After all, conventional wisdom viewed Parkinson's as degeneration of the substantia nigra, that black-pigmented sliver of the brain. But less than a decade later, the hypothesis is gaining ground, as ongoing studies provide clues in its support. If successful, these new investigations could upend long-held views about how Parkinson's develops.

In the past decade, neuroanatomists Heiko Braak and Kelly Del Tredici, both currently at the University of Ulm in Germany, published a series of papers describing the distribution of Lewy bodies—those protein aggregates that are the hallmarks of the pathology of PD—in the central and peripheral nervous systems of deceased patients. To detect these lesions, they used an antibody to α-synuclein, the main protein component of these aggregates. α-synuclein is a normal protein found in many types of nerve cells, but something about the disease process of PD causes the protein to misfold and, as a result, clump together inside the cells.

Based on painstaking observations of hundreds of tissue samples, Braak and colleagues initially proposed that the α-synuclein pathology progresses in predictable stages defined by its distribution. The pathology advances from the peripheral nervous system to the brainstem, and from there upward to the midbrain and to higher brain regions, following paths laid out by connecting neurons. This staging system resonates with that described previously by Braak and colleagues for Alzheimer's disease (Braak and Braak, 1991 and online seminar by H. Braak).



The pathology associated with Parkinson's disease progresses from the peripheral nervous system to the brainstem, and from there it advances to the midbrain and higher brain regions. *Image credit: H. Braak and K. Del Tredici*

"The breakthrough in the field was that they proposed that the process starts nowhere near the substantia nigra," says John Duda of the Philadelphia Veteran's Affairs Medical Center. Up until then the substantia nigra, located in the midbrain or mesencephalon, had been the main focus of PD research. The motor symptoms that constitute the diagnosis of the disease—tremor, rigidity, slowness of movement or instability while standing up—are thought to result from the loss of dopamine-producing brain cells in this region and subsequent lack of transmitter input into the striatum, an important motor control area. Current medicines for PD typically consist of the dopamine precursor levodopa and dopamine agonists, but these treatments lose effectiveness over time.

Despite the focus on the substantia nigra, most PD patients have additional, non-motor symptoms, and PD is coming to be understood as a much broader disease. Chronic constipation, loss of smell, and REM sleep disorders often occur before the motor problems (O'Sullivan et al., 2008 and ARF related news story). A large epidemiological study, the Honolulu-Asia Aging Study, showed that men who reported less frequent bowel movements had a significantly higher risk of developing PD within the next 24 years (Abbott et al., 2001; Abbott et al., 2003).

One of the attractive features of Braak's staging scheme is that the areas of the nervous system littered with Lewy bodies at the earliest stages of disease could account for these non-motor symptoms. The staging system, wrote Braak in an e-mail to ARF, "has drawn attention to the damage in other transmitter systems—in other words, apart from and before the nigrostriatal system. In addition, it can serve as a framework for relating the pathology in other parts of the nervous system (gastrointestinal tract, spinal cord, and so on) to that in the brain."

What the Data Show

In their first paper in 2003 (Braak et al., 2003), Braak, Del Tredici, and colleagues examined postmortem tissues from 168 autopsied patients belonging to one of three groups: 41 patients had been diagnosed with sporadic PD; 69 had no clinical symptoms of PD but had Lewy bodies in their brains; and 58 people had no PD and no evidence of Lewy bodies. Whereas most pathologists use tissue sections that are, at most, 10 microns thick, Braak and colleagues developed a new technique using 100 micron-thick sections, allowing them to visualize pathology over large distances, so that they would not miss any changes that would escape detection in a thinner sample. "Braak is a hugely gifted pathologist," says Michael Schlossmacher, a neurologist at the University of Ottawa in Canada, echoing a sentiment expressed by most researchers in the field.

Using this technique, Braak and colleagues found that, in samples with mild pathology, which Braak called Stage 1, the Lewy bodies are typically confined to the olfactory bulb and the dorsal motor nucleus of the vagus nerve. Because the vagus nerve connects the brain to the enteric nervous system (ENS), the authors proposed that the disease could start in the gut and move along the vagus nerve in an upstream, or retrograde, direction toward the brain. In Stage 2, Lewy bodies continue to ascend into the brainstem, reaching the medulla oblongata and pontine tegmentum, parts of the brainstem that control swallowing, sleep, and other autonomic functions sometimes affected in PD. By Stage 3, pathology starts to show up in the amygdala (an almond-shaped mass of neurons involved in processing fear and other emotions, but also the sense of smell) and in the infamous substantia nigra; this is the stage when the motor phase of the disorder begins. In Stage 4, pathology in areas affected in earlier stages worsens, and Lewy bodies progress to the forebrain and encroach on a portion of the cerebral cortex (the temporal mesocortex), whereas the neocortex, the part of the brain involved in higher functions, remains unaffected. In Stages 5 and 6, the pathology is full blown, appearing initially in the anterior association and prefrontal areas of the neocortex and then spreading to the posterior association areas, which are involved with memory and learning, and planning movement. Defects in these areas could explain many of the cognitive problems associated with advanced PD. "There is no evidence in our material for involvement of the cerebral cortex in the absence of lesions in the brainstem," reads their 2003 paper published in the Neurobiology of Aging, essentially making the point that pathology rises up from lower to higher regions of the brain as PD gets worse.

In a subsequent study, Braak applied his pathology skills to the enteric nervous system (ENS). Earlier work had indicated that Lewy bodies could be detected in the ENS, but those studies had gone largely ignored. "The [sporadic] sPD-associated involvement of the ENS initially reported two decades ago found relatively little resonance in comparison to the literature devoted to lesions in the CNS," reads their 2006 paper published in Neuroscience Letters (Braak et al., 2006). Braak and colleagues examined five autopsy patients who had Lewy bodies in the CNS—three had been diagnosed with PD and two had no clinical symptoms of the disease. In all five patients, Braak and colleagues found Lewy bodies in both the Meissner's and Auerbach's plexus, the two layers that make up the ENS.

Because the ENS lesions were found both in PD cases and in asymptomatic individuals who only had Lewy bodies in the lower brainstem, the results confirmed the authors' view that the disease could start off in the ENS. But Braak and colleagues went further to postulate that the disease could be set off by a yet-unidentified pathogen in the gut (Braak et al., 2003). Then, Braak and Christopher Hawkes, a neurologist now at Barts and The London School of Medicine and Dentistry, U.K., revised this hypothesis to suggest that the pathogen could simultaneously enter the nose, by inhalation, and the gut, by swallowing nasal secretions, and then progress to the brain from two directions, providing a "dual-hit" (Hawkes et al., 2009).

Although Hawkes personally favors the explanation that the causative pathogen is a virus, he said it could also be a toxin, bacteria, or any inflammatory agent that causes α-synuclein to misfold and aggregate. Although Lewy bodies have not been found in nasal passages, the olfactory bulb is chock full of these lesions. From there, they could reach the amygdala in the temporal lobe of the brain through forward, or anterograde, motion, hopping across synapses of connecting neurons. At the same time, the pathology starting in the gut would move in a retrograde direction up the motor vagus nerve fibers, reaching the brainstem and then progressing to the amygdala and substantia nigra in Stage 3 of the disease. "These two paths meet up in the temporal lobe of the brain," said Hawkes. "By that time, the patient is quite ill."

Although Braak and colleagues did not assign a time course to the spread of disease, the process could take several decades to occur.

Not Everyone Agrees on the Interpretation

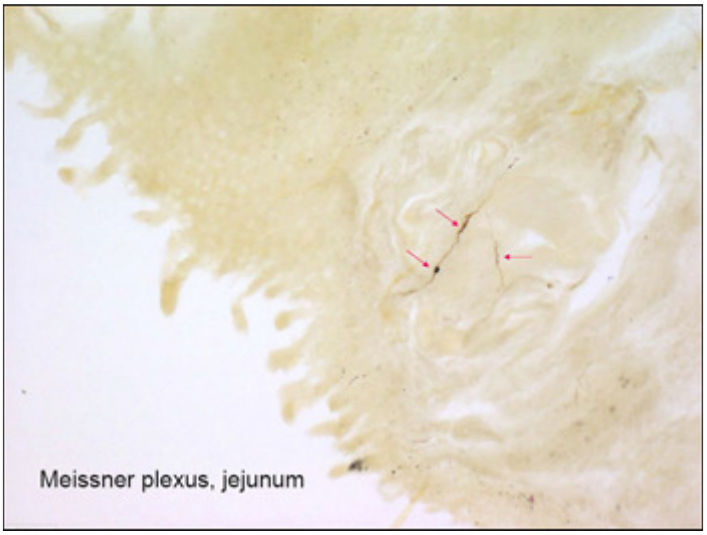
While most researchers agree that α-synuclein pathology can be found in many regions of the brain, many have disagreed with Braak's proposed staging sequence, saying that it does not apply to all patients and questioning its clinical relevance. In addition, certain aspects of the hypothesis, such as its viral origin or its spread, remain speculative. The danger is that "this idea has had a profound effect on how experimentalists are approaching the disease and which animal models they think are the best," Robert Burke, a pathologist at Columbia University in New York City told ARF.

Others, however, say that, although there may be exceptions to the staging system and some of the details of the hypothesis may be wrong, the scheme as a whole is benefiting the field. "The dopaminergic research has not been going anywhere for some time now," said Schlossmacher. "We have to do something different, and Braak made us think outside the box." The value of Braak's hypothesis, say supporters, is that it has provided new ideas for them to test. "There are many who strongly support the hypothesis and others who question it. For me, the Braak hypothesis has been a major source of inspiration for asking lots of interesting questions in animals and other experimental models," said Patrik Brundin of Lund University in Sweden. "Research is about putting forward hypotheses and then testing them."

Part 2 and Part 3 of this series highlight the main points of contention raised by Braak's staging scheme and the new line of investigations the hypothesis has inspired.—Laura Bonetta.

Parkinson's: It Started With a Gut Feeling

11 July 2011. When neuroanatomists Heiko Braak and Kelly Del Tredici proposed a new theory on the origin and progression of Parkinson's disease (PD)—suggesting that it starts outside the central nervous system, induced by a virus or other pathogen, and then spreads to different areas of the brain in stages—they started a debate in the field. The husband-and-wife team based their hypothesis on the locations throughout the nervous system of Lewy bodies—large protein aggregates inside nerve cells that consist primarily of the protein α-synuclein and are the pathologic mark of PD. Every aspect of their proposal, from the notion that disease pathology shows a predictable pattern of distribution, to the suggestion that the pathology starts in the gut and not the substantia nigra, to the idea that the pathology might spread across synapses from one neuron to the next, has found supporters and critics (see Part 1 of this series). "I am a major believer in Braak's hypothesis," said Richard Smeyne of St. Jude Children's Hospital in Memphis, Tennessee. "But the field is definitely divided—half the people are saying yes and the other half is yelling no."



The discovery of Lewy bodies in the intestine of patients led neuroanatomists Heiko Braak and Kelly Del Tredici to propose that the disease might start there. *Image credit: H. Braak and K. Del Tredici*

Not everything about this work rubs critics the wrong way, however. "There is good consensus in the field that if you take a patient who during life was diagnosed to have Parkinson's and look at the brain postmortem, that patient will show not just the conventional loss of substantia nigra neurons, but also the presence of Lewy bodies in areas like the brainstem, dorsal motor nucleus of the vagus nerve, the forebrain, and so

on," said Robert Burke at Columbia University, New York City. "That simple scenario has a good consensus, but Braak's hypothesis went far beyond that."

Picking the Issues Apart

For one thing, Braak and colleagues proposed that the pathology associated with PD advances systematically through the nervous system in six stages, sequentially moving from the vagus nerve up the brainstem to the substantia nigra in the midbrain and eventually reaching the forebrain and cerebral cortical areas. They based this staging scheme on the assumption that disease pathology would not occur in an area of lower vulnerability without also being present in areas of higher vulnerability.

But since the hypothesis was first proposed in 2003, several groups have looked at the distribution of Lewy bodies in the nervous system of autopsied patients and found some that do not follow this scheme. "We looked not only at the presence and distribution [of α-synuclein], but also the intensity of deposition in cases coming to a Parkinson's Disease Brain Bank," wrote Ronald Pearce of Imperial College London, U.K., in an e-mail to ARF. "Several cases did not have vagal nucleus pathology, and some had spinal cord pathology and no vagal nucleus pathology, thus 'skipping' the vagus nucleus" (Kalaitzakis et al., 2008). A review of the literature by the respected Austrian neuropathologist Kurt Jellinger revealed "sparing of medullary nuclei in 7-8.3 percent of clinically manifested PD cases with [α-synuclein] inclusions in midbrain and cortex corresponding to Braak Stages 4 and 5, whereas mild parkinsonian symptoms were already observed in Stages 2 and 3" (Jellinger, 2008).

But the fact that there are exceptions does not necessarily diminish the value of Braak's staging system. "It is a useful construct that could apply to many but not all cases of disease," said John Trojanowski at the University of Pennsylvania in Philadelphia. "I appreciate the staging scheme. It is not 100 percent absolute, but it is a good generalization."

According to Braak, the staging system is reproducible in about 80-90 percent of Parkinson's patients. Some of the discrepancies may also reflect variable protocols for assessing and diagnosing tissues. In his studies, Braak examined tissue samples that were 100 microns thick. That is much thicker than the samples most pathologists use, which typically span 10 or fewer microns. "If you see pathology in an area affected in Stage 5 but do not see it in regions corresponding to Stages 3 or 4, it might just mean that it's not in the 10-micron section you examined," said John Duda, at the Philadelphia VA Medical Center. "You would need to examine 10 of those 10 micron-thick sections to replicate what Braak did." Even so, "very few Parkinson's patients completely violate [Braak's] staging," Duda added. "It's a very good scheme, if you accept the notion that it is biology and that there are always exceptions."

Another issue complicating the staging system is the connection between Lewy body pathology and the clinical symptoms of PD. Braak had postulated that the early Stages 1 to 3 of disease develop in patients who have not yet been diagnosed with classical motor symptoms of disease. Those motor symptoms, according to Braak's scheme, start to

develop in Stage 3, when pathology has spread to the substantia nigra. Cognitive problems and dementia would occur when the neocortex becomes affected in Stages 5 and 6 (see Part 1).

However, a number of studies show widespread pathology in people who were not diagnosed with any clinical symptoms of disease. Irina Alafuzoff of Uppsala University Hospital in Sweden and colleagues examined brain tissues from 226 autopsied patients who had signs of Lewy body pathology in the brain. They found that only 50 percent of patients with a widespread distribution of Lewy bodies, corresponding to Braak Stages 5 or 6, had been diagnosed with PD or were demented (Parkkinen et al., 2008). The results raise two different questions, according to Alafuzoff: "1) Is this pathology significant regarding the symptoms, or 2) do those with symptoms have some other alteration that makes their brains sensitive to the pathology?" she wrote in an e-mail to ARF.

Braak based his staging system on the detection of Lewy bodies. However, whereas smaller aggregates of α-synuclein have been shown to cause neuronal cells to die, a growing number of scientists now believe the formation of the larger Lewy bodies may actually serve to protect neurons from damage. "Lewy bodies are the pathological hallmark used in diagnosis, but they appear not to be associated with cell loss or to correlate with the severity of clinical symptoms," says Walter Schultz-Schaeffer, a neuropathologist at the University Medical Center in Göttingen, Germany.

Thus, a number of researchers have suggested that other markers of disease, such as cell death or synaptic dysfunction, would be more appropriate for developing a staging scheme for PD. Schultz-Schaeffer is examining the relevance of smaller deposits of α-synuclein found at the synapse of neurons as markers of disease progression (Schulz-Schaeffer, 2010). "Braak's staging is reproducible," says Schulz-Schaeffer. "But now we should put more focus on the synapses." In Alzheimer's disease, by comparison, the development of fluid and imaging biomarkers have transformed the focus of disease staging from postmortem biology to preclinical measures in living people (Jack et al., 2010).

Time Course on Trial

One of the more provocative claims of Braak's proposal is that, based on the pathology detected in postmortem tissues, the disease starts far away from the substantia nigra. Critics say the basic premise for this conclusion is flawed. "It is a basic error to take single snapshots of different patients and put them all together in a timeline," argued Burke. "You can't say 'Based on what I see, I would propose that the disease begins here.'"

Others, however, counter that this limitation is inevitable when trying to describe a dynamic process based on such samples. "Unless we find a suitable animal model of disease or figure out how to bring people back to life, we will never be able to prove it," said Smeyne. None of the available animal models of PD accurately mimic the disease in humans (see ARF AD/PD 2011 story), and no radioactive tracers exist that can detect protein aggregates in living patients by PET scans or other methods. Such tests are in

clinical development for Alzheimer's disease (see ARF related news story), and there is significant interest in doing the same for PD.

The two sites where PD pathology begins, Braak claimed, are the enteric nervous system (ENS) of the gut and the olfactory bulb (see image above). The ENS is particularly intriguing because it is relatively straightforward to take biopsies of this portion of the nervous system in living patients, unlike the brain or the olfactory bulb. Thus, pathology in the ENS could serve as a marker of early disease or disease progression.

Several investigators are starting to examine Lewy body pathology in the ENS of living PD patients and healthy volunteers. Pascal Derkinderen's group at the Inserm U913 of the University of Nantes, France, examined colonic biopsies from 29 PD patients and 10 controls. They found Lewy pathology in one of the two layers of the gut (the submucosal plexus) in 21 of the patients and none of the controls (Lebouvier et al., 2010). "We started this work based on the Braak hypothesis," said Michel Neunlist, a coauthor on the paper. "The first thing we wanted to do was to see whether we could detect the lesions, and we showed that the ENS bears the same lesions as the brain. We now have some interesting observations to suggest that we can anticipate over time the stage of the disease based on ENS examination." Other groups, including those of Jeffrey Kordower at Rush University Medical Center in Chicago and of Patrik Brundin at Lund University in Sweden are conducting similar studies focusing on patients with early symptoms of disease, but those results have not yet been published.

Results from these studies should yield important information about the value of ENS pathology as a possible biomarker for PD, but whether or not the disease truly starts in the gut, as proposed by Braak, is still fodder for debate. "There are all kinds of studies now showing that the enteric nervous system is extremely sensitive to environmental insults," said Smeyne. Epidemiological research suggests that in human patients, constipation might be one of the early signs of PD, preceding motor symptoms by decades (e.g., Abbott et al., 2001; Abbott et al., 2003). Animal studies provide some support for this conclusion as well. In collaboration with Smeyne, Robert Nussbaum at the University of California in San Francisco developed a transgenic mouse expressing a mutated version of the human α-synuclein gene. This strain develops α-synuclein aggregation in the gut at three months of age. The mice have signs of constipation and reduced defecation similar to what is seen in PD patients. Because this mutation causes some familial forms of PD, the results provide a link between PD and a disease process in the gut. "This mouse model mimics what we see in the early stages of PD," says Smeyne. In the model, the pathology does not, however, progress to the central nervous system (Kuo et al., 2010).

On the other hand, Thomas Beach and colleagues at the Sun Health Research Institute in Arizona examined autopsy tissue from 92 people obtained through the Brain and Body Donation Program, a longitudinal study of elderly volunteers who are neurologically normal or have diseases like PD and Alzheimer's (AD). These researchers found no evidence that PD starts in the gut. Beach and colleagues looked for aggregates of phosphorylated α-synuclein, a form of α-synuclein typically found in Lewy bodies,

throughout the volunteers' bodies. They found that such aggregates are widely distributed, affecting virtually all organ systems and tissues. In no case, however, did phosphorylated α-synuclein aggregates appear in the spinal cord or any peripheral site without also being present in the brain (Beach et al., 2010). "I think we showed quite conclusively that the histopathology in the body does not generally occur prior to that in the brain," wrote Beach in an e-mail to ARF.

A Viral Spread?

Perhaps the most speculative aspect of Braak's hypothesis is that PD is caused by a pathogen, possibly a virus or another agent that spreads through the nervous system in a prion-like manner. Part 3 in this series discusses accumulating evidence showing that this idea is not entirely far fetched.—Laura Bonetta.

Parkinson's: An Unlikely Proposal Gains Momentum

12 July 2011. Heiko Braak's and Kelly Del Tredici's staging scheme for Parkinson's disease (PD) raised an intriguing question. Could PD start in the belly and spread from there, along paths laid out by neurons, to successive areas of the brain in a predictable sequence (see Part 1 of this series)? How this might possibly work has become the subject of intense investigation.

The two neuroanatomists at the University of Ulm, Germany, posed the question based on the distribution pattern of Lewy bodies, microscopic protein aggregates containing the protein α-synuclein, in the nervous system of autopsied PD patients. α-synuclein is normally a soluble protein in neurons, but something about the disease makes it fold into the wrong three-dimensional structure, causing it to clump together.

In 2003, Braak and Del Tredici suggested that this disease process is set off "by a yet-unidentified pathogen that is capable of passing the mucosal barrier of the gastrointestinal tract and, via post-ganglionic enteric neurons, entering the central nervous system" (Braak et al., 2003). There is no evidence that PD is an infectious disease. Even so, viruses have been implicated in a number of neurological diseases, and some indirect clues do suggest that a virus might play a role in PD. For example, although controversial, epidemiological data have linked the development of post-encephalitic parkinsonism to the 1918 "Spanish flu" outbreak (Ravenholt and Foege, 1982).

To explore this connection, Richard Smeyne of St. Jude Children's Hospital in Memphis, Tennessee, and colleagues inoculated mice with a strain of the H5N1 bird flu virus via the nose and showed that the virus can move through the gut and the brain and induce pathological changes that are reminiscent of those seen in PD. These included functional loss of dopamine in neurons in the substantia nigra and an increase in α-synuclein expression and aggregation (see ARF related news story on Jang et al., 2009). "The pattern of infection starting in the enteric nervous system and traveling to the central

nervous system via the vagus nerve parallels the progression of PD as described by Braak," Smeyne said.

One idea that is gaining momentum is that, instead of a virus or some other agent spreading through the nervous system to induce the pathology associated with PD, the pathology itself, in other words, the misfolded form of α-synuclein, is what spreads from one neuron to the next (see image).

The identification of Lewy bodies in nerves leading from the peripheral to the central nervous system has led to the hypothesis that Parkinson's pathology spreads via transneuronal or trans-synaptic transmission. *Image credit: H. Braak and K. Del Tredici*

Several studies in vitro and in vivo have indicated that the soluble form of α-synuclein is released at synapses and taken up by other neurons. One of the first of those studies, reported by Seung-Jae Lee, now at Konkuk University in Seoul, South Korea, dates back to around the time Braak first proposed his hypothesis (Lee et al., 2005). "The general reaction of the PD community at the time was understandably not very enthusiastic. Many were probably hesitant to believe our results, and even if they did, they did not know what to make of them," wrote Lee in an e-mail to ARF. "We learned about Braak's staging for synucleinopathy around the same time. It was not as well known or well received by the research community as it is today. But when I first read about Braak's hypothesis, I immediately realized the potential implications of α-synuclein release. So I formulated my own hypothesis of α-synuclein aggregates spreading through cell-to-cell transfer."

Recent research supports Lee's hypothesis. For example, Pamela McLean's group at Harvard Medical School in Boston has shown that α-synuclein oligomers are taken up by neurons in culture, transported through the axon to the cell body, and, once there, cause cell death. Moreover, the heat shock protein Hsp70—a chaperone that assists in protein folding and is produced in higher amounts when cells come under toxic or inflammatory stress—reduces the formation of α-synuclein oligomers and related toxicity (Danzer et

al., 2011). Together with studies from other groups (see ARF related news story on Desplats et al., 2009), this work raises the possibility that some neurons might transmit a specific conformation of α-synuclein, possibly induced by inflammation or some other mechanism, that then seeds the aggregation of α-synuclein in adjacent neurons. "The latest experimental results are very exciting and tend to point to disease progression via transneuronal or trans-synaptic transmission," Braak wrote in an e-mail to ARF.

One of the most compelling indications of this proposed spread comes from examinations of PD patients who had received transplants of fetal nigral dopaminergic nerve cells and died several years after the surgery. In 2008, the laboratories of Jeffrey Kordower at Rush University Medical Center in Chicago, Illinois; Patrik Brundin at Lund University in Sweden; and Ole Isacson at Harvard Medical School in Boston independently described results from the autopsies of eight such patients. Two of the groups identified three patients who had Lewy bodies in the transplanted fetal tissues (see ARF related news story on Mendez et al., 2008; Kordower et al., 2008; Li et al., 2008). "The likelihood of dopaminergic nigral neurons developing Lewy pathology at such an age in their native surroundings is exceedingly small. It can be inferred, therefore, that the lesions resulted from more than a decade of interaction between the host tissue and the transplanted nerve cells," wrote Braak and Del Tredici in an accompanying commentary (Braak and Del Tredici, 2008).

The Lewy bodies showed up in the transplants of patients who had survived 10 years or more after transplantation, but not in people whose transplants were fewer than 10 years old, implying that it takes about this long for α-synuclein pathology to spread. Since those original studies, additional patients with α-synuclein pathology in their transplants have been identified, bringing the total number of such patients to eight, according to Brundin. The most recent case was published on May 18, 2011, in the Journal of Parkinson's Disease.

Again, how the pathology got to the transplants is subject to debate. "There is no question that they found Lewy bodies in transplants," said Robert Burke of Columbia University in New York City. "But you cannot draw the conclusion that the α-synucleinopathy was transmitted to these cells. There could be many other explanations. One is that, if you put cells in a toxic environment such as the brain of a PD patient, they can develop aggregates."

To distinguish among possibilities, researchers have turned to animal models. Brundin's group grafted wild-type mouse embryonic mesencephalic neurons into the brains of transgenic mice that had been engineered to produce large amounts of human α-synuclein. When they examined brain tissues from these mice, they detected human α-synuclein in the transplanted tissues from the wild-type mice. Thus, the human α-synuclein in the brain cells of the transgenic mice had entered the nerve cells in the transplants (Hansen et al., 2011).

Kordower's group came to similar conclusions using a different model. They grafted fetal rat brain tissues into the brains of adult rats that had been treated with a toxic chemical

known to induce α-synuclein misfolding and aggregation. One month after the transplant, the researchers injected viruses containing the human α-synuclein gene into the rats' brains at a sufficient distance from the grafts so that none of the graft cells would be injected. When they later examined brain tissues from these rats, they found that a small number of grafted neurons expressed the human α-synuclein, and in some cells the protein was misfolded and aggregated (Kordower et al., 2011). "Clearly, propagation of α-synuclein can occur," said Kordower. "Whether it does occur in patients remains to be proven."

Prion diseases, like Creutzfeldt-Jakob disease in people or bovine spongiform encephalopathy and scrapie in animals, are infectious, meaning that they can spread from one person or one animal to another. That has never been shown to be the case for PD. But the studies by Lee, McLean, Kordower, and Brundin suggest that PD might share some characteristics with prion diseases in terms of how α-synuclein spreads from neuron to neuron, and under some circumstances, causes other α-synuclein molecules to misfold and stick together. This line of investigation parallels studies of aggregate migration of the amyloid-β peptide (see ARF related news story on Eisele et al., 2009) and tau (see ARF related news story on Clavaguera et al., 2009; and ARF related news story on Frost et al., 2009).

"For me, this is extremely exciting. Four years ago we would not be talking about this," said Brundin. "The Braak hypothesis got us talking about a virus. But the actual protein that is transferring is a new concept that we are now investigating."—Laura Bonetta.