One of the high points of being a practicing clinical neurologist is making a diagnosis of early idiopathic Parkinson’s disease and initiating successful levodopa treatment of the disorder. The spectacular initial results of this treatment that we frequently witness have been immortalized by Hollywood in the 1990 movie Awakenings with Robert DeNiro’s depiction of a young man affected with the disease, who experiences a short-lived miraculous reversal of the effects of his disorder following initiation of levodopa therapy.

Just as with DeNiro’s depiction, we have become all too well aware that dopaminergic therapy of Parkinson’s disease is most gratifying for both patient and doctor alike at the beginning of the treatment, only to be followed by a spiraling succession of disappointments that compromise the lives of our patients and challenge the very limits of our clinical skills and acumen. How can it be that we have such great success treating these patients at first, only to have all of the optimism engendered by this success dissipate into utter oblivion over the next two decades?

Even though recent therapeutic advances, particularly the surgical ones provided by deep brain stimulation and poten-

There’s more to the story than the substantia nigra. Here’s how the latest thinking has changed our picture of PD, and the implications for clinicians.

By Stephen M. Gollomp, MD, Philadelphia
tially by cellular replacement therapy, have engendered great enthusiasm throughout the neurological community and in the world at large, it is evident that the treatment issues in Parkinson’s disease extend far beyond our earlier simplistic assumptions and observations.

Over the past several years, our insights into the neuropathology and neurochemistry of Parkinson’s disease have evolved dramatically, making it possible for us to develop a more comprehensive model of the disorder and have a fuller understanding of the limits of our preconceived notions and current therapeutic approaches.

As you are all well aware, one of the principal tenets of modern neurology since the mid-20th century, as first described by Hornykiewicz and colleagues, has been that Parkinson’s disease is a disorder confined to degeneration of central nervous system pigmented nuclei, principally the substantia nigra. A corollary to this observation has been the realization that the large pigmented cells of the substantia nigra compacta are the source of the major dopaminergic projection to the striatum, that dopaminergic deficiency correlates with the motor disorder of Parkinson’s disease and that dopamine replacement therapy is a potent treatment for this motor disorder, as first observed by George Cotzias.

As any clinician who cares for these patients soon recognizes, the manifestations of Parkinson’s disease extend far beyond those affecting the motor system with cognitive alterations and impairment, sleep architecture disturbances, impairment of the senses of smell and taste, and autonomic dysfunction causing the majority of the disability induced by the disorder that is frustratingly unresponsive to our ministrations. Even more disappointing is the fact that our treatments themselves sometimes further seriously compromise our patient’s functional capabilities. Consequently, our treatment of the condition becomes a disappointing exercise for physician and patient alike as the disease progresses. With these thoughts in mind, we believe it is important to explore the current observations of our neuropathological colleagues to further the clinician’s conceptualization of the approach to treatment of our patients.

Braak’s Six Stages of PD
The neuropathology community currently looks upon Parkinson’s disease as a multifaceted disorder of the central nervous system. It can considered a slowly progressive neurodegeneration that first nibbles at the edges of the central nervous system, gradually evolving centrifetally to involve deeper CNS brainstem structures and then spreading centrifugally from the brainstem to encompass the cerebral cortex. Without question, the disorder is not solely confined to the dopaminergic systems, though this is the system that is most affected when patients first present to us for diagnosis and treatment. Generally, when we neurologists become involved with Parkinson’s patients, we are wading into the process mid-stream.

We will amplify upon this concept, which correlates well with the evolution of the clinical syndrome of Parkinson’s disease. Braak and his colleagues have articulated these observations in a series of publications over the past few years. We will draw upon these observations and those of many others to present an updated framework for thinking about Parkinson’s disease.

Based upon these neuropathological observations, Braak has delineated six distinctive stages to the unfolding pathological picture of Parkinson’s disease. Throughout all these six stages the same essential cellular abnormality gradually unfolds over a progressively wider extent of the central nervous system. As we have known for a very long time, the essential cellular hallmark is intracellular inclusions, Lewy bodies, within the cytoplasm of involved neurons.

As part of the presentation of these distinctive inclusion bodies, one can see spindle or threadlike branching Lewy neurites within cellular processes, along with granular aggregations and the more classical spherical pale bodies, first described by Lewy. These intracellular inclusions consist mainly of aggregations of a misfolded protein, alpha-synuclein. This protein is ubiquitous in central nervous system neurons, but is quite variably distributed amongst various neuronal cell types. Vulnerable neurons require sufficient amounts of normal alpha-synuclein to develop the abnormal protein aggregates that ultimately leads to Lewy neurite formation. The neurons that are most vulnerable to this process have very long, thin caliber unmyelinated or poorly myelinated axons.

Under normal circumstances, alpha-synuclein remains soluble in the cytoplasm, binding with high affinity to the membranes of synaptic vesicles and other membranes rich in acidic phospholipids. For reasons that are yet to be clarified, this membrane binding capacity of alpha-synuclein is lost in these neurons with long, lightly myelinated axons predisposed to develop the cellular hallmarks of Parkinson’s disease. In these neurons, a protein conformational change takes place, which results in the development of an insoluble B-sheet concretion of self-aggregating, misfolded alpha-synuclein molecules. Additional proteins participate in this aggregation process, including synphilin-1, phosphorylated neurofilaments and ubiquitin.

The precise cellular mechanism by which these proteins interact to induce the formation of the insoluble protein aggregates is the subject of very intense investigation. The accumulation of these insoluble protein aggregates seems to
Rethinking Parkinson’s

lead to the induction of cell death in these predisposed neurons by as yet ill-defined mechanisms. What is even more intriguing about this concept is the recent development by Olanow and his colleagues of a rodent model of Parkinson’s disease induced by the proteosomal inhibitor, epoxomicin, which closely mimics the spectrum of the disease behaviorally and neuropathologically, as reflected by aggresomes containing alpha-synuclein and ubiquitin in the brainstem nuclei affected by the disease. The story of misfolding of a normal protein rendering it toxic to cellular function is a familiar one in neurodegenerative disease, echoed in Alzheimer’s disease, Huntington’s disease and many other disorders.

The Myth of Levodopa Toxicity

So where is dopamine in this picture? Aren’t oxidation products of dopamine metabolism neurotoxic, killing neurons and leading to Parkinson’s disease? Haven’t we been told for years to minimize the use of levodopa and delay its use because we are killing substantia nigra neurons and potentially worsening Parkinson’s disease? Well, guess what: a host of experimental products have directly impacted the neurotoxic potential of dopamine oxidation hypothesis, inevitably leading us to conclude that issues surrounding alterations of dopamine metabolism are an epiphenomenon of Parkinson’s disease rather than being etiologically relevant.

As will be discussed later in this article, it is very clear that the neuropathological degenerative process in Parkinson’s disease begins in the lower brainstem, completely sparing the substantia nigra and dopaminergic neurons. It has been observed for years that a variety of other catecholaminergic and peptidergic neuronal systems are affected in Parkinson’s disease that could not be directly impacted by the neurotoxic effects of oxidizing dopamine. Later in the course of the disease, there is little question that a vast array of non-dopaminergic gray matter nuclei in the limbic system and the neocortex are affected, leading to the nonmotor complications of the disorder that so bedevil the treatment of our patients. All of these observations demonstrate the inadequacies of the dopamine oxidation hypothesis, inevitably leading us to conclude that issues surrounding alterations of dopamine metabolism are an epiphenomenon of Parkinson’s disease rather than being etiologically relevant.

The cellular pathology that leads to Parkinson’s disease first begins by nibbling at the edges of the nervous system with involvement of the dorsal motor nucleus of the vagus and the adjoining intermediate reticular zone, which have very long unmyelinated axons projecting to the enteric nervous system (Braak stage I). Other adjoining nuclei that are subserved by short myelinated axons, such as the solitary tract and the nucleus ambiguus, never demonstrate accumulation of Lewy neurites at any point during the evolution of Parkinson’s disease. At this point, Lewy neurites are also noted within the vasoactive intestinal polypeptide neurons of Auerbach’s plexus within the intestine.

Based upon these pathological observations, one can predict that the earliest manifestations of Parkinson’s disease would be gastrointestinal dysfunction. In fact, constipation, a very nonspecific and common symptom in the elderly population, frequently anticipates the development of the motor symptoms of the disorder by nearly two and a half decades. Based upon this information, the frequent decline of gastrointestinal function amongst the older members of our general population should not be looked upon with an entirely cavalier attitude. These symptoms have an anatomic basis and, in at least some circumstances, are anticipatory of the development of Parkinson’s disease.

Looking for Clinical Correlates

As the disease progresses (Braak stage II), the cellular changes begin to involve the lower raphe nuclei and the magnocellular portions of the reticular formation, specifically the gigantocellular reticular nucleus. In addition, changes begin to appear in the locus ceruleus region. With the involvement of these structures, one would anticipate that the clinical manifestations would expand to include disturbances of the sleep-wake cycle. As a potential anticipatory symptom of Parkinson’s disease over a decade before its motor onset, REM sleep behavior disorder has been increasingly recognized and could clearly be the result of affection of these structures at this stage.

At this point, in spite of extensive pathological findings confined to the medulla and lower pons, as well as the intestine, with relatively subtle associated clinical symptoms, there has been no involvement of the motor system structures, particularly the substantia nigra, and as a result, absolutely no motor manifestations of the disease would have been clinically detectable. Clearly, this implies that if we were capable of recognizing the disease at this juncture, it might be possible to intervene with some type of effective therapy to completely truncate the inevitable unfolding process that leads to the full-blown picture of Parkinson’s disease.

As the patient enters stage III of Braak’s scheme, Lewy neurites begin to appear in the pars compact of the substantia nigra. Concurrently, some involvement is noted within the amygdala and the basolateral nuclei, including the olfactory nuclei. In addition, the segmental pedunculopontine nucleus and the magnocellular nuclei of the basal forebrain, both cholinergically mediated systems, demonstrate neuronal inclusions. The oral raphe nuclei and the hypothalamic tuberomamillary nucleus also become involved.

At this stage, the disorder has clearly become well entrenched in multiple neuronal systems throughout the midbrain that utilize long, thin and poorly myelinated axons.
Given the anatomic distribution of these pathological findings, one would anticipate that our patients would begin to report impairment of sense of smell and taste (frequently retrospectively), to manifest the subtle classical motor findings of idiopathic Parkinson’s disease and also begin to demonstrate the very subtle neurocognitive changes that we well recognize with careful testing in our patients at this point.

Clinically speaking, this is the stage that we recognize idiopathic Parkinson’s disease and frequently initiate pharmacotherapy. It is at this stage that we experience with our patients the honeymoon period in the treatment of Parkinson’s disease that both doctor and patient find so encouraging and rewarding, but, as we have come to learn, should not lull us into a sense of complacency as to what the future may ultimately hold. Nonetheless, it is at this stage for one to two decades that we focus our vast armamentarium of therapeutic tools for the treatment of Parkinson’s disease.

It is at this point that our interventions have a truly spectacular impact on our patient’s ability to carry out their activities of daily living. When fluctuations and dyskinesias intrude upon this relatively blissful time, we can successfully employ our various pharmacologic tricks with meaningful success and can follow them up in the appropriately selected patient with electrical stimulation strategies applied to sub-cortical nuclei, temporarily regaining yet more meaningful function on a more sustained basis. However, given the underlying neuropathology already discussed, it is really no great surprise that our efforts at this stage are ultimately sometimes quite futile and misdirected. In particular, a careful analysis of the staging of the disease at this point would suggest that very aggressive cellular implantation and support strategies directed solely at dopaminergic cells are ill-conceived and doomed to failure. The pathological findings presage a period of gradually waning function with the growing list of non-motor, non-dopaminergically mediated symptoms that begin to dominate the daily life of the patient affected with Parkinson’s disease.

The hallmark of Braak’s stage IV is the presence of Lewy neurites in specific portions of the cerebral cortex. These portions lie at the transition zone between the allocortex and the neocortex, the anteromedial temporal mesocortex. This region is a critical choke point for the transfer of information from higher order cortical sensory association areas to the amygdala, entorhinal region and hippocampal formation, transferring information onward to the prefrontal cortex. Therefore, is of little surprise that clinically at this stage our patients are experiencing significant neurocognitive alterations of multiple higher order and limbically mediated activities, such as affect, memory, and attention.

Most of the neuronal systems affected at this juncture are not dopaminergically modulated and therefore would not be anticipated to be positively impacted by any of our current typical Parkinson’s disease interventions. At this stage, the non-motor complications of the disease begin to come to the fore as the primary sources of disability for our patients. It is at this point that we begin to hear about the newer, more distressing symptoms of the autonomic dysfunction, such as dyshidrosis, thermoregulatory dysfunction, urinary abnormalities, and sexual dysfunction. Orthostatic hypotension might also be a troublesome symptom.

Now our patients and their caregivers report neurocognitive change with altered emotionality, including depression, compulsive behavior, and panic. The patients are not frankly demented at this juncture, though there are definable, subtle defects of attention and memory that are recognized in everyday life by both patient and caregiver. They are now also demonstrating markedly altered sleep architecture with more

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<th>Braak Stage</th>
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<tr>
<td>I</td>
<td>Dorsal motor nucleus of vagus, VIP neurons of Auerbach’s plexus</td>
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<tr>
<td>II</td>
<td>Raphe nuclei, reticular formation, locus ceruleus</td>
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<td>III</td>
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<td>IV</td>
<td>Temporal mesocortex,</td>
<td>Apparent dysautonomia, neurocognitive change</td>
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<tr>
<td>V</td>
<td>Depigmentation of substantia nigra, prefrontal and sensory association neocortex,</td>
<td>Mild dementia, hallucinations, motor impairment, dyskinesias, increased dopaminergic sensitivity, impaired postural control</td>
</tr>
<tr>
<td>VI</td>
<td>Involvement of entire neocortex</td>
<td>Marked motor impairment, medication intolerance, dementia</td>
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Table 1. Staging of Parkinson’s Disease Progression
apparent REM behavior disorder, periodic limb movements of sleep, prominent restless leg syndrome and fragmented sleep. Many of these symptoms are seemingly compounded by dopaminergic therapy with prominent negative associations with dopamine agonist therapy. There is a growing intolerance of polypharmaceutical treatment. There is also a growing desperation on the part of the patient, the patient's family and the physician that a new, more troubling phase of Parkinson's disease is being entered.

Late-stage Progression
Entry into Braak's stage V is demonstrated by the complete denuding of the pigmented neurons in the substantia nigra along with an increasing involvement of the neocortex with the inclusion body pathology within prefrontal and higher order sensory association areas. This stage is reflected clinically by a worsening of many of the symptoms described above and their increasing refractoriness to any of our pharmaceutical interventions.

Frequently, our patients at this stage are clinically demented and suffering with profound visual hallucinations. It is not uncommon for us to render a clinical diagnosis of diffuse cortical Lewy body disease. Admittedly, this clinical diagnosis may well represent an artificial demarcation of the spectrum of idiopathic Parkinson’s disease. It is at this point that many palliative interventions are being introduced and dopaminergic interventions are being reduced or withdrawn, as their effects on the compromised neocortex are intolerable for patient and caregiver. We also begin to see the phenomenon of caregiver burnout and must begin to consider the possibility of institutional placement for our patient. This is also the time that our patients are frequently at risk of suffering severe injury due to marked deterioration of their postural control mechanisms.

Braak's stage VI represents the end-stage of this multi-decade neurodegenerative disorder. Its hallmark is the spread of the inclusion body pathology throughout the entire neocortex rendering our patients incapable of caring out their most personal activities, necessitating intensive support throughout the day. This is the time that virtually all of our patients require institutionalization of one form or another. All of the optimism engendered by our treatment strategies has long since dissipated, as there is no longer the anatomical substrate available for any meaningful amelioration of the dire clinical situation.

The Importance of Early Intervention
We have attempted to present in this article an updated realistic paradigm for a clinical understanding of Parkinson’s disease in light of recent advances in neuropathology and neurochemistry. One must now view Parkinson’s disease as a disorder that might well begin two to two-and-a-half decades before the patient ever presents to a physician clinically and that the entire span of this disorder might well extend up to four or more decades in some instances.

The physician must realize that by the time he or she has become involved in the care of the Parkinson’s disease patient, the underlying neuropathological process has been evolving at an inexorable pace for many years and that the interventions that will be implemented may have a spectacularly positive impact over the next one to two decades that may lull physician and patient into a complacent state. Nonetheless, there will come a time when the patient's underlying neuropathological process reaches Braak's stage V, when their clinical syndrome will essentially become refractory to all of our current and anticipated clinical interventions.

Based upon this analysis, it becomes evermore compelling for us to develop strategies specifically directed at the molecular and cellular neuropathology that underlies this disorder. It becomes evermore important for us to learn ways to recognize this disorder as early as possible, potentially at an entirely preclinical phase (Braak’s stage II), at which point one can only hope that neuroprotective strategies could conceivably halt the disorder before it is ever manifest clinically. Presently, our tools and paradigms for accomplishing such a task are most limited. Nonetheless, with increasing recognition of the true temporal sequence of the evolution of Parkinson’s disease neuropathology, it should be possible to reframe our approach to the disorder in a therapeutically meaningful way.

We are not yet ready to do a great deal better than what could be done for Robert DeNiro’s character in the late 1960s, but we certainly know so much more about Parkinson’s disease at this time, which should lead us to reorient our thinking about the disease that is more in line with its true clinical extent and neuropathology.

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