Accelerating Research on Genes and Environment in Parkinson's Disease

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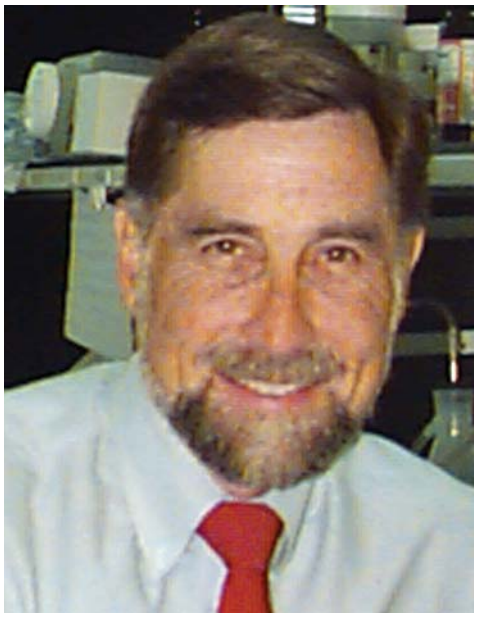

Dr. Langston is the scientific director, chief operating officer, and founder of the Parkinson's Institute in Sunnyvale, California. His current research interests include the study of mechanisms of neuronal degeneration, the etiology of Parkinson's disease, and the development of new strategies to slow or halt disease progression. Dr. Langston serves on numerous editorial boards and advisory committees, and is also chief scientific advisor for Michael J. Fox Foundation for Parkinson's Research.

Although many accomplishments can be attributed to Dr. Kenneth Olden's distinguished career during his tenure at the National Institute of Environmental Health Sciences (NIEHS), one of the most long-lasting may well be his recognition of the potential relationship between environmental factors and human neurodegenerative disease and that the time had come to take a proactive approach toward advancing the science in this area. Until recently when we thought of risk factors for diseases that lurk in the environment, menacing agents such as asbestos, mercury, lead, and a wide cast of other known environmental pollutants would have come to mind. But the connection of potentially damaging environmental exposures and degenerative brain diseases such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), or even Alzheimer's disease is a relatively new concept for most people, scientists and nonscientists included. However, this perception is rapidly changing, in no small part as a result of Dr. Olden's astute scientific sensors and keen vision of the future. In this article, I review the evolution of ideas and research on the cause of Parkinson's disease and provide an overview of where we are now. The final section of this article examines the future of this research and highlights what NIEHS, under Dr. Olden's leadership, has done to help make it all happen.

The History of Theories on the Cause of Parkinson's Disease

In his original article in 1817, James Parkinson (Parkinson 1817) theorized that the disease that bears his names was caused by stress, an argument that may still have some merit today. As the end of the 19th century approached, debate over the cause sharpened as to whether the disease was genetic in nature [a position

Although it seems likely that genetics plays a contributing role in typical, sporadic Parkinson's disease, the now compelling twin studies provide solid evidence that nongenetic factors are important contributors as well. Putting all this together presents the next great challenge for those of us conducting research on the disease.

favored by the distinguished English neurologist W.R. Gowers (Gowers 1888)] and the likelihood that it was due to something in the environment, an idea that was espoused by the famous French neurologist J.M. Charcot (Charcot 1878). In the early 20th century, environmental causes again came to the forefront with the great flu pandemic of 1918–1920 known as Von Economo's encephalitis. Many patients who survived the flu later developed what is now known as postencephalitic parkinsonism. For a while this was thought to be the cause of Parkinson's disease, but as these cases began to die out, it was clear that Parkinson's disease was not disappearing. Focus shifted back toward genetics again in the 1940s through the 1960s, with a number of groups reporting a higher familial incidence of Parkinson's disease in relatives of patients with the disease, suggesting a strong genetic component. In retrospect, many of these studies were flawed when considered in light of modern epidemiologic techniques.

However, these shifts in opinion that spanned well over a 100 years seem tame when considered in light of the events that occurred over the last two decades of the 20th century. The first of these broke onto the scientific scene in 1982, with an outbreak of "parkinsonism" in a number of young heroin addicts in northern California (Langston et al. 1983). What was so remarkable about the clinic syndrome was that these young individuals exhibited pure, unalloyed parkinsonism, without features of damage to other parts of the nervous systems that virtually all neurotoxicants known to induce parkinsonism typically caused (Ballard et al. 1985). After several weeks of intensive medical sleuthing, it was finally determined that a clandestine chemist just outside the San Francisco Bay Area was making a synthetic heroin in his garage but had made an error in chemistry and produced the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, now widely known as MPTP. When the MPTP-tainted heroin hit the streets, young addicts who self-administered it developed severe parkinsonism over a period of days. We now know that MPTP is one of the most selective neurotoxins ever discovered. After entering the brain, it is converted into 1-methyl-4-phenylpyridinium ion, or MPP^+, which is taken up into dopaminergic neurons, where it selectively inhibits complex I of the mitochondrial respiratory chain and leads to degeneration of these nigrostriatal neurons. These are the very same neurons affected by Parkinson's disease, accounting for the extraordinary similarity between the signs and symptoms of the two disorders. Because of the similarity of MPP^+ and the herbicide paraquat and the fact that such a simple compound could induce so many of the features of Parkinson's disease, an intensive search for environmental agents that might cause the disease was launched by many groups and continues to this day. Indeed, a variety of studies have pointed toward environmental agents such as herbicides and insecticides as increasing the risk for the disease (Tanner 1989). As further evidence to the biologic plausibility of this hypothesis, the naturally occurring pesticide and complex I inhibitor rotenone has now been shown to be selectively toxic to the substantia nigra (Betarbet et al. 2000), as has paraquat (McCormack et al. 2002). Furthermore, in the last 20 years, myriad epidemiologic studies have shown that the risk for Parkinson's disease is increased by exposure to a variety of environmental agents, with pesticides topping the list (Tanner 2003).

The second major event at the end of the 20th century with profound implications for the cause of Parkinson's disease also began with the clinical observation of a cluster, but this time the cluster was a familial one involving a large family of Italian decent known as the Contursi kindred (Golbe et al. 1990). This family was found to have multiple generations of individuals affected by progressive parkinsonism. Importantly, pathological examination in at least one patient had shown the presence of Lewy bodies, intracellular inclusions that are a hallmark of idiopathic Parkinson's disease, making it a very close fit for the typical disease. In 1997 the causative mutation was identified in this kindred, and it proved to be in the gene responsible for encoding for a protein known as α-synuclein (Polymeropoulos et al. 1997). It was quickly postulated that this gene might be responsible for a substantial portion of patients with Parkinson's disease. However, within a year of this discovery, there were two surprising developments. First, the mutation in this family proved to be extraordinarily rare, limited to a very small number of families worldwide. Second, the protein α-synuclein was found to be an important component of Lewy bodies, not just in the cases with mutations but in all cases of Parkinson's disease, and even in Lewy bodies associated with other disorders such as a condition known as dementia with Lewy bodies (DLB; Spillantini and Goedert 2000; Spillantini et al. 1997). Consequently, within a short time, Parkinson's disease entered the domain of a group of diseases known as "protein folding disorders," thus changing the course of basic research on the disease. But a first-class mystery still remains to be solved: how does synuclein become involved in the neurodegenerative process that occurs in the vast majority of patients with Parkinson's disease who do not have mutations in this gene? Nonetheless, more and more pieces of the puzzle were falling into place, and as a result, by the arrival of the 21st century, it was unequivocally clear that the pace of research on the cause of Parkinson's disease was rapidly accelerating.

Enter, the NIEHS

Although I have never discussed this with Dr. Olden, I suspect his keen eye had been watching this story evolve beginning somewhere in the 1980s. However, the situation was certainly a complex one, and it was still not clear how these various pieces would come together at that moment. No "smoking gun" had been found as an environmental cause of the disease, and as noted above, mutations in the gene encoding for synuclein had proved to be exceptionally rare [two more have been discovered as of this writing: Kruger et al. (1998) and Zarranz et al. (2004)]. On the other hand, the possibility remained that one or many more yet to be discovered genes would prove causative in many more if not most patients with Parkinson's disease. I suspect that the tipping point came for Dr. Olden with the publication of a twins study in 1999 (Tanner et al. 1999). This study involved all living twin pairs who had served in World War II. After the war, the National Academy of Sciences set up a registry to follow all these twin pairs for medical research purposes, and continues to follow them today. In the early 1990s, our group, led by Carolyn Tanner, began a study in this cohort to determine the concordance of Parkinson's disease in both identical (monozygotic) and fraternal (dizygotic) twins. Our hypothesis was that if the disease were inherited, there should be a significant difference in concordance between these two groups. The results of this study were clear-cut and highly significant. In the twin pairs in whom the disease began after 50 years of age (which constitutes > 95% of all Parkinson's disease), the concordance rates were virtually identical, suggesting that nongenetic factors play an important role in the disease. Interestingly, in patients younger than 50, concordance was dramatically different between monozygotic twins (where four of four twin pairs were concordant) and dizygotic twins (where only 2 of 12 twin pairs were concordant). This strong evidence of heritability in younger-onset patients may well reflect that most of the genetic forms described to date typically have a young onset. The caveat for this component of the study is that the number of twin pairs younger than 50 was small. Overall, the conclusion that can be drawn from the study is that nongenetic factors must play a substantial role in patients with typical Parkinson's disease. Importantly, this study has recently been replicated using the Swedish Twins Registry (Pedersen et al. 2002).

It was not long after the publication of this study that Dr. Olden visited our institute to survey current research on the epidemiology and toxicology of Parkinson's disease. Soon thereafter, the NIEHS announced a series of workshops and seminars on etiologic factors and Parkinson's disease and sponsored the 19th International Neurotoxicology Conference on

"Parkinson's Disease, Environment and Genes" in the late summer of 2001. The conference was co-organized by Dinato Di Monte and Deborah Cory-Slechta and brought together an impressive assemblage of epidemiologists, geneticists, clinicians, and individuals from a variety of basic research disciplines; it is considered one of the most stimulating and productive scientific meetings on gene–environment interaction in Parkinson's disease. In retrospect, this meeting proved to be a prelude to the thinking of Dr. Olden and his staff, which was a vision that helped shape research in a way that had not been seen before, at least not in field of Parkinson's disease.

Centers for Coordinated Parkinson's Epidemiologic Research Are Born

On 6 December 2001, NIEHS announced at $20 million national initiative to investigate gene–environment interaction in Parkinson's disease. To quote from the Request for Application (RFA) (NIEHS 2001):

> A variety of lines of evidence suggest that both environmental and genetic factors contribute to sporadic Parkinson's Disease (PD), the most common form of the disease. Identification of the full complement of relevant environmental and genetic components, and an understanding of their interactive roles in the neurodegenerative process, is lacking. Such information is critical for designing effective prevention and intervention strategies. To accelerate the pace of progress in this important area and the translation of findings into the public health arena, the NIEHS is creating a Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) consortium program to foster multidisciplinary research approaches to elucidate gene–environment interactions in PD. This program seeks to provide the science-based foundation for efforts to prevent and/or ameliorate the devastating effects of this disease.

This competitive and comprehensive program was truly unique in that it required full collaboration of all funded centers from the beginning, and in that sense it was a truly integrated joint effort between laboratories throughout the United States, even before the first penny was expended. But what was truly novel, at least for those of us in the Parkinson's disease research community, was that the RFA clearly recognized there were now enough pieces of the Parkinson's puzzle in place to warrant more than the more traditional investigator-initiated grant programs. It left little doubt that the NIEHS had concluded that research on the cause of Parkinson's disease had advanced to the point at which it was time to be proactive and to begin to sculpt the direction of the research aimed at finding the cause of the disease.

The RFA was impressive in other ways as well. It clearly outlined the current state of knowledge of the cause of Parkinson's disease, ranging from very basic aspects such as the suspected role of oxidative stress at the cellular level to such fascinating epidemiologic observations as indications that cigarette smoking and caffeine consumption protect against the development of the disease. The common thread ranging throughout the RFA was that the disease is likely due to one or more environmental influences in combination with one or more genetic susceptibility factors. Stated another way, it embodied an axiom that I have heard Dr. Olden use on more than a few occasions: "Genetics loads the gun, but environment pulls the trigger."

The three main goals of the program as it has evolved are *a*) to identify genetic and environmental factor interactions that contribute to Parkinson's disease, *b*) to develop a mechanistic understanding of how gene–environment interactions trigger the pathophysiological processes that ultimately produce the disease, and *c*) to develop a knowledge base that enables translation of research findings into new strategies for prevention and intervention in Parkinson's disease.

From a broad perspective, the program provides a road map for current and future research, with an emphasis in least seven scientific research avenues: *a*) mutations and polymorphisms in relevant Parkinson's disease genes, *b*) environmental risk factors, *c*) oxidative stress, *d*) neuroprotection, *e*) protein aggregation and degradation, *f*) development of animal models, and *g*) inflammation. This reads like a "most wanted" list of the cast of characters when it comes to our suspects as causative factors in Parkinson's disease and was welcomed by the scientific community as an exceptional opportunity to accelerate research in all of these areas.

The three successful competing centers were Emory University (Timothy Greenamyre, principal investigator), University of California Los Angeles (Marie-Françoise Chesselet, principal investigator), and the Parkinson's Institute (with the author of this article as principal investigator). Between these three centers, a rich diversity of individual projects has been initiated. Many of these have common themes, including the effects of oxidative stress, dopamine oxidation, and

iron in the nigrostriatal system; the role of protein aggregation and overexpression in nigrostriatal degeneration; a wide variety of studies on the interaction of all these aspects and various pesticides (rotenone and related compounds, as well as paraquat); interactions of synclein and parkin with exposures to these and other neurotoxicants; the role and interactions of the dopamine uptake system with these proteins; studies of the proteasomal system and its relationship to abnormal protein function; and a variety of epidemiologic studies to investigate genetics and environmental exposures in cohorts ranging from Iceland to southern California and the National Academy of Sciences World War II Twins Registry. One study is aimed at directly investigating the potential neuroprotective effects of nicotine in animal models, representing an example of "reverse translational research" by virtue of taking one of the most robust of all epidemiologic findings in Parkinson's disease—the inverse relationship between cigarette smoking and the risk for the disease (Hernan et al. 2002)—back to the laboratory to determine the neurochemical mechanism(s) that might underlie this observation. More information can be found on this innovative and proactive approach to advancing research on a specific neurodegenerative disease in a focused and integrated way by visiting the CCPDER website at http://www.niehs.nih.gov/ccpder/research.htm. This site contains summaries of each of the individual projects and the respective lead scientists for each; it is highly recommended for anyone interested in learning more about the program.

One of the aims of this entire process is to encourage, facilitate, and foster intensive interaction, coordination, and collaboration, with the hope that eventually the "whole will become more than the sum of the parts." While this has without doubt occurred with increasing collaborations between centers, there have already been some dramatic and totally unanticipated developments that have been, at least in part, fostered by the CCPDER program.

The California Parkinson's Disease Registry

Perhaps one of the most important research tools that the newly forged collaborations and CCPDER program helped stimulate has been the establishment of the California Parkinson's Disease Registry. The need for reliable and unbiased population-based data on Parkinson's disease has arguably become most urgent for research directed toward discovering environmental determinants of the disease. Although a large number of case–control studies have repeatedly shown increased risk for Parkinson's disease associated with a variety of environmental factors, the increases in risk have typically been only in the range of 2- to 3-fold, and as noted above, to date no smoking gun has been found. Unfortunately, true population-based studies are few and far between. Rather, most studies are clinic or hospital based, which can be plagued by referral bias and other confounding factors. Furthermore, hospitalization records are inadequate for tracking Parkinson's disease because most care is provided in outpatient settings. In short, although there are many studies using selected populations of patients with Parkinson's disease, to date we have no real denominator. We do not know with certainty how prevalent Parkinson's disease really is or whether the disease is changing with time. Nor do we know with certainty whether specific subpopulations or geographic areas are more affected than others. Given the state of the science, this lack of knowledge is proving to be a major bottleneck, preventing research progress in this area. A registry that requires the reporting of all cases of a particular disease is the only way to solve this problem and avoid the bias inherent in almost all other approaches. Establishing a registry therefore has the potential to make a dramatic contribution to efforts to find cause or causes of Parkinson's disease.

California is an ideal place to establish such a registry. In addition to the state's enormous size, it has longstanding experience in this area, with its statewide cancer and birth defect registries. Consequently, California has extensive experience with the creation of and strict adherence to confidentiality guidelines through its existing registries. The state has also been a forerunner in the nation when it comes to establishing environmental surveillance and tracking systems for many pollutants and has a strong track record for environment research. In fact, California has mandated reporting of pesticide and toxicant use for decades, and as noted above, exposure to such agents is one of the leading hypotheses regarding the cause of Parkinson's disease. But perhaps its most important strength is its rich diversity (race/ethnicity, geography, rural/urban location, socioeconomic status, occupation), which provides an ideal climate to investigate risk factors for Parkinson's disease.

It may have been fortuitous, then, that two of the three successfully competing CCPDER institutions (the Parkinson's Institute and the University of California Los Angeles) are located in California. This helped provide a critical mass of scientific leadership, which, when combined with the willingness of Assemblyman Dario Frommer to introduce the bill (California Assembly Bill 2248, 2004), the untiring efforts of an inspired group of patient advocates, and Governor Arnold Schwarzenegger's willingness to sign the bill into law on 30 September 2004, have made this registry a reality. I believe this is a historic step and will be regarded as a landmark in the history of our search for the cause of Parkinson's disease. But there is just one more fact that must be mentioned. Because of the enormous budgetary problems faced by California, this bill would not have passed if the NIEHS and the Michael J. Fox Foundation for Parkinson's Research had not committed starter funds for a pilot study. Once again, Dr. Olden to the rescue.

A Look at the Future

Looking back over the last 20 years, the research field for Parkinson's disease has seen many theories on mechanisms of cell death appear on the research horizon, including oxidative stress, excitotoxicity, mitochondrial dysfunction, apoptosis, inflammation, abnormal protein folding/aggregation, and most recently proteasomal dysfunction. As noted above, many of these are captured in the various CCPDER subprojects. This final section provides a brief snapshot of where the field is now and some speculation as to what we can expect in the next few years. I believe two important lines of research are having a high impact on current directions in research. The first is the continuing stream of newly discovered mutations that cause various forms of inherited parkinsonism.

To step back a moment, after the discovery of mutations in the gene encoding for α-synuclein, it was not long before the cause of another form of genetic parkinsonism began to unravel. For some time, an autosomal recessive form of young-onset parkinsonism had been recognized in Japan. In 1998 Kitada et al. (1998) reported a causative mutation in the encoding region for a protein now known as parkin. By now the number of mutations and deletions that have been reported to cause this form of parkinsonism is now well over 50. The disease has a young onset, often shows prominent dystonia and fluctuations, exhibits L-dopa responsiveness, and pathologically shows nigral cell degeneration, but Lewy bodies are for the most part lacking. Parkin is an E-3 ubiquitin ligase, so it may play a role in protein handling and proteasomal function. The next form of genetic parkinsonism that was discovered is in the encoding region for a protein known as DJ-1 and was reported in families from both Holland and Italy (Bonifati et al. 2003). The parkinsonism is said to be relatively pure, and the age of onset is again relatively young. To date there have been no pathologically studied cases. DJ-1 may function as a protease (Bandyopadhyay and Cookson 2004) and may also have a role in the regulation of transcription. Interestingly, the protein appears to be sensitive to oxidative stress (Canet-Aviles et al. 2004; Kinumi et al. 2004; Mitsumoto and Nakagawa 2001). When exposed to hydrogen peroxide or the redox cycling agent paraquat, DJ-1 undergoes an acidic pI shift (from 6.2 to 5.8) (Canet-Aviles et al. 2004), providing a link with one of the neurotoxicants that affects the dopaminergic system. The third in the series of newly reported parkinsonogenic mutations is known as *PINK*1 (PTEN induced putative kinase 1), which is an autosomal recessive form of parkinsonism recently reported by Valente et al. (2004). Mutations were identified in two Italian families (a W437Stop mutation) and in a Spanish family (a G309D mutation). The average age of onset is in the sixth decade; the parkinsonism is fairly typical (including L-dopa responsiveness) and the course fairly benign. The protein appears to be a mitochondrial kinase, and Valente et al. (2004) have shown that overexpression of PINK1 but not the G309D mutant protects cells against proteasome-inhibitor–induced mitochondrial damage, yet another interesting potential link between parkinsonism (no pathological cases have been reported), mitochondrial function, and proteasomal function. Finally, and quite recently, the gene for *PARK*8 [Parkinson disease (autosomal dominant) 8] has been identified by two different groups in the gene encoding for *LAAK*2 (leucine-rich repeat kinase 2), a large protein containing leucine-rich repeats and Ras/GTPase, tyrosine kinase-like, and WD40 domains (Paisan-Ruiz et al. 2004; Zimprich et al. 2004). Families were identified from England, Spain, and the United States. Parkinsonism is dominantly inherited, and between the two reports, a total of five different mutations were identified. What seems to be truly unique about *PARK*8

is the stunning degree of neuropathological diversity that patients with mutations have manifested, including *a*) typical Lewy bodies with nigral cell degeneration, *b*) relatively pure nigrostriatal degeneration, *c*) a DLB-like picture, and *d*) supranuclear palsy-like pathology (Zimprich et al. 2004). Patients in some families demonstrated not only parkinsonism but also dementia and amyotrophy. Although it is very difficult to predict how this story will unfold, the authors suggest that this protein may be crucial to the initiation of a number of neurodegenerative diseases, perhaps through phosphorylation of both synuclein and tau, which in turn could be a key event leading to protein misfolding and neurodegeneration (Zimprich et al. 2004).

I believe one of the most important recent observations in the genetics arena relates to a new twist in the α-synuclein story, which is that synuclein overproduction alone can cause a parkinsonian condition. This discovery occurred as a result of identifying both triplications and duplications of the synuclein gene in several kindreds of dominant parkinsonism (Chartier-Harlin et al. 2004; Farrer et al. 2004; Hofer et al. 2004; Ibanez et al. 2004). Thus, normal synuclein itself can lead to a parkinsonian distribution of neuronal degeneration, which provides yet another link between typical Parkinson's disease. Thus, the protein could provide a vital clue to the pathogenic process in typical Parkinson's disease.

The second recent observation likely to have a high impact on current directions in research relates to a recent study of McNaught et al. (2004). These investigators administered two proteasomal inhibitors (epoxomicin and PSI) to rats over a 14-day period and then observed a progressive deterioration in motor function over a 2-week period, which improved after administration of the dopamine agonist apomorphine. Examination of the brains of these animals showed not only nigral cell loss with a corresponding striatal dopamine depletion but also neurodegeneration in the locus coeruleus, dorsal motor nucleus of the vagus, and the nucleus basalis of Meynert, a pattern of cell loss that is strikingly similar to that seen in Parkinson's disease and is not observed in any other of the toxicant-induced animal models of Parkinson's disease. Furthermore, intracytoplasmic α-synuclein/ubiquitin-containing inclusions were seen in the areas of neurodegeneration that were reminiscent of Lewy bodies.

How does all this begin to come together? First, it seems fair to say that more and more signs point to the role of protein dysfunction, with the spotlight continuing to shine on synuclein. What may be the most important observation to date is that even normal synuclein is capable of causing a form of parkinsonism and may thus help explain the distribution of lesions in typical Parkinson's disease. The proteasome story adds yet another dimension and again points to "protein handling" as a key player. Whether this is just another potential contributor to failed synuclein handling or points to a completely different mechanism of cell death remains unknown at the moment, but clearly more pieces of the puzzle are now in front of us.

What is missing at this point and continues to represent a great unknown is a reason why some people get the disease and others do not. We all have synuclein in our brains (it is estimated to make up about 2% of protein content in the brain), yet the lifetime risk for the disease is only about 2%. Furthermore, although it seems likely that genetics plays a contributing role in typical, sporadic Parkinson's disease, the now compelling twin studies provide solid evidence that nongenetic factors play an important role as well. Putting all this together presents the next great challenge for those of us conducting research on the disease. One novel hypothesis that our group is actively pursuing at the current time is that minor or low-grade alterations in α-synuclein expression due to variations in its promoter region (Chiba-Falek and Nussbaum 2003; Farrer et al. 2001; Pals et al. 2004) could represent a genetically determined risk factor for the disease, with environmental agents acting as potential triggering or "seeding" agents that accelerate aggregation beyond the point at which normal cellular machinery can successfully cope with the process, and abnormal aggregation leads to disease. And there is some very interesting experimental evidence to support this. *In vitro* studies have shown that the fibrillization rate of α-synuclein is concentration dependent and that certain pesticides such as rotenone, paraquat, and dieldrin accelerate the rate of α-synuclein fibril formation (Uversky et al. 2001). If such exposures occur in the setting of lifelong low-grade overexpression of synuclein, the end result could be what we call Parkinson's disease. Furthermore, as pointed out by McNaught et al. (2004), proteasomal inhibitors are widely distributed in the environment and are produced by bacteria and fungi

that affect crops and infect wheat and flour. They are found globally in the soil in gardens and farmland, and thus in rural areas and well water. The latter observation is of particular interest because one of the seminal observations that originally launched many of the studies on environmental agents and Parkinson's disease was a study from Saskatchewan, Canada, in 1986 (Rajput et al. 1986) that reported a striking association between well-water consumption and Parkinson's disease. To this day, the cause of this association remains unknown.

To bring this story full circle, once again a specific collaboration fostered by the CCPDER program (and funded by the Michael J. Fox Foundation for Parkinson's Research) is helping to push the science forward in unexpected ways. Working with two CCPDER subprojects, one of which involves the study of Parkinson's disease in pesticide applicators (headed by Caroline Tanner), and the second of which is a study of Parkinson's disease in two counties in southern California where there is known heavy pesticide exposure (headed by Beate Ritz), we plan to determine if changes in the synuclein promotor region combined with specific environmental agents significantly enhance the risk for Parkinson's disease. This study would be difficult without the exceptional exposure data available in these two populations, and to the best of my knowledge this is the first such study attempting to directly link the effects synuclein expression and specific environmental exposures to the risk for Parkinson's disease in human populations. If successful, this research venture will represent yet another example of the foresight and vision exhibited during Dr. Olden's tenure as the director of the NIEHS, as the collaborative infrastructure created by the CCPDER program helped make this, and other similar projects possible.

Summary

There is an increasing sense of anticipation in the medical and scientific community that finding the cause of Parkinson's disease is becoming an achievable goal. In this article, the history of the search for the etiology of this mysterious disease is reviewed, focusing on both genetic and environmental theories. A snapshot of where the science is at the current time is provided, along with some speculations as to were the next round of discoveries are most likely to be made. There is little doubt that research is moving forward at an intense pace, and it is becoming increasingly clear that a variety of scientific disciplines, ranging for epidemiology to protein chemistry, are likely to be required to unravel the cause or causes of the disease. This exciting state of affairs is captured in a recent initiative by the National Institute of Environmental Health Sciences (NIEHS) known as the Collaborative Centers for Parkinson's Disease Environmental Research. This program is proactive, emphasizes the contributions of both genes and environment in the disease, and embodies many of the scientific avenues that will likely be required to push the search for the cause or causes forward. It is concluded that many of the critical pieces of the puzzle needed to solve this disease are now before us, and that creative and inspired leadership at the national level, such as that demonstrated by NIEHS, is needed more than ever at this important juncture in the scientific history of Parkinson's disease research.

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Notes

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