The Coming Epidemic of Neurologic Disorders: What Science Is – and Should Be – Doing About It

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Abstract: The Earth's population is aging fast, and the coming sharp increase in the number of people over age sixty-five will bring with it an epidemic of age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Currently, no cures exist for the major neurologic disorders. Unless cures can be found, by 2050 the cost of these diseases will exceed $1 trillion annually in the United States, and the burden for other countries will scale with their populations. Despite exciting advances in our understanding of these diseases, both government research funding and the efforts of industry have failed to keep pace with this unmet medical need. Private philanthropy has done better, but the total dollars spent on developing diagnostics and therapeutics for neurologic disorders still lags far behind that spent on much less prevalent diseases. The challenge for biomedical research in the next forty years is to identify markers that would allow early detection of high-risk cohorts, and to develop therapies that either will prevent the diseases from starting at all in susceptible populations or will arrest their progression before severe damage to the central nervous system has occurred.

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What would you think if you were told that the entire population of the four largest cities in the United States had suddenly come down with an incurable, fatal disease? You would probably suspect a terrorist biowarfare attack or else the emergence of some horrible new strain of bird flu or Ebola-like virus. Barring a medical miracle, something very like that is certain to happen in about forty years' time. By 2050, the United States is predicted to have thirty-two million people over the age of eighty, and unless something is done to prevent it, about sixteen million of them will have Alzheimer's disease. That's more than the populations of New York, Los Angeles, Chicago, and Houston put together.

The United States is not alone in this explosion of the elderly and potentially infirm. Throughout the world today, there are more people aged sixty-five and older than the entire populations of Russia, Japan, France, Germany, and Australia – combined.

That seems like a lot, but it is miniscule compared with what is coming. From 1950 to 2050, the world population will have increased by a factor of 3.6; but those sixty and older will have increased by a factor of 10, and those eighty and older will rise by a factor of 27.

Figure 1 shows how the world's demographics are driving this outcome. Right now, only a handful of countries have 20 percent of their population over the age of sixty-five; by 2050, most countries will. That has never happened before in human history. For hundreds of thousands of years, the age distribution of the human population has been a pyramid, with a large number of healthy, productive young people at the bottom supporting a much smaller number of sicker, nonworking old people at the top. (That's right: life is a Ponzi scheme.) But a perfect storm of low birthrate in the developed world combined with increased life expectancy in most countries is causing the pyramid to invert. At the moment, the fastest-growing demographic group in the United States consists of octogenarians and above.

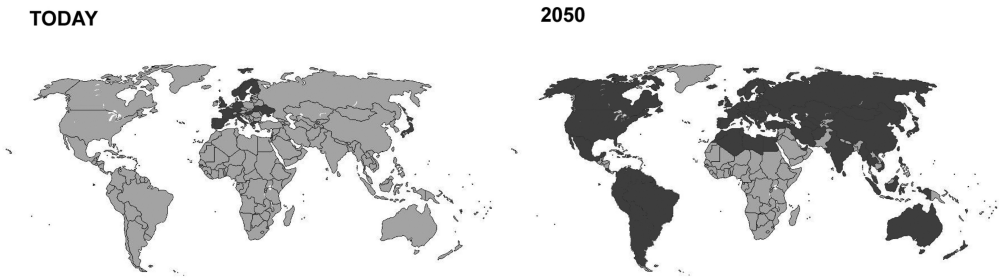
If older people were generally healthy, this trend would not be alarming. Unfortunately, age is a risk factor for most of Hamlet's thousand natural shocks that flesh is heir to: the incidence of most cancers, stroke, and heart disease rises with age, for example. But it is the major neurologic disorders that show the most dramatic age-dependence, with an incidence for most of them that increases exponentially after about age sixty. If you are fortunate enough to live to your mid-eighties, you have about a one in two chance of being unfortunate enough to suffer from either Alzheimer's or Parkinson's disease.

When we consider the financial and human costs of a future in which tens of millions of people will be afflicted with these devastating disorders, it becomes clear that we cannot afford to let that future materialize. Today, the economic cost of untreatable neurologic diseases exceeds $350 billion per year in the United States alone. By 2050, it is estimated that a single one of these diseases, Alzheimer's, will cost the country $1 trillion annually (the total Gross Domestic Product is currently about $15 trillion). Statistics for other developed countries scale by their populations.

The human cost is almost incalculable. Most Alzheimer's and Parkinson's patients are cared for at home, and the combined psychological and financial burden on their caregivers is crippling. It is estimated that there are fourteen to fifteen million unpaid Alzheimer's caregivers devoting seventeen *billion* hours to looking after a relative or friend with the disease, and that their combined economic loss is greater than $200 billion per year. These numbers will, of course, only increase as the number of patients increases during the coming decades. It used to be said during the Cold War years that you couldn't understand the Russian psyche until you appreciated the fact that, statistically, every family in the Soviet Union lost a close relative in World War II. In forty years' time, statistically, almost every family in the United States will have a relative with Alzheimer's or Parkinson's disease, and much of the rest of the developed world will be in the same situation.

How are governments and biomedical research funding agencies responding to this looming crisis? One has to say, not all that well. In the United States, for example, federal support for Alzheimer's research is, on a per-patient basis, about thirty times less than federal funding for HIV/AIDS research. (That is not to imply that AIDS funding is too great, but to suggest that Alzheimer's funding is woefully inadequate.) Encouragingly, President Obama recently announced a war on

Figure 1
Worldwide Increase in the Share of Population over the Age of Sixty-Five



Black shading denotes countries where those over the age of sixty-five make up more than 20 percent of the population today and are projected to in 2050. Data for this figure were taken from various sources, principally the World Health Organization and the United Nations. Although the demographic information for different countries is of varying reliability, the trend is clear. Source: Figure created by author.

Alzheimer's disease, with a goal of finding a cure by 2025. This is an admirable objective, and he has called for about $50 million in new research funds to support it in the coming budget year. Still, that is far below the more than $2 billion that would be needed to bring funding for this disorder into line with its present and future impact on the United States.

Nor has that darling of political conservatives, the private sector, exactly stepped up to the plate. Many drug companies, for reasons that will be explained below, have actually been quitting the central nervous system disease sector recently, despite the gigantic profits that would accrue to anyone first-in with an effective Alzheimer's or Parkinson's drug.

Ironically, this bailing out and inadequate funding is occurring at a time when unprecedented advances have been achieved in our understanding of these hitherto mysterious diseases, with new discoveries coming at an ever-increasing rate. To understand why the prospect of finding treatments has never been better, and yet the very companies that are needed to bring such treatments to the clinic appear to be scared off, it is useful to look at what we now know about neurodegenerative illnesses.

There are many disorders of the brain that are characterized by the slow dying of neurons, the nerve cells that send electrochemical signals through the brain's circuitry. The major disorders, in terms of prevalence, are (1) the dementias, which include Alzheimer's disease, Lewy Body dementia, Huntington's disease, and the so-called frontotemporal dementias; (2) the movement disorders, the chief of which is Parkinson's disease; and (3) the motor neuron diseases, of which the most common is amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease, after its most famous victim. Each of these diseases presents with symptoms that can be understood, at least in part, by the specific death of neurons in a particular region of the brain (although generally many other regions are also affected, particularly in the latter stages of the disease). Progression can be rapid, as in the case of ALS, where death typically occurs three to five years after the appearance of symp-

toms, or very slow, as in most cases of Parkinson's disease, which may progress to fatality over a twenty-year period. There is no cure for any of these diseases, and the few existing treatments either only relieve symptoms for a period of time or have very little effect on progression.

Despite these apparent differences in presentation and primary site of degeneration, it is now clear that there are two striking commonalities among these disorders. The first is that in or around the damaged neurons, one can often observe dense aggregates of tangled-up protein molecules, with a specific, primary protein component that is largely characteristic of each disease. For example, the senile plaques that are the histopathological hallmark of Alzheimer's disease contain large amounts of a misfolded small protein called Abeta. Lewy bodies, characteristic of Parkinson's disease and Lewy Body dementia, are primarily composed of aggregates of the protein alpha-synuclein.[1] This observation suggests that protein misfolding and aggregation may play a role in the pathology of these diseases.

The second commonality is that the major neurodegenerative disorders come in two flavors: a sporadic form that is not inherited and accounts for the majority of cases, and a rarer genetic form that runs in families in a predictable, Mendelian pattern. (The exception is Huntington's disease, which appears always to be genetic.) With the complete sequencing of the human genome earlier in this century and advances in genetic mapping techniques, it has now become possible to identify many, though not yet all, of the genes whose mutation is responsible for the inherited forms of some of these disorders; and one of the first observations made was that the gene coding for the major protein component of the specific aggregates was usually one of them. Moreover, when the mutant forms of the proteins were made and studied, it was typically found that the mutations made the protein unstable and prone to aggregation, both in the test tube and in cultured nerve cells. Occasionally, it was also possible to link mutations in some of the other genes that did not code for that protein but were responsible for cases of the disease, with increased aggregation of the same protein.[2]

Thus, over the past dozen or so years, a model has emerged for the rare, familial forms of most of the major neurodegenerative diseases that can be summarized as follows: in order to function, protein molecules must fold properly, like an origami bird with wings that flap. But some mutations, either in the gene that codes for the bird itself or in other genes that somehow help the bird to fold (or affect its stability when it is folded, or in some cases its location inside the cell), lead to a misfolded bird – a crumpled wad of paper, if you will. Over time, these wads accumulate and clump together until, for reasons still not understood, the neurons in which the aggregates build up begin to die.

The challenge then became to relate this model to the more common, sporadic forms of the disease, which tend to be idiopathic (that is, to have no known cause). And the exciting development has been that in some cases, it has been possible to do that. For example, environmental exposure to certain pesticides is a risk factor for Parkinson's disease, and in animal models exposure to such pesticides not only produces some Parkinson's-like symptoms but also occasionally gives rise to Lewy body-like aggregates containing alpha-synuclein.[3] In another example, genetic risk factors for some of the sporadic diseases have also been identified; that is, we have located genes whose mutation increases the chance that one will get the non-inherited form of the disease but does not guarantee that one will. And in a few cases, these risk-associated mutations turn

out to be *in the same genes* where different mutations produced the familial form of the disease.[4]

There is now general agreement that, for the most part, the detailed molecular mechanisms of most, if not all, of these disorders are likely to be broadly similar, and that they involve the demented origami of protein misfolding and aggregation. To be sure, different diseases affect different proteins, each of which folds into quite a different paper animal when it functions properly, but each of which wads up and aggregates in a similar way in its disease. There is less agreement on whether the dense aggregates one can see easily are the cause of the disorder or its consequence. One theory that is gaining followers is that the actual toxic species are smaller clumps of protein that are not visible. Why this process should be age-dependent is not clear; but considering the known fact that all cells have some quality-control machinery that recognizes wadded up protein as potentially dangerous and either refolds it properly or disposes of it, a logical assumption might be that if this process is imperfect, over time the untreated misfolded protein could slowly accumulate to toxic levels. This assumption is important to test, because if it is true it has profound implications for how the diseases might be diagnosed and treated.

Continuing the origami analogy, this model suggests several strategies for therapy. If a particular protein's misfolding is causing the disease, then drugs that prevent misfolding – acting, if you will, as a kind of molecular Scotch tape to hold the origami animal in its proper shape – might prevent or delay the onset of the disease. The Scotch tape method has given promising results in clinical trials for some quite different, rare genetic diseases that are also caused by unstable mutant proteins.[5] Another approach would be to increase the efficiency of the quality-control system that deals with misfolded proteins so that it can handle more of them over a longer period of time. This idea is being tested in a number of start-up companies. Yet another approach is based on the assumption that breaking up the large aggregates that one can see – the senile plaques in Alzheimer's disease and the Lewy bodies in Parkinson's disease, for example – would be of therapeutic benefit. Several companies and academic laboratories are pursuing this strategy, typically by using antibodies to dissolve the dense aggregates, although in some cases drugs are also being sought that would do the same thing. Of course, if the large aggregates are not the toxic species, this approach may fail. To date, there is no convincing evidence that the strategy is sound, but no real evidence that it isn't, either.

Besides these advances in our understanding of the mechanisms of the diseases and the new therapies they suggest, there is another reason for optimism: it may actually be easier to treat neurodegenerative diseases than it is to treat, say, cancer. If you want to cure a cancer patient, whether by surgery or radiation or chemotherapy or anti-tumor antibodies, you had better be near perfect, because if you leave even a few rogue cells alive, the cancer is likely to return, often more aggressively than before. And it is very hard to be perfect. But neurodegenerative diseases generally develop late in life, and most progress slowly. If the average age of onset of Parkinson's disease could be raised from sixty-five to eighty, we would count that as a victory. If Parkinson's took forty years to progress to fatality instead of twenty, most people with the disease would die of something else long before its symptoms became untreatable. One doesn't need perfection: it might be enough just to tweak the system a bit –

and that should be a lot easier, at least in theory.

Given all these positive developments, why are pharmaceutical companies deserting the arena, and why are the funding agencies not pouring even more money into such promising lines of research? One reason, of course, is that times are hard, and finding additional research dollars is neither easy for corporations nor politically popular for governments. But even if we assume that the economy will eventually recover, there are other major obstacles to translating these new discoveries into cures.

The first is, ironically, the size of the market. Suppose you had a drug that was likely to prevent one of the major neurodegenerative diseases. In that scenario, we wouldn't be looking to give that drug to the five million people who have Alzheimer's or the one million who have Parkinson's; we're talking about potentially giving it to everyone over the age of, maybe, fifty – in other words, about a hundred million people in the United States alone. You might think drug companies would hyperventilate over a market that big, and they do, but out of fear, not greed. If you give a drug to a hundred million apparently healthy people, no matter how safe that drug seemed to be in clinical trials involving a much smaller number of individuals, there are likely to be tens of thousands who will suffer severe side effects, possibly including death, because no clinical trial can adequately control for the enormous genetic, dietary, and environmental diversity of the human race. An example is the recent scandal over the pain drug Vioxx, which seemed to be relatively safe in the limited patient population for which it was developed. It was later marketed to a much broader population, where it caused severe cardiovascular problems in some people, leading to estimated thousands of deaths by heart attack and stroke.[6]

Because of the Vioxx catastrophe, no drug company will bring an Alzheimer's or Parkinson's prevention drug to market unless there were some way of determining who was likely to get the disease eventually, with a high degree of certainty, or who already had it, even if they had not yet begun to show symptoms. Unfortunately, there is no reliable way to do that for the approximately 90 percent of the cases that are not genetic – at least not yet. New developments in imaging techniques such as MRI and PET scanning are promising, but they are too expensive to be used for screening large numbers of people. In a number of companies and laboratories, efforts are under way to find what are called biomarkers – changes in gene expression or protein levels or metabolism – that would indicate a disease is in its earliest stages or is almost certainly going to start soon. The hope of being able to *prevent* neurodegenerative diseases rests on the success of these efforts.

So may the hope of *treating* such diseases in people who already have them. When a patient presents with symptoms of the so-called early stage of Alzheimer's or Parkinson's disease, for example, huge numbers of neurons have already died, and a number of secondary processes, such as inflammation, have set in. Arresting a disease process that far advanced may be almost impossible; even if possible, it is unlikely to result in restoration of the functions (memory, smooth movement) that have already been lost. Once again, if treatment to halt progression is to have a chance of working, it may be essential to identify that an individual has the disease before significant symptoms appear – another job for imaging methods and biomarkers that we do not yet have.

The second major obstacle is the lack of good animal models for nearly all the neurodegenerative diseases. Therapeutic development for any disease proceeds in

well-established stages, one of which is determining if the treatment is safe in certain animals. While not perfect, our animal models for toxicity are not bad, so many therapies that are safe in animals are later shown (at much greater cost, of course) also to be safe in people (so-called Phase I clinical trials). Most failures of treatments that are tested in human trials occur in the next stage, Phase II, which is designed to determine if the therapy is efficacious against the disorder in question. Consider what that means: after spending hundreds of millions of dollars to develop a drug that treats disease X in mice and dogs and even monkeys, almost half the time that drug will not produce the desired clinical result in humans. The obvious conclusion from this depressing fact is that our animal models for disease are often not very good, and among the worst are the animal models for age-related neurodegenerative diseases, probably because the lifespan of any model animal simply does not approach the threescore years and ten that are typically required for these diseases to emerge in people. Consequently, to generate any animal model at all, abnormal gene expression or some form of chemical stress, or both, is necessary, and the resulting model never shows the same slow progression (or even, in many cases, the same aggregates in the same neurons) as the human disease. Absent decent animal models, drug companies understandably shy away from a field in which they stand a good chance of spending a fortune developing a treatment that will have an even higher than normal failure rate in Phase II clinical trials.

The third obstacle is the clinical trials themselves – or, more precisely, their design. Until recently, for example, all the clinical trials of potential Alzheimer's drugs were carried out on late-stage Alzheimer's patients, and the readout for efficacy was improvement in cognition. Yet cognition is not an easy thing to measure with precision, and most Alzheimer's patients do not show a steady cognitive decline anyway, but rather a choppy one. Even an apparent improvement may not be due to the drug at all. Moreover, the brain of a late-stage Alzheimer's patient is so severely ravaged by the disease that it actually has holes where healthy tissue used to be. To expect a therapeutic to show a measurable benefit in such cases is naive at best, and perhaps even foolhardy.

These, then, are the challenges that must be overcome by biomedical research – and soon, if the coming epidemic is to be averted. Considering the current state of our knowledge, and the barriers to therapeutic development, I offer the following suggestions for improved progress in the fight against neurodegenerative diseases:

1) Biomarkers must be found that either signal the start of the disease long before symptoms appear, or that identify people whose risk of developing the disease soon is so high that it justifies treating them even though they do not yet have the disorder.

2) We must answer the question of whether the macroscopic aggregates are themselves toxic to neurons, or are a reservoir for the (smaller) toxic species, or are actually an attempt by the organism to protect itself from protein misfolding by sequestering the clumps. Absent this information, the optimal strategy for prevention and treatment is unclear. Clinical trials of plaque-clearing antibodies now under way may shed light on this issue: if they show efficacy, then the third possibility can probably be ruled out.

3) Recent exciting data that suggest that the toxic species may be able to spread from neuron to neuron, like an infec-

tious agent, need to be confirmed.[7] If they hold up, then new avenues for therapy to retard disease progression are suggested, including blocking the release of the toxic species from an "infected" cell or blocking its uptake by a neighboring cell.

4) Strategies for stabilizing the proteins that misfold in these diseases – the molecular Scotch tape approach – need to be pursued vigorously and evaluated carefully. This line of attack has a number of appealing features but also many uncertainties, such as how early in the progression of the disease must such a drug be administered in order to be effective.

5) Clinical trials for all these diseases need to be designed more intelligently and creatively. Surrogate diseases may represent an attractive approach: for example, carriers for the inherited, recessive lysosomal storage disorder Gaucher disease are at greatly elevated risk for Parkinson's disease,[8] raising the intriguing possibility that a treatment for the small number of people who actually have Gaucher disease could be used to reduce the risk for Parkinson's disease in the much larger number of Gaucher carriers. Clinical trials for Gaucher disease are much easier to design and carry out than trials for neurodegenerative diseases.

6) The traditional silos that balkanize medicine – and biomedical research – by organs and phenotypic presentation need to be broken down so that the connections between different diseases can be exploited to find new approaches for therapy. As an example, Alzheimer's patients are at much lower risk for all forms of cancer than age-matched controls; and now that people are living longer with cancer, it can be seen that the reverse is also true: cancer survivors are at significantly lower risk of Alzheimer's disease.[9] Could the cure for, say, Alzheimer's disease be sitting on some drug company's shelf as a failed cancer drug that was never tried on the right disease? More than just improved communication between oncologists and neurologists is needed to follow up fascinating leads like this one. What is needed is an entirely new way of thinking about disease: not in traditional terms of organs and tissues but in terms of pathways and processes inside the cell.

7) The current inadequate funding for neurologic disorder research must be redressed. One of the few problems that can often be solved by throwing more money at it is our understanding and ability to treat human disease: consider the successes of the war on cancer and the fight against HIV/AIDS. True, large increases in funding do lead to a lot of mediocre science being funded, but they also lead to a lot of great science being funded. And they also lead to cures – not immediately, to be sure (the time from basic research discovery to approval of a clinical treatment can easily be fifteen to twenty years), but eventually. One thing is certain: if increases in funding draw first-rate scientists to a field, inadequate funding drives many of them away. Private philanthropy can make a big impact here, and it may not be an exaggeration to say that without private philanthropy, we would be in much worse shape than we are in terms of progress, not only on neurodegenerative diseases but in medicine in general. Sanford I. Weill, the chairman of the Board of Overseers of Weill Cornell Medical College, puts it this way: "The life-saving benefits now possible thanks to biomedical research

happen largely through philanthropy, and the commitment of donors who recognize that we are on the cusp of a revolution in medicine. They are the ones who step into a leadership role and make it possible. It is the greatest legacy we can leave to our families, friends, and future generations."

Companies are right that drugs targeted for the central nervous system are painfully difficult to create and very difficult to win approval for. It might be time for governments to assume some of the risk of doing so, not by trying to develop such drugs themselves – pharmaceutical development is no job for amateurs – but by underwriting some of the cost. A $2 billion/year fund, available by peer-reviewed competition to companies that have a promising clinical candidate and a sensible clinical trial design (see #5), might bring those companies back into the sector or take some biotech-developed drugs deep into human trials without costly partnering.

Neither the private nor the public sector will give this area the attention it needs without pressure from the lay public. Taking a page from the HIV/AIDS activists' book, the patients afflicted with these disorders need to speak loudly, and with one voice. Up to now, each disease has existed largely in its own universe, with foundations and patient-oriented groups focused on their particular disorder. If we realize that many of these seemingly different diseases have similar underlying causes, often present together, and that their seemingly distinct pathologies may mask their interrelatedness, then progress in any one disease may legitimately be seen as progress in many, if not all.

All these things are possible if we have the will and resources to do them. We cannot afford to fail, because if we do, the future is beyond bleak. A child born today will be about forty years old when, projections say, sixteen million of his or her fellow Americans will have Alzheimer's or Parkinson's disease (and a significant number will have both). That child will also be living in a world where the health care system is bankrupt, the social fabric is rotting, and nearly every family knows the despair and horror of watching a loved one slowly succumb to a hideous illness.

But trend is not destiny; the future is what we make it. The challenge for biomedical research in an aging world is to help create a future where both young and old can prosper. We must take up this challenge now, because the clock is ticking.

ENDNOTES

[1] The differences between these diseases are probably at least as important as their commonalities, but in the interest of clarity, the similarities are emphasized here. Reviews tend to be disease-specific, but one that treats the subject more generally is Eszter Herczenik and Martijn F. Gebbink, "Molecular and Cellular Aspects of Protein Misfolding and Disease," *The FASEB Journal* 22 (7) (July 2008): 2115 – 2133.

[2] For examples from Parkinson's disease, see Joshua M. Shulman, Philip L. De Jager, and Mel B. Feany, "Parkinson's Disease: Genetics and Pathogenesis," *Annual Review of Pathology* 6 (February 28, 2011): 193 – 222. A good treatment of the Alzheimer's case is Rita J. Guerreiro, Deborah R. Gustafson, and John Hardy, "The Genetic Architecture of Alzheimer's Disease: Beyond APP, PSENs and APOE," *Neurobiology of Aging* 33 (3) (March 2012): 437 – 456.

3 An excellent recent review is Shin Hisahara and Shun Shimohama, "Toxin-Induced and Genetic Animal Models of Parkinson's Disease," *Parkinson's Disease* 2011 (2011): 951709.

4 Ian Martin, Valina Dawson, and Ted M. Dawson, "Recent Advances in the Genetics of Parkinson's Disease," *Annual Review of Genomics and Human Genetics* 12 (September 22, 2011): 301 – 325.

5 For an overview of the method, see Dagmar Ringe and Gregory A. Petsko, "What are Pharmacological Chaperones and Why are They Interesting?" *Journal of Biology* 8 (9) (October 13, 2009): 80. Genetic disorders called lysosomal storage diseases have been treated with particular success by this method. A recent review is Giancarlo Parenti, "Treating Lysosomal Storage Diseases with Pharmacological Chaperones: From Concept to Clinics," *EMBO Molecular Medicine* 1 (5) (August 2009): 268 – 279.

6 Janice Hopkins Tanne, "Merck Pays $1bn Penalty in Relation to Promotion of Rofecoxib," *BMJ* 343 (November 28, 2011): d7702.

7 Although this might sound like a virus, or like Mad Cow Disease, there is no evidence that these proteins are infectious from person to person. What is now widely believed is that the neurodegeneration starts in some particular set of neurons and then can be propagated to other parts of the brain along the connections those neurons make with others. For Alzheimer's, the newest observations are Li Liu, Valerie Drouet, Jessica W. Wu, Menno P. Witter, Scott A. Small, Catherine Clelland, and Karen Duff, "Trans-Synaptic Spread of Tau Pathology *In Vivo*," *PLoS One* 7 (2) (2012): e31302; and Alix de Calignon et al., "Propagation of Tau Pathology in a Model of Early Alzheimer's Disease," *Neuron* 73 (4) (February 23, 2012): 685 – 697. Similar findings have been reported for the pathogenic molecules in ALS – for example, Magdalini Polymenidou and Don W. Cleveland, "The Seeds of Neurodegeneration: Prion-like Spreading in ALS," *Cell* 147 (3) (October 28, 2011) – and Parkinson's disease: see Christopher J.R. Dunning, Juan F. Reyes, Jennifer A. Steiner, and Patrik Brundin, "Can Parkinson's Disease Pathology be Propagated from One Neuron to Another?" *Progress in Neurobiology* 97 (2) (May 2012): 205 – 219.

8 Wendy Westbroek, Ann Marie Gustafson, and Ellen Sidransky, "Exploring the Link between Glucocerebrosidase Mutations and Parkinsonism," *Trends in Molecular Medicine* 17 (9) (September 2011): 485 – 493. See also S. Pablo Sardi, Priyanka Singh, Seng H. Cheng, Lamya S. Shihabuddin, and Michael G. Schlossmacher, "Mutant GBA1 Expression and Synucleinopathy Risk: First Insights from Cellular and Mouse Models," *Neurodegenerative Diseases* 10 (April 2012): 195 – 202.

9 This striking inverse correlation has been shamefully neglected, both in research and in research funding. It also applies to Parkinson's disease (except for melanoma, where having Parkinson's *increases* the risk for melanoma, and vice versa) and schizophrenia. A good, brief review (albeit from a particular perspective) is Rafael Tabarés-Seisdedos, Nancy Dumont, Anaïs Baudot, Jose M. Valderas, Joan Climent, Alfonso Valencia, Benedicto Crespo-Facorro, Eduard Vieta, Manuel Gómez-Beneyto, Salvador Martínez, and John L. Rubenstein, "No Paradox, No Progress: Inverse Cancer Comorbidity in People with Other Complex Diseases," *The Lancet Oncology* 12 (6) (June 2011): 604 – 608. For an excellent discussion of the schizophrenia case, see Yang Wang, Guang He, Lin He, and John McGrath, "Do Shared Mechanisms Underlying Cell Cycle Regulation and Synaptic Plasticity Underlie the Reduced Incidence of Cancer in Schizophrenia?" *Schizophrenia Research* 130 (1 – 3) (August 2011): 282 – 284.