Comment

The next epidemic

Gregory A Petsko

Address: Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, MA 02454-9110, USA.
Email: petsko@brandeis.edu

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In about 50 years, more than a quarter of the world will be over 65 years of age. It's even worse for some countries: the projections are that at that time, Japan and Germany could have 50% of their population in that category. The figure for the US is estimated to be about one-third. The fastest growing demographic segment in most developed nations is people 85 and older. We are witnessing something utterly unprecedented in human history: an explosion of people well past their reproductive years.

Evolution ceases to care about an organism when it has done its job of passing its genes to the next generation. As far as we know, natural selection does not increase the fitness of an individual for later life; indeed, there is some reason to think that longevity may be harmful in an evolutionary sense. Older, non-reproducing organisms consume resources that might better serve their younger, breeding brethren. And chief among these resources is medical care, because old age is a risk factor for just about everything bad that can happen physically.

Cancer (most types, anyway) and heart disease are just two of the conditions that afflict the elderly much more frequently than the young. Osteoporosis, pneumonia and other potentially fatal infectious diseases are amongst the others; and the list is a long one. But in almost no case is the deleterious effect of aging more dramatic than in the case of neurologic diseases. With the exception of a few rarer ones such as amyotropic lateral sclerosis (Lou Gehrig's disease) and Huntington's disease, which do their damage earlier, the incidences of Alzheimer's disease and other dementias and of Parkinson's disease and other movement disorders increase exponentially starting at about age 60, such that by the time a person reaches their mid-80s, their chance of showing symptoms of at least one of these conditions approaches 50%. The prevalence of Alzheimer's alone doubles every 5 years past age 60. Right now, in the US, there are about 1 million people with Parkinson's disease and about 5 million with Alzheimer's disease (the corresponding figures for the UK are just under a million Alzheimer's cases and about 200,000 Parkinson's cases). Exact figures are impossible to get because there is overlap in symptoms between cognitive and movement disorders in many patients and definitive diagnosis is often not possible until autopsy. But what is clear is that the major neurologic diseases cost the US about a third of a trillion dollars a year, out of a gross domestic product of $12.7 trillion. If you think that's a lot, and it is, then brace yourself: in fifty years, unless something is done, all of these figures will at least triple. There will be 15 million US Alzheimer's patients, 3 million with Parkinson's disease, and the annual cost will be over 1 trillion dollars. Every other western nation will experience similar increases. No economy can survive that.

One reason the future looks so bleak is that there is at present not a single effective treatment for any of the major neurologic disorders. Promising ones are claimed to be in the pipeline for the big killers like stroke and Alzheimer's, but then, we've been hearing those promises for at least three decades. And the 'lesser' scourges such as Parkinson's disease and other movement disorders are considered to have prevalence too low for most major pharmaceutical companies to be interested in developing therapeutics for them. So bloated, and debt-laden, have some drug companies become after the recent round of mergers that a disease offering only a million patients is considered unlikely to generate the return on investment needed.

This would appear to leave a clear field for biotechnology companies, but they haven't exactly been leaping into the breach either. Many appear to be scared off by the difficulty in doing clinical trials for diseases like Parkinson's (to be fair, big drug companies are worried about the same thing). Neurodegenerative diseases are typically slowly progressing with variable rates of decline and complex symptomology. Picking a suitable clinical end-point is hard enough, but when you add to it the likely time required for a trial for a disease like Parkinson's, which typically has a

20-year progression, it's understandable that even the major pharmaceutical companies are wary.

Governments often need to step in when the private sector is reluctant, and to some extent they have, but much of the innovative research in neurodegenerative diseases is funded, at least initially, by private foundations set up by patient advocacy and support groups. Thanks to them, there has been progress, but things are still moving very slowly.

Ironically, neurologic diseases may be a lot easier to treat than disorders like cancer. If you want to cure cancer, you had better be perfect, because if you let even one rogue cell escape, that may, in theory at least, be enough to start a fatal metastasis. I don't know about you, but I'm far from perfect - just ask my research group. But if you want to 'cure' Alzheimer's or Parkinson's disease, which are typically late onset and slowly progressing, you don't have to be perfect. Delay the average age of onset by a decade or two and the problem becomes much less serious. Slow the rate of progression by just one order of magnitude and a fatal disease may no longer be a significant problem for most people. In other words, for neurodegenerative disorders, all that may be required is to buy enough time.

Increasing evidence suggests that genomics should be a significant contributor to doing just that. Because the most common forms of the major neurologic diseases are sporadic and idiopathic, it was long thought that genetic factors played a relatively minor role in susceptibility (compared with, say, environmental factors and diet). But recent twin studies in Scandinavia and elsewhere paint a very different picture. Monozygotic twins show a high correlation in incidence of Alzheimer's disease compared with nonidentical twins, where the correlation is low. The best current guess is that more than 75% of the susceptibility to sporadic Alzheimer's disease may be due to genetic factors. The figure for Parkinson's disease is estimated to be lower, below 50%, but still substantial. Since most neurologic disorders don't present with symptoms until a sizeable fraction of the relevant neurons have already died off, many neurologists have felt that preventative measures were a better long-term strategy than trying to arrest the progress of the disease. The problems are: how do you measure efficacy of prevention for a sporadic disease, and how do you avoid having to give the preventative drug to the entire elderly population? The recent sad story of Vioxx, an arthritis painkiller that had to be withdrawn from the market after it was linked to increased incidences of heart attacks and strokes, shows what can happen when a drug is administered to a larger population than absolutely need it.

But if the tools of genomics allow us to identify genetic risk factors for the sporadic disease, then preventative measures can focus on reducing the risks for that population only, down to 'normal' levels, which in fact may be very small. The recent discovery that Ashkenazi Jews who are carriers for Gaucher disease are at increased risk of developing Parkinson's disease represents, I think, just the beginning of what should be a massive effort to identify the haplotypes that predispose individuals to a high risk of neurodegenerative disease.

Meanwhile, the incipient epidemic still needs to be checked. The best hope short-term probably lies with drugs that slow or arrest the neuronal decay. Finding them requires that the clinical trials problem be solved, but I don't think that may be as daunting as it seems. All of the major neurologic diseases have rarer, closely related conditions that are much more rapid in their progression and that have death as a clinical end-point. For example, although Parkinson's disease progresses very slowly, multiple system atrophy, which has similar pathology and appears to involve many if not most of the same molecular players, is usually fatal within about five years of diagnosis. Using these faster diseases as surrogates for the slower may be a way to design clinical trials with a clear outcome (survival) and an acceptable duration. But that requires accurate and early diagnosis of these conditions, which currently is very difficult to do, as they all resemble one another in many of their symptoms. Microarray analysis of gene expression and other genomics tools may help overcome this problem, which right now represents the major obstacle to progress.

The hope then is that genomics will make it feasible for biotechnology companies and large pharmaceutical firms to expand the scope of their efforts in neurologic diseases. If they don't, we could be looking at a future in which the human life span is continually extended but the quality of that later life is horrible. I don't know about the H5N1 virus and the avian flu; as I've written previously in my column (*Genome Biology* 2005, **6:**121), the prospects for that epidemic are uncertain. But the coming neurologic crisis is an epidemic that is as sure as anything I know of. And this one won't be confined to a third world country, or to some place safely remote. The clock is ticking for all of us.