Chapter 1

Introduction
Patients are repeatedly asked, "When will there be a cure?" Doctors say in 5 years, in 10 years, or, more vaguely, "in our life-time." And the patients are asked, "How much money will it take?" And again, doctors say $100 million a year for 5 years or 10 years. The figure $100 million is the cost of 2 United States Senate campaigns.

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Parkinson's disease (PD) is a chronic, progressive, and disabling disease described by James Parkinson in 1817 at the start of the Industrial Revolution. Is PD an outgrowth of the Industrial Revolution? Is it the result of a toxic by-product of the Industrial Revolution—one that poisons the internal environment of the brain? Or is PD a result of the increased life-span that is itself a by-product of the Industrial Revolution? A perverse "bargain" where we live longer only to develop diseases not known in the past?

1.1 The Lewy body

In 1913, Lewy, a pathologist, discovered within certain nerve cells of people with PD, a round structure, or body, the Lewy body. Lewy correctly assumed the body was a marker, a tombstone, of cell death. In 1996, 83 years after Lewy, doctors found that Lewy bodies contain a protein called alpha-synuclein that's coded by a gene on Chromosome-4. They subsequently found that Lewy bodies contain at least two other proteins, parkin and ubiquitin; that are coded by other genes on other chromosomes. The genes are "blue prints", sets of instructions, that enable each cell to make the proteins it needs to carry-on it's specific activity. How genes are translated into proteins, how the proteins are assembled, how they're transported to where they're need, and how after they've "out-lived" their need, they're removed is under study. This will result in new insights into how cells live or die, and will offer us a chance to halt or cure PD.

Drugs such as MPTP, metals such as manganese, brain injuries such as in boxing, and viruses such as those causing encephalitis, can cause brain cells to die resulting in PD. But the dying cells do not contain Lewy bodies. Thus it's reasoned the process that kills them is different from PD. As an example, if you die from a bullet, an infection, or
a poison, you're just as dead. But the process of dying is different. And so are the ways of preventing it. Lewy bodies may contain the secrets of PD. And their importance may transcend PD. Thus in examining the brains of people after death, for each person with PD there are 10 with Lewy bodies without PD. Are they at risk for PD? Presently PD affects 1% of all people age 60 years or over. If we live longer, will PD affect 10% of all people over age 60?

1.2 The substantia nigra

In 1919, 102 years after Parkinson, and 6 years after Lewy, Tretiakoff, a pathologist, discovered a loss of pigmented nerve cells in a region of the brain called the substantia nigra. This is where PD starts. Lewy had "marked" the dying cells but he hadn't realized they were grouped together. Although the loss of pigment is obvious to the naked eye, and although many pathologists had studied PD, none had seen what Tretiakoff saw. There are 400,000 cells in the substantia nigra. They start to pigment after birth and are fully pigmented at age 18. The pigment is a normal product of cell metabolism. The pigment doesn't cause the cell to die, rather the loss of pigment is a marker of its impending death. The symptoms of PD follow the loss of cells. When you loss 240,000 cells, 60% of the cells in your substantia nigra, you develop symptoms. It's said that all of us (with or without PD) lose 2000 nigra cells each year. And, if we lived the Biblical "Four score and forty years," or 120 years we would all have PD. Sometime, and it's not known when, or why, the cell loss accelerates: perhaps with 4,000, or 6,000, or 8,000 nigra cells dying each year.

Finding when PD starts, before 240,000 cells have died, and finding why will dramatically change our treatment. The cells could die because of an inherited defect, a "flaw in its blue prints." Or the cells could die because of an internally produced chemical, a "naturally" occurring free radical. Or the cells could die because of contact with an external chemical, an environmental toxin, one that breeched the cell's defenses. Depending on the cause, appropriate treatments could be devised to counter-act it.
1.3 Parkinson-Like Diseases

PD-like diseases resemble PD and may, initially, be diagnosed as PD. Within 2 to 5 years other features may appear that distinguish them from PD. In most PD-like diseases the cell loss is not associated with Lewy bodies. There are several PD-like disorders.

1.3.1 Progressive Supranuclear Palsy (PSP)

For each 100 PD people there are 2 to 5 PSP people. On examination of the brain after death there are plaques and tangles. Plaques are structures outside nerve cells that contain the protein amyloid. Tangles are structures inside the cells and consist of twisted strands of a protein called tau. These changes are similar to those of Alzheimer disease. But whereas PSP affects the same regions as PD, Alzheimer affects different regions. The relationship of plaques and tangles to Lewy bodies is being studied.

1.3.2 Multi-System Atrophy (MSA)

For each 100 PD people there are 2 to 5 MSA patients. There are 3 variants of MSA, each affecting different regions of the brain; hence the name: Multi-System Atrophy. These include Shy-Drager, Striatonigral Degeneration (SND), and Olivopontocerebellar atrophy (OPCA). On examination of the brain after death the variants of MSA differ from PD by the regions involved and the absence of Lewy bodies. In addition MSA people have a distinct change in a type of cell, a support cell not a nerve cell.

1.3.3 Guam Parkinson Disease-Amyotrophic Lateral Sclerosis (ALS)

This disease affects 10% of the natives of the island of Guam. Extrapolated to the United States this would be 28 million Americans! Guam PD-ALS may begin with PD symptoms or with ALS symptoms: muscle wasting (which occurred in Lou Gehrig the baseball star). On examination of the brain, Guam PD-ALS people have a loss of cells associated with plaques and tangles—changes similar to those in PSP and Alzheimer.

1.3.4 Post-Encephalitis Parkinsonism (PEP)

Between 1918-1926 an encephalitis epidemic, "sleeping sickness", von Economo’s encephalitis swept the world. The epidemic affected 15 million people, 6 million of whom developed PEP. Other viruses: eastern equine, herpes, Japanese-B, western
equine, can, occasionally, can cause PEP. On examination of the brain after death PEP people show a loss of nerve cells associated with tangles.

1.3.5 Parkinson and Alzheimer

As PD worsens nerve cells in other regions die. And, in advanced PD, Alzheimer-like changes: plaques and tangles appear in addition to Lewy bodies. This changes the substantia nigra and other regions of the brain. This is called Dementia with Lewy Bodies or Diffuse Lewy Body Disease. For each person with PD whose disease starts in the substantia nigra, there may be one person whose disease starts in the thinking part of the brain. This person is diagnosed as having dementia and not PD. The processes are probably the same but the regions are affected differently. PD is like being hit in the arms and legs, and later perhaps being hit in the head. Dementia is like being hit in the head, and later, perhaps, being hit in the arms and legs. About 30% of PD people eventually develop dementia. This is usually secondary to the changes of Dementia with Lewy Bodies. However, some people also have the changes of Alzheimer. About 30% of Alzheimer people develop PD-like changes. About 15% of PD people have a family history of dementia. Whether this is Dementia with Lewy bodies, or Alzheimer, or both is being studied. And 15% of Alzheimer people have a family history of PD.

1.4 Epidemiology of Parkinson's Disease

1.4.1 Searching for the Etiology of PD

It is critical to be aware of clinical, pathological and neurochemical factors that define a disease. Although animal models can give invaluable clues, ultimately the establishment of disease etiology(ies) will have to occur in the human condition itself. This is the partly the province of analytical epidemiology, in which risk factors, both genetic and environmental, are identified.

In the case of PD, the cause(s) is/are unknown, but variable combinations of genetic and environmental factors are likely to be involved. So far, there are only rare multigenerational families with PD that have single gene defects (e.g., the α-synuclein
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missense mutation on chromosome 4 involving several Italian and Greek kindreds, as well as other genetic mutations). Although there is a higher likelihood of PD in first- or second-degree relatives of Probands, the vast majority (85%) of cases are sporadic. In such a complex (multifactorial) disorder, one is likely to find a number of environmental exposures associated with genes that confer susceptibility to their deleterious effects.

1.4.2 Epidemiological Issues in PD

There have been inconsistent findings regarding several risk factors for PD, including rural living, well water use, pesticide exposure, and occupational metal exposure, among others. Contributing to this inconsistency are methodological issues such as the nature of the specific exposures that have been assessed, the means of their assessment, differences between studied populations, poor selection of suitable control subjects, and, in some cases, a failure to adjust for confounding variables. Many studies have been afflicted with a referral bias (e.g., using cases that have been referred to tertiary care centers), and a number have contained few cases and controls.

1.5 Questions to be answered

The questions to be answered to find the cause and cure PD are:

What's the "attraction" of PD for the pigmented cells of the substantia nigra? Not all pigmented cells are affected. Why some and not others?

What's the "attraction" of PD for cells in other regions?

Are Lewy bodies part of the PD "death" process? Or an attempt at repair? Should we stop them? Or encourage them?

In less than 1% of PD people a gene causes PD. Three such genes are known. Are these unusual genes? Are there more than three?

The proteins alpha-synuclein, parkin, and ubiquitin, are clumped on Lewy bodies. Why?

Does a gene, or a toxin trigger a process of "cell death?" Is "cell death" normal, nature's way of ridding the brain of extra or damaged cells? Or is "cell death" bad?

MPTP, manganese, brain injuries, and viruses can cause a PD-like disease. How relevant is this to PD?

How relevant are any of the PD-like diseases to PD?
Do PD people who become demented have the same disease as demented people who develop PD?

Cells can be repaired by growth factors. Will growth factors lead to a cure?

Dying cells can be replaced by human stem cells. Stem cells may "cure" the slowness of PD but can they prevent or "cure" the dementia?

In PD there are problems with the mitochondria, the storage batteries of the cell. Are these problems relevant to PD?

A famous daughter of a person with PD who watched her father suffer and die after 20 years with PD said, "If I had known it was, eventually, this bad-- I would have given everything I had to stop it. A thousand dollars a year sounds cheap-- now!" A millionaire with PD, when he could no longer walk, and needed 2 nurses all the time, 24 hours a day, said, "If I had know it was like this, really known, I would have spent everything to stop it. What good is my money-- now."