The Dynamics of Neurological Disease: Current Views and Key Issues

"It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.
The First approach’d the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"
The Second, feeling of the tusk,
Cried, – "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!" [etc.]

John Godfrey Saxe

From the Preface

1) The human CNS is complex. It contains something on the order of 86 billion neurons, organized into multiple subsystems, surrounded by 85 billion supporting glial cells. Neurons are totally dependent on these support cells for their normal functions. Each neuron connects to multiple other neurons for an estimated 94 trillion synaptic connections. There should be nothing particularly controversial about anything in this paragraph for anyone in neuroscience/neurological disease research.

5) For all of these reasons, neurological diseases that are age-related (e.g., Parkinson’s disease, ALS, Alzheimer’s disease, and others) are going to be complex as well. The same applies to neuronal disorders at the other end of the age spectrum (e.g., autism spectrum disorder (ASD)).
1.1 Introduction

Certainly the first thing to consider when contemplating the human nervous system in health or disease is its overall complexity. In regard to the latter, the subject of this book, the sheer number of individual elements alone means that there are going to be multiple ways for any part of the system, any subsystem, or even individual cells such as the types of neurons and glia, to malfunction. Add to this the vast number of interconnections between neurons, circuits, and systems, and the potential for multiple forms of dysfunction grows greater still.

However, before considering how the human central nervous system (CNS) evolves into a disease state, it is important to appreciate just how utterly complex the system actually is.

1.2 The Complexity of Human Neurological Diseases

Few neuroscientists would disagree with the view that the human nervous system in general is quite complex. Indeed, some scholars and lay persons from various disciplines have opined that it is the most complex thing in the universe, or at least the most complex that humans know about. This last clause is essential given the robust hubris of *Homo sapiens*.

Regardless of just how complex the human nervous system is in the context of the rest of the universe, the questions which arise are these: First, how does such a complex system come into existence? Second, for the purposes of this book, how does it break down? It may be worth noting here that the nervous systems of most vertebrates are also relatively complex, particularly those of mammals. Largely for this reason, attempts to provide comprehensive and predictive animal models of neurological diseases are almost certain to run into many of the same problems as those associated with trying to understand the human CNS in the various states in which it may be, or become in the future.

The answer to the first question is the subject of developmental neurobiology, which examines the genetic and environmental factors underlying the formation of nervous system structure and function. In the latter regard, much has been learned about developmental features of the nervous system, the early and late forms of modifications, often termed “neuroplasticity,” and the implications of the latter in particular for the remarkable capacity that any nervous system has to modify itself and thus alter behavioral responses to changing external circumstances (for a general review, see Shaw and McEachern, 2001).

The broad subject matter that comes under the rubric of neuroplasticity has been the focus of innumerable scientific research papers, reviews, and books. I was a co-editor of one of the latter, *Toward a Theory of Neuroplasticity* (Shaw and McEachern, 2001), which attempted to come to grips with the extensive subject matter at the time, a literature that will only have grown in the intervening years. The general topic of neuroplasticity will be considered here only in the context of the second question which is the focus of the chapters that follow.

Restating that question, can an admittedly complex structure/system be destroyed in a simple, perhaps unitary way, or must the innate complexity of the system in the first place make the dissolution of the system complex as well?

The answer is that both can occur, but with very different characteristics, depending on a spectrum of types of injury. For example, acute injury to the brain in the form of
gunshot wounds or other major head trauma can certainly destroy the system rapidly. The myriad cellular chemicals and processes that are almost immediately released by macroscopic damage lead to the microscopic destruction of cells in a time frame of seconds to minutes. In the middle of the spectrum are traumatic injuries to the CNS that cause some level of destruction of neurons and glial cells, which may not be instantly fatal to the individual. In such cases, such as in cortical stroke or spinal cord damage, the initial trauma is often followed by secondary damage to surrounding neural cells and it is the latter that tends to exacerbate the initial injury. Indeed, such secondary damage may eventually be of larger scale and impact than the initial insult (Oyinbo, 2011).

At the other end of the spectrum are the so-called “progressive,” age-related neurodegenerative diseases, which are neither acute in their initial stages, nor, as far as is known, of rapid onset. Rather, these “classical” neurological diseases (i.e., Parkinson’s disease, amyotrophic lateral sclerosis (ALS), and Alzheimer’s disease; Figure 1.1) appear in most cases to be more insidious in onset and progression. In general, there are few

**ESSAY**

**ON THE**

**SHAKING PALSY.**

**CHAPTER I.**

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

**SHAKING PALSY.** (Tremor palpabilis)

Involuntary tremulous motion, with decreased muscular power, in parts not in motion and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running gait; the senses and intellect being unimpaired.

James Parkinson  
Jean-Martin Charcot  
Alois Alzheimer

Michael J. Fox  
Lou Gehrig  
Ronald Reagan

**Figure 1.1** Discoverers of the progressive, age-related neurological diseases and their famous victims (top to bottom): James Parkinson (Parkinson’s disease was first described in his “Essay on the Shaking Palsy”; note that a verified picture of James Parkinson does not seem to be extant) and Michael J. Fox; Jean-Martin Charcot and Henry Louis (“Lou”) Gehrig; Alois Alzheimer and Ronald Reagan.
reasons to believe that these diseases arise in a short time period. There may, however, be exceptions.

For example, forms of what look to be ALS-like motor neuron disorders have arisen relatively rapidly in some Gulf War Syndrome victims (Haley, 2003). Additionally, some ALS-like disorders in young women have been linked, at least temporally, to human papilloma virus (HPV) vaccine adverse reactions (Huang et al., 2009). In addition, there is a rapid-onset form of parkinsonism, now the basis of one of the major animal models of Parkinson’s disease, that arises due to the direct action of the molecule 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). People afflicted with this form of parkinsonism had injected into their veins what they believed to be a synthetic opioid, 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP), a street analogue of meperidine (Demerol). The inaccurate synthesis of MPPP gave MPTP instead (Langston et al., 1983). There are various other examples as well, which will be described in later chapters.

Parkinson’s disease, ALS, and Alzheimer’s disease typically develop slowly, and most evidence suggests that the pre-clinical stages of the diseases arise over the course of years to decades (Ben-Ari, 2008). One view is that some predisposing neuronal factors may arise in utero, similar to the “fetal basis of adult disease” (FeBAD) hypothesis proposed for cardiovascular disorders. This hypothesis and how it may apply to CNS diseases will be discussed in Chapter 10.

In what follows, it is important to stress that while traumatic acute brain injuries, stroke, and so on are the subjects of intensive research and are of clear medical and social importance, the focus of this book is really on the major neurological diseases, which occur progressively, meaning that the various signs and symptoms of any of these diseases will continue to worsen during the time course from clinical diagnosis until death.

It is at least a fair assumption that much the same progressive nature of such diseases occurs prior to the clinical stage, but the reality is that the field does not know much about this part of the progressive process. There are some hints from animal models of the various diseases, insofar as these accurately reflect the human condition (a point I will return to in Chapter 8), that pre-clinical stages actually resemble an early phase of what will become a “cascading failure” in the affected regions of the nervous system at a later time. The term “cascading failure” can be defined as the failure of one part in a system of interconnected parts that triggers the failure of other, successive parts (Bashan et al., 2013). During this cascade, the underlying biochemical and morphological processes build toward the general dysfunctions that begin to characterize the stage in which clinical diagnosis occurs. The point from clinical diagnosis onwards is, at this time, the point of no return for the neurological health of those regions of the nervous system affected, and indeed for the overall health of the patient. This latter point is well illustrated not only by the general lack of success in treating such diseases to date, but also through consideration of the numbers of molecules of all types that are found to be altered following post-mortem examination. The examples typically provided by various genomic, proteomic, and metabolomics arrays demonstrate huge differences between those with the disease state and those without (Figure 1.2).

If the end state of any of these diseases is cluttered with vast numbers of altered structures and molecular processes and thus not likely amenable to treatment, then it may be worthwhile at this juncture to consider the things that those attempting treatment would need to know in order to achieve success.
First, clinicians would need to know something about the actual etiology (or much more likely, etiologies) for that disease. As will be discussed in the following pages, apart from a few genetic mutations, which appear to be responsible for the “familial” forms of these diseases, we do not have much insight into that much larger fraction of neurological diseases that are termed “sporadic,” or of unknown origin. It should also be stressed that just because some forms of neurological disease involve genetic changes, this should not be taken to imply that they are without anything apart from a genetic etiology or that they are completely separate from environmental factors. This point will be made clearer in the discussion of epigenetics in neurological diseases in Chapter 6.

In addition to having clearly demonstrated etiologies, the field would need a fairly accurate time course for the various pre- and post-clinical stages. Thus, if the diseases were of genetic origin, the time course would begin with that mutation; if it were due to a toxic molecule, the time course would begin with the introduction of that molecule.

**Figure 1.2** Typical examples of genomic/proteomic differences in neurodegenerative disease victims compared to control patients. (a) Relative expression levels of the 137 genes differentially expressed in Parkinson’s disease (PD) samples relative to controls. Only genes that met the criterion of being altered by a factor of 1.5 relative to control and which passed the Wilcoxon test at the significant level of p < 0.05 were included. Genes are clustered by their relative expression levels over the 12 samples. Expression levels are color-coded relative to the mean: green for values less than the mean and red for values greater than it. Source: Grünblatt et al. (2004), used with permission from Springer Science and Business Media. (b) Genes differentially expressed in the motor cortex of sporadic ALS subjects: 57 of 19,431 quality-filtered genes (0.3%), represented by 61 probes, were differentially expressed (corrected p < 0.05), with each row in the matrix representing a single probe and each column a subject. Normalized expression levels are represented by the color of the corresponding cell, relative to the median abundance of each gene for each subject (see scale). Genes are named using their UniGene symbol and arranged in a hierarchical cluster (standard correlation) based on their expression patterns, combined with a dendrogram whose branch lengths reflect the relatedness of expression patterns. For each gene, the fold-change (diseased vs. control) and corrected p values are given. Source: Lederer et al. (2007), used under Creative Commons Attribution License. (See color plate section for the color representation of this figure.)
While there is now an existing literature describing “staging” for diseases such as Parkinson’s and Alzheimer’s, staging for ALS remains less defined (see Chapter 9). Regardless, the staging of the pre-clinical diseases is still largely unknown. To address this lack of information, the field would have to fill significant gaps in the basic knowledge of these diseases. For example, not much is known (yet) about risk factors, let alone causal factors. Worse, the likely additive – perhaps synergistic – actions of gene–gene, toxin–toxin, and gene–toxin interactions in neurological disease are only now, and quite slowly, emerging. The general absence of information on such interactions is very problematic for the attempt to understand disease origins since the great likelihood is that these are precisely the sorts of multiple events that are going to cause disease initiation and progression.

Delving downwards to more molecular levels, it would be crucial to have some idea about the activated genes and biochemical pathways at each of the still undefined pre-clinical disease stages. Achieving this level of pre-clinical analysis would be remarkably difficult, especially since the existing literature cannot do so very well even
Based on current genomic, proteomic, and metabolomic studies, such downstream events are likely to be huge in number, but of uncertain significance and time course. In the first case, the problem is one of separating putatively causal events that lead to stages of neurological disease from those that are merely bystander events, or even failed compensatory processes. To date, this goal has been difficult to achieve. At present, existing “biomarker” studies aimed at monitoring neurological disease onset and progression are still rudimentary in specificity, scope, and overall utility (for a review, see Shaw et al., 2007).

With every passing year, it becomes increasingly obvious that a great many genes, proteins, and other molecules are affected in Parkinson’s disease, ALS, and Alzheimer’s disease. The problem for potential therapeutics is not that the field has failed to identify a host of these, but rather the question of what to do with this burgeoning list of potential therapeutic targets. Thus, in cases where hundreds of molecules in the affected parts of the CNS are altered, it becomes quite hard to imagine – let alone achieve – any sort of realistic drug therapy that could deal with myriad downstream alterations in the CNS. Even if one could devise such therapeutics, it would be difficult to expect them to prevent disease progression without triggering nearly endless side effects that might prove equally deleterious to the CNS and to other organ systems.

### 1.3 The Nervous System as an Archetypical Complex System

The nervous system is a prime example of what is termed a “complex system” (Figure 1.3). This concept is not easily defined, but instead is described on the basis of the attributes any such system possesses.

Chapter 4 will delve into complex systems in more detail, but for now some of the key attributes to note are these: Complex systems have multiple, interconnected components, which, in response to an external stimulus, display “emergent properties.” Emergent properties, in turn, lead to “complex adaptive behaviors” and at least one, if not many, changes in system output. A classic example of emergent properties comes from a consideration of social insects. A beehive is composed of many thousands of bees, whose cumulative complex behaviors are those of the colony as a unified entity, not

![Figure 1.3 Schematic illustration of the complexity in DNA to protein interaction and in nervous system interactions.](image-url)
Figure 1.4 Emergent properties. (a) Top: an example of an emergent property, comparing an individual bee to a beehive. The properties of the hive are vastly more complex than those of the bee. Bottom: The “pointillist” painting, "A Sunday Afternoon on the Island of La Grande Jatte" (French: "Undimanche après-midi à l'Île de la Grande Jatte") by the post-impressionist French artist, Georges Seurat. (b) Schematic of emergent properties, showing individual elements of some systems (squares), an additional level of interaction between these elements, and a final emergent feature that is not necessarily predictable from the initial elements.

merely those of the individuals (Figure 1.4). Some other complex systems studied in detail in “complexity theory” include the stock market, political systems, ecosystems, and the weather. There are obviously many more.

Each of these complex systems can experience cascading failures due to the complex interconnections of the component parts. Thus, any failure of one circuit in an electrical device can lead to the destruction of other circuits and the overall failure of the device. Power grids that interconnect can experience cascading failures if one power plant in the network goes down. A more down-to-earth example comes from everyone’s experience of how relationships and/or marriages implode.
It may be instructive to view a common political situation as a metaphor for a declining nervous system. At first, a popular new government operates at high capacity and function, making few mistakes, and effectively coping with any challenges and minor upheavals. As time goes by, a cumulative deterioration begins to occur. The role of aberrant messaging (e.g., failed signaling – Signaling in biological systems has been termed “biosemiosis” or the biology of meaningful communication: Figure 1.5) leads to further signal disruptions. Bad messaging, lies, errors of judgment, and so on increasingly impact public confidence. The government becomes desperate and begins to make a series of even worse decisions. These decisions lead to further scandals. Government members begin to resign. And, in the end, a once-powerful political machine that a few months or years earlier seemed unassailable is brought down.

In the context of a neurodegenerative disease it is possible to postulate that the same general features of cascading failure occur. An initially highly functioning nervous system receives a limited number of insults which at first are coped with effectively by the various compensatory and redundancy features of the system. However, over time, the insults to the system become additive – or even synergistic – and the signaling becomes progressively degraded. Biological signaling in a biosemiotic sense begins to fail, creating additional incorrect messages and, hence, abnormal functions. The nervous system, once so adept at compensation, begins to miscompensate, exacerbating the overall dysfunction of the system. Eventually, the damage is too widespread to control and the overall decline is ensured.

In just such a way, Parkinson’s disease, ALS, and Alzheimer’s disease (and other neurological diseases) may occur. In such a context, neurological disease may represent just one example of the fate of any complex system in which a series of insults and increasingly failed signaling leads to system collapse.

System complexity is thus inevitably tied to the integrity of signaling and it is therefore the very aspect of complexity that needs to be understood first when dealing with human neurological diseases. In fact, it would be nearly impossible to argue that the nervous system of any animal is not at some level complex, at least in regard to function. As an example, some relatively simple nervous systems, such as that of Caenorhabditis
elegans, a very primitive nematode (roundworm) used to model neuronal connectivity, can express rather complex behaviors, including learning and memory (Rankin, 2004; Sasakura and Mori, 2013). The level of interconnected elements even in such a simple nervous system clearly shows that emergent properties – in this case learning – can result from relatively simple neural activity.

At a more elaborate level of nervous system organization, social insects such as honey bees and ants can perform a great variety of extremely complex and purposeful behaviors (for bees, see Von Frisch, 1950). Vertebrate nervous systems are more complex still in the numbers of neurons, neuronal nuclei of specialized cells and functions, and interconnections within and between regions. And, of course, the emergent properties of vertebrates far exceed those of invertebrates. In the same manner, the complexity found in the nervous systems of mammals and the attendant emergent properties exceed those of other vertebrates.

Humans have the most complex nervous systems yet described. By adulthood, human brains have close to 86 billion neurons, at least 85 billion supporting glial cells, and upwards of 1 trillion synaptic connections (Murre and Sturdy, 1995; Azevedo et al., 2009; Walloe et al., 2014). The numbers in the overall human nervous system are without a doubt vastly larger, although those in the human spinal cord and peripheral nervous system, not to mention neural elements in other organ systems, do not yet appear to be known with any certainty. For the spinal cord, one estimate is 13 million neurons and twice that number of glial cells, but this may be at the low end (Glover, 2008).

By way of contrast, consider the common comparison of the human CNS to modern computers (Figure 1.6). Most current electronic devices, including computers, make use of transistors which are semiconductor devices used to amplify or switch electronic signals and electrical power. Microchips are composed of millions of integrated transistors. The transistor count is the most frequently used measure of integrated circuit complexity, and is roughly analogous to the synaptic connections between neurons.

In the world of personal computers, one of the fastest current processors is the Intel Core i7-4960X which is made for high-end desktop use. This processor contains

![Microgram of a region of the human CNS compared to computer circuitry.](https://commons.wikimedia.org/wiki/File:Golgi-stained_neurons_in_the_dentate_gyrus_of_an_epilepsy_patient.jpg)  ![Computer circuit board.](https://www.flickr.com/photos/botheredbybees/2389301872)
1.86 billion transistors. In comparison, a mainframe computer such as IBM’s zEnterprise EC12, released in 2012, has a processor containing 2.75 billion transistors. IBM recently launched a “neuromorphic” computer chip called TrueNorth, which is designed to work like a mammalian brain (Merolla et al., 2014; Service, 2014). It has 1 million digital “neurons” which connect to one another through 256 million “synapses.” It contains 5.4 billion transistors. Even with this as a benchmark, the human brain has something like $10^5$ more neurons and $10^4$ more connections than any single computer.

The point of these comparisons is not to show that the human brain is superior in number of functioning elements (e.g., the numbers of neurons or synapses) given that one can envision future computers achieving comparable numbers. Indeed, a case could be made that the Internet, with its integrated web of computers, may have accomplished – if not exceeded – this level already. Rather, the point to be made is that computers, as complex systems, and the susceptibility of computer programs to signaling errors, may be quite analogous to the kind of susceptibility to failure seen in the human brain. In other words, the ways in which both computers and the human brain break down may be generally similar, as we will discuss later in this chapter.

This latter point returns to the initial question: Can a complex system such as the human nervous system break in a simple way? Obviously, as already discussed, in cases of acute trauma to the head or spinal cord, it can. However, if such trauma is not rapidly fatal, the nervous system of animals and humans shows a remarkable ability to compensate for the damage through the use of redundant neuronal circuits and by rewiring some brain areas.

The human literature is replete with just such examples. One of the more famous cases from the neurology literature is that of Phineas Gage. Gage was an American railway worker who had a large metal tamping rod blown through his head in an accidental explosion in 1848. The rod entered under his jaw and exited the top of his head, taking with it a considerable amount of cortical tissue. In spite of massive brain damage, Gage went on to recover and never lost most of his cognitive or motor abilities. He did suffer from epileptic seizures in later years, but in spite of these he managed to live on for 12 years after the initial injury.

A recent example of neural compensation for traumatic brain injury (TBI) is provided by the case of a Canadian army captain (now retired), Trevor Greene. Greene was struck on the head by an axe wielded by a Taliban insurgent in Afghanistan in 2006. His initial injuries appeared insurmountable. The axe blade had bisected the primary motor regions of the brain, and the overall damage was significant. Doctors at the Canadian Forces medical facility at Kandahar airbase, and later at a US military hospital in Germany, gave Greene’s family little hope for his survival and believed there was virtually no chance of him ever recovering consciousness. In spite of this, Greene did regain consciousness and in the years since the injury he has progressed to the point where he can again talk. His cognitive abilities appear to be relatively intact, and he has regained considerable motor capabilities, the latter which seem to be improving gradually through the use of a form of imaging therapy.

These two cases point to the possibility of CNS recovery in various disorders. They will be addressed in more detail in Chapter 15. As a prelude to the later discussion, it is relevant to ask whether the Gage and Greene examples point to broader prospects for neural recovery from any brain injury. Both cases demonstrate the remarkable redundancy and plasticity of the nervous system, but do they have implications for age-related neurological diseases?
1.4 CNS Signaling Failures: Implications for Neurological Disease

Although an obvious truism, it is worthwhile in the context of the following chapters to remember that the nervous system is basically a signaling device. Information comes in from internal and external sources through various sensory receptors, is transduced into neural signals, and then undergoes multiple levels of processing within the CNS. Adaptive behaviors of the organism result. Just as with much simpler nervous systems, emergent properties also occur. For this reason, it is important at the outset to recognize the importance of the integrity of signaling between the nervous system’s component parts for its successful functioning.

From this view, it follows that failures of signaling at any level are almost certain to have significantly negative consequences for neuronal function overall. At a macroscopic level, signaling errors can follow from events that impact the integrity of neuronal circuits and synapses within and between different regions of the brain. At a more microscopic cellular level, the levels of signaling include signals from DNA to protein and from protein to cell structure and function.

As will be considered in Chapter 5, the relatively small percentage of neurological diseases arising from the identified genetic mutations are in essence signaling errors in which the proteins necessary for normal neuronal function are not made or – often, worse – are made incorrectly. The resultant protein malfunction leads to cellular dysfunction, often eventually culminating in cellular (and, in this case, neuronal cell) death. Various toxins can impact signaling at various levels as well, including by altering gene expression, RNA transcription, the activity of intracellular organelles, and the cellular signals sent to other cells. Alternations at any of these levels will necessarily impact overall neuronal survival of the affected regions. Thus, however it is conceived, or regardless of the cause of the dysfunction, the breakdown of normal neuronal function leading to neurological diseases can ultimately be considered to arise from a type of signaling failure.

It is in this regard that the failure of the nervous system shares properties with the failures of other complex systems that depend on accurate signaling. Chapter 14 will address these concerns in more detail with a discussion of the biological meaning communicated between sending and receiving entities and the implications of such failure.

1.5 History and Key Characteristics of the Age-Dependent Neurological Diseases

Before considering the key age-related, progressive neurological diseases (Parkinson’s disease, ALS, and Alzheimer’s disease), it is perhaps worthwhile to put these into some sort of broad neurological disease perspective.

In general, neurological diseases/disorders are any that affect the nervous system, even if other organ systems are involved, and even if the primary disorder resides in these other organ systems, as in tuberculosis or diabetes.

To get a sense of the range of neurological disorders involved, I refer to those provided by a Canadian organization, Neurological Health Charities Canada (NHCC), an entity representing a range of nongovernmental organizations working on public awareness
and fundraising for individual neurological disorders in Canada. NHCC, in partnership with the Public Health Agency of Canada (PHAC), devoted considerable effort, time, and money to cataloguing and describing incidence and prevalence levels for some 15 neurological disorders or disease conditions. It also provided some studies designed to look at risk factors and patient treatments. Although given in a specifically Canadian context, the list was thought by NHCC/PHAC to be broadly representative of those diseases arising in other countries in the industrialized Western world, and to some extent in the developing world as well. Overall, the final report included results from 18 separate projects (Neurological Health Charities Canada and Public Health Agency of Canada, 2014).

The neurological disorders included in the original mandate included, in alphabetical order: ALS, Alzheimer’s disease and related dementias, brain injuries, brain tumors, cerebral palsy, dystonia, epilepsy, Huntington’s disease, hydrocephalus, multiple sclerosis, muscular dystrophy, Parkinson’s disease and parkinsonisms, spina bifida, spinal cord injury, and Tourette syndrome.

For a variety of reasons, a number of neurological disorders were not considered in the epidemiological surveys. These omissions, not trivial by any means, included some particularly important neurological disorders, such as autism spectrum disorder (ASD), macular degeneration, stroke, and schizophrenia and other mental disorders.

As the NHCC/PHAC studies began to sift through the initial epidemiological data, the overall range of neurological conditions, either included or not, resolved into particular categories: “developmental,” “acute/traumatic,” “age-related neurodegenerative,” and “other.” Some disorders can fit into various categories or subcategories, including:

- **Developmental**: Down’s syndrome, cerebral palsy, spina bifida (ASD would have been in this category had it been in the initial project).
- **Acute/traumatic**: stroke, TBI (of which stroke can be one type), spinal cord injuries.
- **Age-related neurodegenerative**: ALS, Parkinson’s disease and parkinsonisms, Alzheimer’s disease and other dementias, Huntington’s disease (macular degeneration, stroke, and schizophrenia and other mental disorders).
- **Other**: schizophrenia and other so-called “mental disorders,” neoplasms, Tourette syndrome, epilepsy.

Of these, Parkinson’s disease, ALS, and Alzheimer’s disease fit somewhere in the “age-related” general category, but are unique in that each is progressive and likely represents examples of ‘cascading failure’ much like those cited earlier. This feature is typified by the spread from one part of the CNS to others after the initial onset. In ALS and Parkinson’s disease, for example, cognitive decline may be a key sign of the latter stages of both diseases.

Further, as one of the disorders not considered by the NHCC, ASD may initially present as a developmental neurological disorder, but the underlying CNS abnormalities can create the eventual circumstances for later nervous system dysfunction with aging. This notion has not yet been explored, in part due to the simple fact that most of those currently diagnosed with ASD have not yet reached the age at which the age-related neurological diseases enter a clinical diagnosis stage. Nevertheless, Down’s syndrome provides a clear precedent, with many of those with Down’s developing Alzheimer’s-like dementias in middle age (Zigman and Lott, 2007).
In the more acute neurological disorders (e.g., TBI and spinal cord injuries), the initial phases after injury are characterized by secondary damage to adjacent neurons and neural structures. Although often eventually stable after this secondary stage of damage, acute trauma may also have later neurological sequelae. One example involves the development of a “syrinx,” or progressive cavitation of the central canal of the spinal cord, which may follow years after a spinal cord injury. As the syrinx grows, it creates pressure on various descending spinal cord nerve tracts and leads to degeneration of the axons in these tracts. The consequence, if left untreated, is a loss of motor and sensory functions below the syrinx.

1.6 The Fractal Nature of Complexity in the CNS

This chapter opened with a consideration of the dynamics of the nervous system, its overall complexity, and the inevitability of the complex interplay of factors that lead to neurological disease. It may be worthwhile here, at the outset, to consider some evolving concepts concerning cells and genes, as these will serve to inform some of that which follows.

The first point is that the standard cell “doctrine,” in place for over 200 years, is likely to be, if not wrong, then quite incomplete. In brief, cell doctrine as applied to development has been seen as largely unidirectional. That is, dictated by the presumably one-way nature of genetic instructions. Emerging views in cell biology and genetics suggest that this view is not correct. Cells are not simply discrete entities, but rather, at a fractal level, composed of numerous organelles and molecules. They have, as Theise and others have described, a form of “quenched disorder” between being totally random and totally deterministic in their behaviors and interactions (Theise, 2005). Thus, at the nano level of the cell, cell doctrine breaks down as a concept. It also breaks down when considering macro level extracellular interactions. Conventional cell doctrine took the view that intracellular versus extracellular space is a rigid barrier, but this has increasingly been shown to be a limited concept. Similarly, cell lineages, far from being totally fixed, are affected by the same nano and macro considerations (Theise and Krause, 2002; Theise and d’Inverno, 2004; Kurakin, 2005).

The second “classic” notion is that gene transcription from DNA to RNA to cellular proteins is a one-way path. This view, promoted as the “Crick” doctrine, is also coming under scrutiny. In brief, recursive feedback at all levels appears to occur, making gene function highly modifiable (Pellionisz et al., 2013).

These newer conceptualizations of cells and of DNA signaling have clear implications for cell functions and lineages overall, as well as more particularly for the nervous system. If emergent properties can occur at the single-cell level, how much more likely are such properties to emerge in health and in disease in the vast complexity provided by multiple interactions within the human CNS?

To fully appreciate such considerations, it is necessary first to understand what the field of neurological disease research does – and does not – know about some of the diseases of the human nervous system, namely Parkinson’s disease, ALS, and Alzheimer’s disease. Details on this topic will be presented in the next chapter and will provide the basis for much of that which follows.
Endnotes

1 The Third approached the animal,
   And happening to take
   The squirming trunk within his hands,
   Thus boldly up and spake:
   “I see,” quoth he, “the Elephant
   Is very like a snake!”
The Fourth reached out his eager hand,
   And felt about the knee.
   “What most this wondrous beast is like
   Is mighty plain,” quoth he,
   “Tis clear enough the Elephant
   Is very like a tree!”
The Fifth, who chanced to touch the ear,
   Said: “E’en the blindest man
   Can tell what this resembles most;
   Deny the fact who can,
   This marvel of an Elephant
   Is very like a fan!”
The Sixth no sooner had begun
   About the beast to grope,
   Then, seizing on the swinging tail
   That fell within his scope,
   “I see,” quoth he, “the Elephant
   Is very like a rope!”
And so these men of Indostan
   Disputed loud and long,
   Each in his own opinion
   Exceeding stiff and strong,
   Though each was partly in the right,
   \textit{And all were in the wrong!}
MORAL.
   So oft in theologic wars,
   The disputants, I ween,
   Rail on in utter ignorance
   And prate about an Elephant
   Not one of them has seen!

John Godfrey Saxe (1816–1887) and his version of the well-known Indian legend.