

Series Introduction: Neurodegeneration: What is it and where are we?

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J Clin Invest. 2003;111(1):3-10. <https://doi.org/10.1172/JCI17522>.

Perspective

“Neurodegeneration” is a commonly used word whose meaning is believed to be universally understood. Yet finding a precise definition for neurodegeneration is much more arduous than one might imagine. Often, neurodegeneration is only casually mentioned and scarcely discussed in major medical textbooks and is even incompletely defined in the most comprehensive dictionaries. Etymologically, the word is composed of the prefix “neuro-,” which designates nerve cells (i.e., neurons), and “degeneration,” which refers to, in the case of tissues or organs, a process of losing structure or function. Thus, in the strict sense of the word, neurodegeneration corresponds to any pathological condition primarily affecting neurons. In practice, neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner. Conversely, neoplasm, edema, hemorrhage, and trauma of the nervous system, which are not primary neuronal diseases, are not considered to be neurodegenerative disorders. Diseases of the nervous system that implicate not neurons per se but rather their attributes, such as the myelin sheath as seen in multiple sclerosis, are not neurodegenerative disorders either, nor are pathologies in which neurons die as the result of a known cause such as hypoxia, poison, metabolic defects, or infections. Among the hundreds of [...]

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SERIES INTRODUCTION

Neurodegeneration: What is it and where are we?Serge Przedborski,^{1,2,3} Miquel Vila,¹ and Vernice Jackson-Lewis¹¹Department of Neurology,²Department of Pathology, and³Center of Neurobiology and Behavior, Columbia University, New York, New York, USA*J. Clin. Invest.* 111:3–10 (2003). doi:10.1172/JCI200317522.

“Neurodegeneration” is a commonly used word whose meaning is believed to be universally understood. Yet finding a precise definition for neurodegeneration is much more arduous than one might imagine. Often, neurodegeneration is only casually mentioned and scarcely discussed in major medical textbooks and is even incompletely defined in the most comprehensive dictionaries. Etymologically, the word is composed of the prefix “neuro-,” which designates nerve cells (i.e., neurons), and “degeneration,” which refers to, in the case of tissues or organs, a process of losing structure or function. Thus, in the strict sense of the word, neurodegeneration corresponds to any pathological condition primarily affecting neurons. In practice, neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner. Conversely, neoplasm, edema, hemorrhage, and trauma of the nervous system, which are not primary neuronal diseases, are not considered to be neurodegenerative disorders. Diseases of the nervous system that implicate not neurons per se but rather their attributes, such as the myelin sheath as seen in multiple sclerosis, are not neurodegenerative disorders either, nor are pathologies in which neurons die as the result of a known cause such as hypoxia, poison, metabolic defects, or infections.

Among the hundreds of different neurodegenerative disorders, so far the lion’s share of attention has been given only to a handful, including Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS).

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Conflict of interest: The authors have declared that no conflict of interest exists.

Nonstandard abbreviations used: Alzheimer disease (AD); Parkinson disease (PD); Huntington disease (HD); amyotrophic lateral sclerosis (ALS); neurofibrillary tangle (NFT); superoxide dismutase-1 (SOD1); programmed cell death (PCD).

Many of the less common or publicized neurodegenerative disorders, though no less devastating, have remained essentially ignored.

The most consistent risk factor for developing a neurodegenerative disorder, especially AD or PD, is increasing age (1). Over the past century, the growth rate of the population aged 65 and beyond in industrialized countries has far exceeded that of the population as a whole. Thus, it can be anticipated that, over the next generations, the proportion of elderly citizens will double, and, with this, possibly the proportion of persons suffering from some kind of neurodegenerative disorder. This prediction is at the center of growing concerns in the medical community and among lawmakers, for one can easily foresee the increasing magnitude of emotional, physical, and financial burdens on patients, caregivers, and society that are related to these disabling illnesses. Compounding the problem is the fact that while, to date, several approved drugs do, to some extent, alleviate symptoms of several neurodegenerative diseases, their chronic use is often associated with debilitating side effects, and none seems to stop the progression of the degenerative process. In keeping with this, the development of effective preventive or protective therapies has been impeded by the limitations of our knowledge of the causes and the mechanisms by which neurons die in neurodegenerative diseases. Despite this bleak outlook, several neurobiological breakthroughs have brought closer than ever the day when the secrets of several neurodegenerative disorders will be unlocked and effective therapeutic strategies will become available. In this Perspective series, selected genetic and molecular advances relevant to the biology of neurodegeneration – e.g., to apoptosis, oxidative stress, and mitochondrial dysfunction – will be reviewed. While some of these will be discussed in terms of generic mechanisms underlying neuronal death, others will be discussed in the context of a specific disease such as ALS or HD. From the various Perspectives in this series, readers may obtain a comprehensive update on prominent neurodegenerative conditions from both a clinical and a molecular viewpoint. As a preamble to the series, however, it would be useful to discuss some general notions related to neu-

roderegeneration that should help set the stage for the more detailed articles to follow.

Classification of neurodegenerative diseases

The number of neurodegenerative diseases is currently estimated to be a few hundred, and, among these, many appear to overlap with one another clinically and pathologically, rendering their practical classification quite challenging. The issue is further complicated by the fact that, in diseases such as multisystem atrophy in which several areas of the brain are affected, different combinations of lesions can give rise to different clinical pictures (2). Furthermore, the same neurodegenerative process, especially at the beginning, can affect different areas of the brain, making a given disease appear very different from a symptomatic standpoint. Despite these difficulties, the most popular categorization of neurodegenerative disorders is still based on the predominant clinical feature or the topography of the predominant lesion, or often on a combination of both. Accordingly, neurodegenerative disorders of the CNS may, for example, be first grouped into diseases of the cerebral cortex, the basal ganglia, the brainstem and cerebellum, or the spinal cord. Then, within each group, a given disease may be further classified based on its main clinical features. For instance, the group of diseases that predominantly affect the cerebral cortex may be divided into dementing (e.g., AD) and nondementing conditions. Of note, while AD is by far the most frequently cited cause of dementing cerebral cortex pathology (3), dementia can apparently be observed in at least 50 different diseases (4). Moreover, dementia is not exclusively observed in neurodegenerative disorders; it is also frequently observed in ischemic, metabolic, toxic, infectious, and traumatic insults of the brain.

Diseases that predominantly involve the basal ganglia (a series of deep nuclei situated at the base of the forebrain, including the caudate nucleus putamen, globus pallidus, substantia nigra, subthalamic nucleus, red nucleus, and some thalamic and brainstem nuclei) are essentially characterized by abnormal movements. Yet, based on the phenomenology of the abnormal movements, diseases of the basal ganglia can be classified as hypokinetic or hyperkinetic. Hypokinetic basal ganglia disorders are epitomized by PD, in which the amplitude and velocity of voluntary movements are diminished or, in extreme cases, even nonexistent, causing the patient to become a prisoner within his or her own body. Aside from PD, parkinsonism – which refers to an association of at least two of the following clinical signs: resting tremor, slowness of movements, stiffness, and postural instability – is found in a variety of other diseases of the basal ganglia as well. In some (e.g., striatonigral degeneration), there is only parkinsonism, but in others, often called parkinson-plus syndromes, there is parkinsonism plus signs of cerebellar ataxia (e.g., olivopontocerebellar atrophy), orthostatic hypotension (e.g., Shy-Drager syndrome), or paralysis of vertical eye movements (e.g., progressive supranuclear palsy). Because, early on, parkinsonism may be the only

clinical expression of parkinson-plus syndromes, it is difficult to reach an accurate diagnosis before the patient reaches a more advanced stage of the disease. This problem is well illustrated by the fact that more than 77% of patients with parkinsonism are diagnosed in life as having PD (5), but as much as a quarter of these are found at autopsy to have lesions incompatible with PD (6). At the other end of the spectrum are the hyperkinetic basal ganglia disorders, which are epitomized by HD and essential tremor. In these two conditions, excessive abnormal movements such as chorea or tremor are superimposed onto and interfere with normal voluntary movements. Although hyperkinetic basal ganglia disorders are probably as diverse as are hypokinetic basal ganglia disorders, their accurate classification, even during life, is less problematic, in part because specific disease markers such as gene mutations exist for several of these syndromes.

Classification of neurodegenerative diseases of the cerebellum and its connections is particularly challenging because of the striking overlap among the various pathological conditions. Indeed, some diseases of the cerebellum can readily be grouped into three main neuropathological types: cerebellar cortical atrophy (lesion confined to the Purkinje cells and the inferior olives), pontocerebellar atrophy (lesion affecting several cerebellar and brain structures), and Friedreich ataxia (lesion affecting the posterior column of the spinal cord, peripheral nerves, and the heart). However, several other diseases of the cerebellum and its connections cannot be situated in one of these categories such as dentatorubral degeneration, in which the most conspicuous lesions are in the dentate and red nuclei, and Machado-Joseph disease, in which degeneration involves the lower and upper motor neurons, the substantia nigra, and the dentate system.

Among the neurodegenerative diseases that predominantly affect the spinal cord are ALS and spinal muscular atrophy, in which the most severe lesions are found in the anterior part of the spinal cord, and the already cited Friedreich ataxia, in which the most severe lesions are found in the posterior part of the spinal cord. Finally, there is one group of neurological diseases that are often, but not always, considered neurodegenerative because of their chronic course and unknown etiopathogenesis but that, unlike those described above, show no apparent structural abnormalities. These include torsion dystonia, Tourette syndrome, essential tremor, and schizophrenia. Various brain-imaging studies and electrophysiological investigations have revealed significant functional abnormalities in all of these singular neurodegenerative disorders but have not yet enabled us to unravel their chemical neuroanatomical substrates.

Over the past two decades, significant advances in neurohistological techniques such as immunohistochemistry have replaced or supplemented many of the classical histological approaches. Unquestionably, these new techniques have improved the sensitivity and specificity of neuropathological diagnostic criteria and consequently the accuracy of classification of neu-

rodegenerative disorders. However, despite the fact that these new methods can now determine the presence of particular inclusions or deposits or the degree of gliosis in specific brain areas, none of the already refined classifications of neurodegenerative diseases is entirely satisfactory. On the other hand, the incorporation of state-of-the-art basic science techniques such as gene array, PCR, Western blot, and laser-guided microdissection into our arsenal of neuropathological diagnostic tools should provide, in the near future, new clues as to how to effectively classify neurodegenerative diseases. Based on the use of some of these novel technologies, a new school of thought favors classification according not to the diseases' neuropathological hallmarks, but rather to their molecular characteristics. In this novel approach, neuropathological entities that used to belong to very distinct categories are lumped together because of a common molecular defect. For example, HD, spinal cerebellar atrophy and myotonic dystrophy fall into the category of the trinucleotide-repeat diseases (7); Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and fetal familial insomnia fall into the category of the prion diseases (8); PD, progressive supranuclear palsy, and diffuse Lewy body dementia fall into the category of the synucleinopathies (9); and corticobasal degeneration, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), and Pick disease fall into the category of the tauopathies (10). Although the jury is still out on whether this new classification will alleviate the problems previously encountered, we believe that it promises to be less ambiguous and more clinically and therapeutically practical.

What causes neurodegeneration?

With few exceptions, the causes of neurodegenerative diseases are essentially unknown, and even when they have been identified, the mechanisms by which they initiate the disease remain, at best, speculative. For example, while the etiology of HD was identified more than two decades ago, we still do not know with certainty how mutant huntingtin provokes the disease.

One of the most ferocious debates surrounding the etiology of neurodegenerative disorders concerns the relative roles of genetic and environmental factors in the initiation of these diseases. Some neurodegenerative disorders have a clear familial occurrence, suggesting a genetic basis. Among these affected families, the disease runs as an autosomal dominant trait, as in HD and dentatorubral pallidolusian atrophy. Less frequently, the disease runs as an autosomal recessive trait (e.g., familial spastic paraparesis), an X-linked trait (e.g., spinal and bulbar muscular atrophy), or even a maternally inherited trait (e.g., mitochondrial Leber optic neuropathy). In addition to these "pure" genetic neurodegenerative diseases, others are essentially sporadic but show a small contingent of patients in whom the illness is inherited. This is true for PD, AD, and even ALS, of which about 10% of all cases are unequivocally familial. Although rare, these familial cases represent powerful resources to elucidate the molecular bases

and, more importantly, the neurodegeneration mechanisms of their respective sporadic variants.

For those in whom the disease is truly sporadic, which is the vast majority of patients, it appears that any genetic contribution to the neurodegenerative process is minimal (11). Instead, toxic environmental factors may be the prime suspects in initiating neurodegenerative processes. Supporting this view is the observation that some neurodegenerative conditions arise in geographic or temporal clusters. This is the case for the PD-ALS complex, which is, presumably, due to a toxic compound contained in *Cycas circinalis*, an indigenous plant commonly ingested as a food or medicine by the Chamorros of Guam (12). Intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a by-product of the synthesis of a meperidine compound, is also known to produce a severe and irreversible parkinsonian syndrome, which is almost identical to PD (13). While many other examples of toxic exposure-related neurological conditions exist, all occur within a specific geographic, social, or professional context, which is missing from the medical history of most patients suffering from a neurodegenerative disorder. Moreover, several large-scale epidemiological studies have failed to show any definitive association between environmental factors and occurrence of diseases such as PD (14). Collectively, these findings argue that sporadic cases are neither clearly genetic nor clearly environmental, but that, possibly, they result from a combination of genetic and environmental causes. In this vein, the demonstration of a nonsyndromic familial deafness linked to a mitochondrial point mutation (15) provides a compelling argument. In this study, family members who harbored the mutation developed a hearing impairment only if exposed to the antibiotic aminoglycoside, illustrating the significant pathogenic interactions between genetics and the environment. The possibility that such dual mechanisms represent a valuable pathogenic scenario underlying sporadic neurodegeneration warrants serious consideration.

Cell demise in neurodegeneration

As mentioned above, only in a very small group of so-called neurodegenerative conditions are no apparent neuropathological changes found. In all others, overt neuropathology, mainly in the form of a focal loss of neurons with reactive gliosis, is seen. Residual neurons may exhibit varying morphologies ranging from an almost normal appearance to a severe distortion with a combination of abnormal features such as process attrition, shape and size alterations of the cell body and nucleus, organelle fragmentation, dispersion of Nissl bodies, cytoplasmic vacuolization, and chromatin condensation. In several neurodegenerative disorders, spared neurons can also present with various types of intracellular proteinaceous inclusions, which, in the absence of any definite known pathogenic role, are quite useful in differentiating neurodegenerative disorders. This is particularly clear in the case of the variants of PD, which can be stratified based on the presence or the absence of the intraneuronal inclusions called Lewy bodies (16).

The diversity of cell death morphology in neurodegeneration is often neglected, and many authors still consider only two types, apoptosis and necrosis. The former is universally recognized to be active in the sense of being mediated by intracellular signaling pathways, and the latter is traditionally considered passive. There is increasing evidence that this dichotomy is too rigid, especially for neurons, and readers interested in this debate are encouraged to consult the comprehensive review written by Peter Clarke (17). In brief, there is mounting evidence that the mode of cell death in the nervous system, as it can be defined by morphological features, is much more diverse than initially thought (18, 19). At least four main types of distinct neuronal death have been defined: apoptotic, necrotic, autophagic, and cytoplasmic; the detailed morphological description of each of these goes beyond the scope of this article but can be found in ref. 18. The main reason why attention to these different forms of cell death may be clinically important is that several of the distinct forms of cell demise are controlled by distinct molecular mechanisms (20–23). Another widespread misconception relating to the mode of cell death is the belief that only necrosis elicits inflammation. While the inflammatory reaction is indeed generally stronger in regions of necrosis than, for example, in regions of apoptosis, this may simply reflect the greater number of cells dying in necrotic regions. Moreover, those who claim that non-necrotic forms of cell death such as apoptosis do not elicit inflammation are referring to “exudative” inflammation (24), whose hallmarks include the infiltration of the diseased tissue by blood-borne cells including neutrophils and monocytes. Yet, in the CNS and especially in neurodegeneration, even for necrosis the inflammatory response is largely local, meaning that it is mainly made of resident microglia and astrocytes as seen in apoptosis. It is thus fair to conclude that while the intensity of the glial reaction may vary among the forms of cell death detailed in ref. 17, the occurrence of gliosis is not a hallmark of necrosis only.

With the few exceptions indicated above, neurodegenerative disorders have in common that they affect specific subpopulations of neurons at the level of specific structures of the nervous system.

In some neurodegenerative diseases, such as olivopontocerebellar atrophy, multiple brain structures within the nervous system are affected, usually at separate sites, while nearby and often intermingled neuronal subtypes are spared. In these so-called system neurodegenerative diseases, the spatial pattern of the lesions often becomes better defined as the disease progresses. It is clear that the distribution of blood vessels is not essentially responsible for determining the spatial pattern of the lesions. On the other hand, in many system neurodegenerative diseases, as is emphasized in ref. 25, the different lesions appear to be functionally and anatomically interconnected. Such a “linked” degeneration is observed in ALS, in which both the corticospinal track and the spinal cord lower motor neurons are affected, and in progressive supranuclear palsy, in which both the globus pallidus and the subthalam-

ic nucleus are lesioned. Although such transneuronal degeneration is a well-recognized phenomenon (26), very little is known about its molecular basis except that this trans-synaptic demise seems to occur by programmed cell death (27, 28). As is emphasized by Oppenheimer and Esiri (25), transneuronal degeneration does not account for all of the combinations of lesions that are found in system neurodegenerative diseases. For example, the authors point out that in Friedreich ataxia there is degeneration of the spino cerebellar tracts and the dentate nuclei, but not of the Purkinje cells, which, supposedly, constitute the link between these two lesions.

Not in all neurodegenerative disorders are large numbers of nervous system structures at risk. Indeed, in several neurodegenerative diseases the lesions appear to be restricted to one or a few brain regions, especially at the beginning of the disease. This is particularly well illustrated in spinal muscular atrophy, in which the degenerative process is limited to a loss of lower motor neurons; and in ALS, in which damage to the upper and lower motor neurons may represent the sole neuropathological change at the beginning of the disease, and other areas, including the substantia nigra, may become affected later (29). Still, the initial site of neuropathology remains the most severely affected throughout the disease, forming a sort of neurodegenerative gradient. In diseases like striatonigral degeneration, the neurodegenerative process is quite symmetrical from the onset, while in others like PD, one side of the brain is usually more severely affected than the other. This is clearly noticeable clinically and is demonstrable by brain-imaging techniques (30).

The locations of the principal lesions have been well established in most if not all known neurodegenerative disorders, but it remains difficult to determine the extent of degeneration that affects more than one group of neurons and, consequently, to define the exact neuropathological topography of certain diseases. This problem stems from at least three issues. First, lesions are often missed through incomplete examination of the brain and spinal cord. Second, quantitative morphology in postmortem samples seldom uses the rigorous counting methods necessary to generate reliable neuron numbers (31). Third, sick neurons, which will not necessarily die, often lose the phenotypic markers used to identify and count them (32). For these reasons, reported estimations regarding the distribution and the magnitude of neuronal loss in neurodegenerative disorders may, with perhaps a few exceptions, have to be taken with a grain of salt.

Onset and progressive course of the disease

Most patients suffering from a neurodegenerative disorder know approximately when their symptoms began. Because, almost invariably, there is significant cellular redundancy in neuronal pathways, the onset of symptoms does not equate with the onset of the disease. Instead, the beginning of symptoms corresponds to a neurodegenerative stage at which the number of residual neurons in a given pathway falls below the

number required to maintain normal functioning of the affected pathway. This means that the onset of the disease occurs at some earlier time, which, depending on how fast the neurodegenerative process evolves, can range from a few months to several years. In most instances, the lack of presymptomatic markers and of knowledge about the true kinetics of cell demise precludes our ability to determine disease onset.

It is also interesting to consider why a sudden worsening of a patient's condition is sometimes observed. Although we cannot exclude that the neurodegenerative process may suddenly accelerate, especially under the influence of intercurrent deleterious factors such as infection, it is more likely that the rate of neuronal death remains about the same throughout the natural course of the disease. Yet the relationship between the clinical expression of a disease and the number of residual neurons does not have to be linear or even constant. So a patient may remain clinically unchanged during a prolonged period of time, despite a loss of many cells, and then abruptly deteriorate as the number of neurons drops below a functional threshold.

All neurodegenerative disorders progress slowly over time, often taking several years to reach the end stage. Does this observation indicate that sick neurons succumb to the disease only after a protracted agony? It must be remembered that neuronal degeneration corresponds to an asynchronous death, in that cells within a population die at very different times. As a corollary at any given time, only a small number of cells are actually dying; among these, many, if not all, are at various stages along the cell death pathway. However, standard clinical, radiological, and biochemical measurements, which are so critical to assessing the disease, generate information on the entire population of cells. Therefore, the rate of change in any of the usual clinical parameters essentially reflects the decay of the entire population of affected cells and provides very little insight into the pace at which the death of an individual cell occurs. Still, if one looks at the large body of *in vitro* data, it appears that, once a cell gets sick, the entire process of death proceeds rapidly. Given these facts, the protracted clinical progression may reflect a small number of neurons dying rapidly at any given point in time.

Fatality in neurodegenerative disorders

Neurodegeneration is thought to shorten the life expectancy of affected patients. If this concept is unfortunately true in many instances, it should be emphasized that not all "mortal" neurodegenerative disorders are fatal *per se*. Only those in which the affected neurological structures impair ability to control or execute such vital functions as respiration, heart rate, or blood pressure are unquestionably deadly. These include ALS, in which the loss of lower motor neurons innervating respiratory muscles leads the patient to succumb to respiratory failure. Alternatively, in diseases like Friedreich ataxia, the association of neurodegeneration with heart disease (33) can also cause the death of the patient, although, in this case, death is due not to any neuronal loss but instead to serious cardiac problems

such as congestive heart failure. In most other neurodegenerative disorders, death is attributed neither to the disease of the nervous system nor to associated extra-nervous system degeneration but rather to the resulting motor and cognitive impairments that increase the risk of fatal accidental falling, aspiration pneumonia, pressure skin ulcers, malnutrition, and dehydration. Also, to our knowledge, there is no evidence that neurodegeneration increases the odds of developing comorbidity, such as with cancer, stroke, or heart attack, which remain the leading causes of death in industrialized countries. In conclusion, while a few specific neurodegenerative disorders directly cause death, most instead facilitate the occurrence of secondary health problems that carry a high mortality rate. Although this distinction may seem a matter of semantics, we believe that it is significant, not only for the management of patients, but also for our understanding of the actual consequences of the neurodegenerative process.

Neurodegeneration and aging

Many elderly individuals exhibit mild motor and cognitive alterations reminiscent of those found in neurodegeneration. This observation gave birth to the popular idea that aging might be a "benign" form of neurodegeneration. This idea was supported by the notion, widely accepted until recently, that normal aging, like neurodegeneration, is inevitably associated with neuronal death. From as early as the 1950s, decreased numbers of neurons in different regions of the brain were reported in aged humans with no overt neurological or psychiatric conditions (34). Subsequent studies have estimated these losses to be as high as 100,000 neurons per day, which could easily explain the cognitive decline and decrease in brain weight traditionally associated with normal aging (34). However, with the development of more accurate procedures for counting neurons, this view has been modified over the last several years, particularly as stereological procedures for estimating neuron numbers have been applied to aging research (35). As reviewed by Morrison and Hof, the application of stereological techniques has shown in several species, including humans, that the age-related decline in neuron number via neuronal death is not significantly involved in normal aging, at least with respect to the neocortex and to the hippocampal subregions most implicated in memory, such as entorhinal cortex and CA1 (35). These results, therefore, challenge the notion that neurodegeneration invariably occurs in normal aging.

If significant neuronal loss is lacking, some other pathological features of neurodegeneration, such as the presence of Lewy bodies, so typical of PD, and neurofibrillary tangles (NFTs) and senile plaques, so typical of AD, can be detected in brains of asymptomatic aged individuals (36, 37). The critical question thus becomes: Do these changes occur "normally" during aging or reflect a "presymptomatic" stage of these diseases? Because it is impossible to perform longitudinal neuropathological studies, it is impossible to deter-

mine whether these individuals would have developed full disease expression if they had lived longer. In fact, hitherto, there been no definitive evidence supporting such a progression (35). Instead, neuropathological and functional brain-imaging studies have revealed striking quantitative and qualitative differences between aged nondemented and demented individuals (35, 38), suggesting that aging and neurodegeneration may represent very distinct entities. For instance, in the nondemented elderly, no NFTs are observed in the frontal and temporal cortices and only a few NFTs are found in the entorhinal cortex and the hippocampal CA1 subregion, even in the absence of any neuronal loss (35). Conversely, in the demented elderly, even with the mildest cognitive impairments, some NFTs are observed in the frontal and temporal cortices and high densities of NFTs are found in the entorhinal cortex and the hippocampal CA1 subregion together with significant neuronal loss (35).

Therefore, the definition of normal aging is critical to any conclusion about the effect of the passage of time on the brain. Despite intense clinical-neuropathological correlative investigations, to date, experts remain unsure about whether the fact that a change is commonplace makes it normal and, conversely, whether changes, however slight, that are known to be associated with definite diseases of the nervous system are necessarily pathological. It is still difficult to know exactly to what extent neurons are damaged or lost in aged humans as a result exclusively of the passage of time. It seems clear, however, that the impact of the passage of time on the number of neurons is much less important than was previously believed, and that compelling evidence is lacking to support the idea that aging is a form of neurodegeneration *at minima*.

Conclusion

Current classifications of neurodegenerative diseases are based on a clinicopathological approach, i.e., defined by a presentation of symptoms and signs linked to neuropathological findings. Without undermining the usefulness of the clinicopathological approach for diagnosis and treatment in current neurological practice, this approach to classification should be reassessed. As indicated earlier in this review, it would probably be more meaningful to classify neurodegenerative diseases by their molecular characteristics, redefining the diseases as the consequence of biochemical processes, some of which may operate in more than one disease. By doing so, we may reveal pathogenic mechanisms that are common to some of these diseases, and open new therapeutic avenues that may be effective in several unrelated neurodegenerative diseases.

In this introductory review, we have tried to provide an overview of the complexity of the field of neurodegeneration, as well as to lay the groundwork for the upcoming set of articles that will complete this Perspective series.

As we have mentioned, HD has received a great deal of attention in the field of neuroscience, as it is a prototypic model of a genetic neurodegenerative disease. While it is well established that a triplet-repeat CAG

expansion mutation in the huntingtin gene on chromosome 4 is responsible for HD, Anne B. Young (39) will bring us on the chaotic trail of research that aims to define the normal functioning of this newly identified protein, as well as to elucidate the intimate mechanism by which the mutant huntingtin kills neurons. Although much remains to be done, this article provides us with an update on the most salient advances made in the past decade in the field of HD, suggests pathological scenarios as to how mutant huntingtin may lead to HD, and, most importantly, discusses the many steps in the process of functional decline and cell death that might be targeted by new neuroprotective therapies (39).

While HD is by nature a genetic condition, PD is only in rare instances an inherited disease. Despite this scarcity, many experts in the field of neurodegeneration share the belief that these rare genetic forms of PD represent unique tools to unravel the molecular mechanisms of neurodegeneration in the sporadic form of PD, which accounts for more than 90% of all cases. Accordingly, Ted Dawson and Valina Dawson review, in their Perspective, the different genetic forms of PD identified to date (40). They then summarize the current knowledge on the normal biology of two proteins, α -synuclein and parkin, whose mutations have been linked to familial PD (40). The authors also discuss how these different proteins may interact with each other and how, in response to the known PD-causing mutations, they may trigger the neurodegenerative processes (40).

The recognition that many neurodegenerative diseases are associated with some sort of intra- or extracellular proteinaceous aggregates has sparked major interest in the idea that these amorphous deposits may play a pathogenic role in the demise of specific subsets of neurons in various brain diseases. Along this line, what could be a better example of “proteinopathic” neurodegenerative disease than AD, which features NFTs and senile plaques? In this context, Todd Golde (41) reviews the presumed role of amyloid β protein ($A\beta$) in the initiation of AD and outlines the molecular scenario by which $A\beta$ may activate the deleterious cascade of events ultimately responsible for dementia and cell death in AD. In light of this information the author discusses the different therapeutic approaches that may be envisioned for AD (41). He also summarizes the state of our knowledge about risk factors and biomarkers for AD that can be used to detect individuals at risk for developing the disease, and to follow its progression once it has developed (41).

Interestingly, in another dreadful neurodegenerative disease, ALS, of which about 2% of the cases are related to a mutation affecting the enzyme superoxide dismutase-1 (SOD1), the presence of abnormal protein aggregates has also been hypothesized to participate in the neurodegenerative process. Nevertheless, the evidence supporting such a role in ALS is much more tenuous than in AD, and many appealing alternative pathogenic hypotheses have been put forward to explain the mechanism by which spinal cord motor neurons die in ALS, especially in response to mutant SOD1. For

instance, Guégan and Przedborski, in their article (42), approach the pathogenesis of ALS in general and of familial ALS linked to SOD1 mutations in particular, through the lens of programmed cell death (PCD) (42). In this article, we review the large core of data that pertain to the question of PCD in ALS, covering morphological and molecular findings that support the contribution of this molecularly regulated form of cell death to ALS neurodegeneration (42). We also discuss how particular molecular components of the PCD machinery can be targeted in ALS to develop new neuroprotective strategies for the treatment of this invariably fatal disease (42).

Moving away from disease-specific pathological mechanisms, Eric Schon and Giovanni Manfredi (43) address the topic of mitochondrial defects as a potential generic deleterious mechanism in neurodegeneration. In this article, the authors remind us that while there are well-defined mitochondrial diseases, which express themselves most often as myopathies or encephalopathy or both, mitochondrial defects have been implicated in a dazzling number of neurodegenerative diseases as well (43). To help the reader to better apprehend the difficulty in readily recognizing the signature of a mitochondrial component in neurodegenerative diseases, Schon and Manfredi review key molecular principles that govern mitochondrial biology (43). Based on this information, they then discuss in depth the fundamental issues of how the proposed mitochondrial alterations in neurodegenerative diseases may arise and whether these defects are the cause or the consequence of the neurodegenerative processes (43).

To continue with generic cytotoxic mechanisms, Harry Ischiropoulos and Joseph S. Beckman review, in their Perspective (44), the many lines of evidence supporting a role of oxidative and nitrative processes in the pathogenesis of numerous neurodegenerative diseases. These authors review the various cellular pathways that may be at the origin of the oxidative stress in neurodegeneration (44). They remind us that the most recent data have also identified nitric oxide-derived reactive nitrogen intermediates as critical contributors of protein modification and cell injury, and that consideration should be also given to inappropriate regulation of iron and other divalent redox metals, such as copper, as well as to redox-inactive zinc (44). Ischiropoulos and Beckman conclude by taking the stance that oxidative processes are critical in the pathogenic mechanisms of neurodegenerative diseases, and that promising therapeutic interventions geared toward mitigating oxidative processes may represent valuable therapeutic avenues for both acute and chronic neurodegeneration (44).

As this brief summary shows, each article in this Perspective series will discuss in depth a selected aspect of neurodegeneration. While each will focus on a very different topic, all will share a common theme: the neurobiology of neurodegeneration, and translational research that, in our opinion, represents the most effective way to bring basic science discoveries to clinical trials.

Acknowledgments

The authors acknowledge the assistance of Brian Jones with the preparation of this manuscript as well as the support of the NIH; National Institute of Neurological Disorders and Stroke grants R29 NS37345, RO1 NS38586, RO1 NS42269, and P50 NS38370; US Department of Defense grant DAMD 17-99-1-9471; the Lowenstein Foundation; the Lillian Goldman Charitable Trust; the Parkinson's Disease Foundation; the Muscular Dystrophy Association; and the ALS Association.

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