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A new nosology for neurodegenerative dementias: cognitive proteinopathies - Shifting from “Where” to “What”

Una nueva nosología para las demencias neurodegenerativas: proteinopatías cognitivas – del 'dónde' al 'qué'

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Review

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Abstract

Over the next 100 years, the neuropathology of each of these diseases was studied in greater detail. For instance, alpha-synuclein was identified in Parkinson's disease, beta-amyloid and phospho-tau in Alzheimer's disease, and tau and TDP-43 in Pick's disease. At the same time, typical and atypical forms of these pathologies began to be described. In frontotemporal disease, for instance, the classic behavioral variant and the rare aphasic variant have been described. Similarly, Alzheimer's disease has both classical (amnesic) and atypical variants including frontal, posterior cortical, aphasic and, more recently, Down's disease. Alpha-synuclein is the most important factor in Parkinson's disease, which is associated with Lewy bodies disease. However, in parkinsonian syndromes such as progressive supranuclear palsy or corticobasal degeneration, the change is a tauopathy. Therefore, these phenotypes, which only describe

"where" the lesion is located cannot be maintained. For example, a patient presenting with a behavioral disturbance such as apathy and disinhibition may have tauopathy, or TDP-43-opathy, or even beta amyloidosis. Over the last 10 years, neuropathological, and genetic research, as well as the emergence of biomarkers, has enabled us to diagnose the syndrome and identify the protein change that causes it during life. This is insignificant in the context of the new diagnostic criteria, and the new treatments targeting abnormal proteins or altered pathways, such as anti-amyloid, anti-tau, anti-sortilin antibodies. In the coming years, we will therefore move from diagnosing "where" to diagnosing "what" disease produces these symptoms.

Keywords: Dementia, Neurodegenerative Diseases, Proteostasis Deficiencies, Nervous System Diseases.

Resumen

Durante el último siglo, los avances en la neuropatología han permitido caracterizar con mayor precisión las enfermedades neurodegenerativas. Se han identificado proteínas patológicas clave como la alfa-sinucleína en la enfermedad de Parkinson, el beta-amiloide y la fosfo-tau en la enfermedad de Alzheimer, y la tau y TDP-43 en la enfermedad de Pick. A medida que estas proteínas fueron mejor comprendidas, también emergieron nuevas clasificaciones clínicas que diferencian formas típicas y atípicas. Por ejemplo, la enfermedad frontotemporal incluye tanto una variante conductual clásica como una afásica, mientras que el Alzheimer puede presentar variantes frontales, afásicas o corticales posteriores, además de la forma clásica amnésica. Tradicionalmente, el diagnóstico se ha basado en los síntomas clínicos y su localización cerebral, es decir, en el "dónde" ocurre la lesión. Sin embargo, este enfoque ha demostrado ser limitado, ya que síntomas similares pueden deberse a diferentes mecanismos patológicos. Por ejemplo, la apatía o la desinhibición pueden ser causadas por tauopatías, TDP-43-patías o incluso beta-amiloidosis. En la última década, la incorporación de biomarcadores y hallazgos genéticos ha permitido identificar, en vida, las proteínas causantes del daño, facilitando diagnósticos más precisos y personalizados. Este cambio de paradigma tiene implicaciones clínicas profundas, ya que las terapias actuales, como los anticuerpos anti-amiloide, anti-tau o anti-sortilina, se dirigen específicamente contra las proteínas patológicas. En este nuevo escenario diagnóstico y terapéutico, la medicina neurológica está transitando de un enfoque centrado en el "dónde" a uno centrado en el "qué", es decir, en la naturaleza molecular subyacente de la enfermedad.

Palabras claves: Demencia, Enfermedades Neurodegenerativas, Deficiencias en la Proteostasis, Enfermedades del Sistema Nervioso.

INTRODUCTION

The term "neurodegenerative dementias" refers to a group of disorders where the patient gradually loses cognitive abilities like memory, language, and problem-solving skills. This is due to the degeneration of neurons and networks in the brain (1). The brain's systematization was a defining feature at the neurology at the beginning of the nineteenth century. At that time, neurodegenerative diseases were described based on phenotypic manifestations resulting from the involvement of different central nervous system networks (e.g. extrapyramidal, cerebellar, memory or behavioral). Later, they were defined as diseases resulting

from systematic degeneration of different neuroanatomical pathways, which are related to different neuropathological disorders. According to clinical presentation, neurodegenerative diseases fall into two groups movement disorders (akinetic-rigid., hyperkinetic, ataxic and motor neuron disorders) and cognitive disorders (Alzheimer's disease, frontotemporal dementia and prion disease) (1).

In 1817 Sir James Parkinson published "An Essay on the Shaking Palsy," describing a condition characterized by motor extrapyramidal syndromes (akinesia, rigidity and tremor) associated with degeneration of the extrapyramidal system. In 1868 Charcot proposed the term Parkinson's disease, however the neuropathology remained unknown until 1912. Pick´s initial description in 1892 was based on the clinical presentation of a patient with progressive aphasia and behavioral disturbances resulting from degeneration of the frontal and temporal lobes, but there was no microscopic data. This clinical description and the focal atrophy formed the basis of the "disease" (2). In 1906 Alois Alzheimer published his case study of a patient named Augusta Deter, who exhibited cognitive impairment associated with parietotemporal atrophy characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles in the brain. In 1910, Emil Kraepelin was the first to name this disease Alzheimer's disease in his book (3).

In medicine, there has long been a wide variety of ways in which diseases are defined and categorized (4). To define a disease, three conditions had to be met: 1) an abnormal function or structure with 2) identifiable signs and symptoms and 3) an underlying cause or mechanism. Nosology is the science of defining and classifying diseases (4). Identifying the necessary and sufficient conditions for classifying and diagnosing diseases is of great importance in law, ethics, epidemiology, and of course, medicine (5).

Nosology and Neurodegenerative Diseases

The aim of nosology is to establish a structured framework for understanding the various characteristics of disease, including their causes and symptoms, thereby facilitating the diagnosis, treatment and study of disease by healthcare professionals.

More broadly, nosology helps to create diagnostic criteria, grouping diseases into categories based on common features, and facilitating and understanding of the relationships between different conditions.
In the nineteenth century, neurodegenerative disease with dementias were principally characterized by sign and symptoms associated with an abnormal neurological system associated with the word "where" (6). These conditions, which may be considered syndromes, do not fully meet the criteria for disease, yet they can still have a significant impact on health. The exact causes of neurodegenerative dementias are not fully understood, but it is believed that they involve a combination of genetic, environmental, and lifestyle factors. Protein misfolding and aggregation play a significant role in the development of these diseases.

The 20th century saw major breakthroughs in the study of neurodegenerative diseases. The development of advanced imaging techniques, such as brain magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, enabled better visualization of the brain function and its structures. The discovery of specific proteins associated with these conditions, such as beta-amyloid and tau in Alzheimer's disease, alpha-synuclein in Parkinson's disease, and tau, TDP 43 (TAR DNA-binding protein 43) and FUS (fused-in sarcoma protein) in frontotemporal dementia also provided valuable insights into their underlying molecular mechanisms. Neurodegenerative diseases are associated with the alteration to normal proteins in the nervous system. These diseases caused by the misfolding, aggregation, or accumulation of specific proteins, which leads to cellular dysfunction and tissue damage.

The misfolded proteins often form toxic oligomers or insoluble aggregates that disrupt normal cellular functions (1). Proteinopathy is a term used to describe a group of diseases involving the accumulation of abnormal proteins within cells or tissues. This disrupts normal cell function and causes various health problems.

These diseases are often neurodegenerative, meaning they primarily affect the nervous system, but they can also impact other organs. Examples of proteinopathies include synucleinopathy, amyloid β proteinopathy, tauopathy, TDP-43 proteinopathy, FET/FUS proteinopathy and PrP proteinopathy. According to their clinical presentation, proteinopathies can be divided into two groups: one with a predominant focus on movement disorders (akinetic-rigid., hyperkinetic, ataxic and motor neuron disorders) and other with predominant cognitive disorders (Alzheimer's disease, frontotemporal dementia and prion disease). However, most of the proteinopathies are associated with a combination of cognitive and movement disorders in varying proportions.

Another neuropathological discovery in Alzheimer's disease was the typical amyloid and tau lesion signatures were present only in early-onset dementia associated with familial or sporadic disease. However, in sporadic patients with late-onset Alzheimer's disease, which accounted for 98% of cases, amyloid deposits and tau pathology were predominant but other additional abnormalities were also found including TDP-43, tau and alfa-synuclein deposits as well as vascular disease (7). The presence of multiple pathologies in late-onset dementias is not unique to Alzheimer's disease. Similar situations can be found in other neurodegenerative dementias, such as frontotemporal dementia, Lewy body dementia, and hippocampal sclerosis. Mixed pathology in ageing is the norm rather than the exception (1).

In the second part of the 20th century, authors began describing several clinical phenotypes produced by the same neurodegenerative disease, and the same phenotype could be produced by different proteinopathies **(see Figure 1)**.

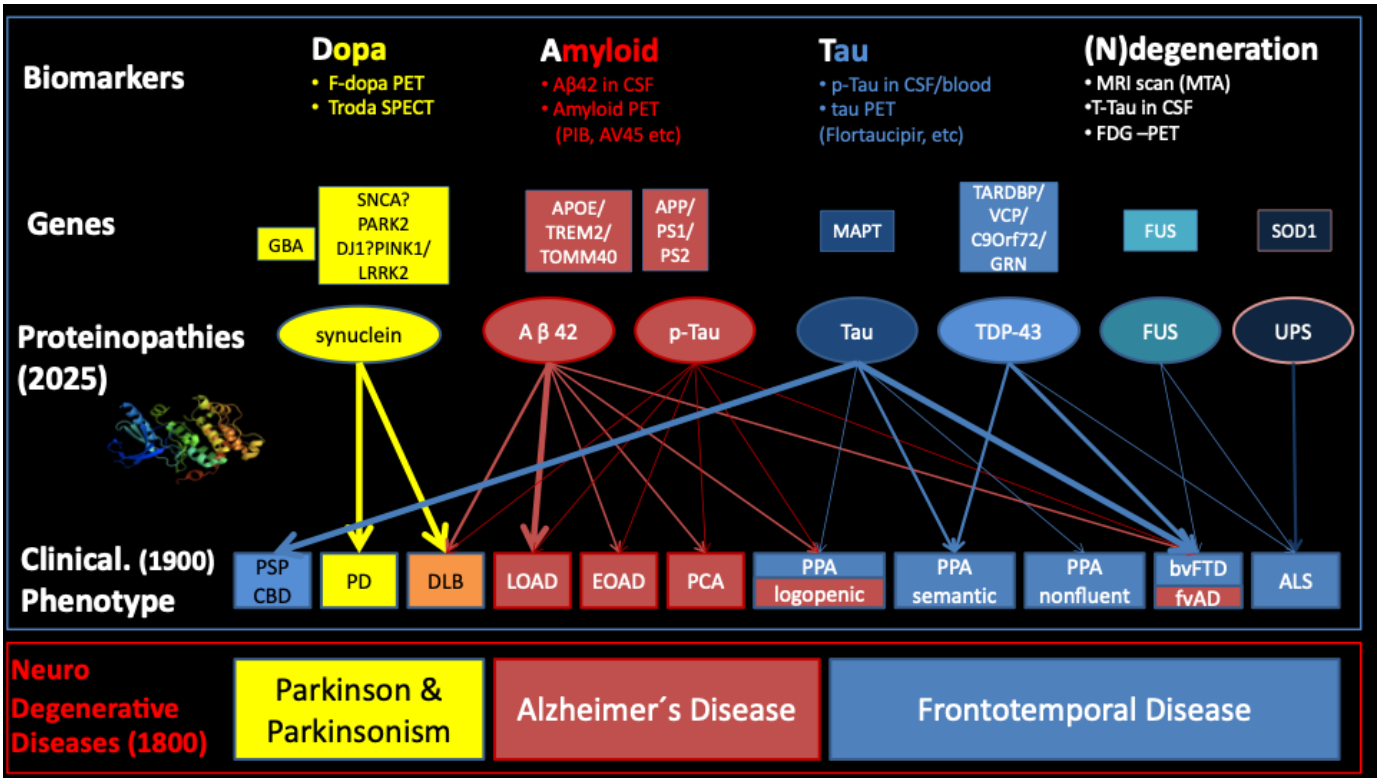

Figure 1. From neurodegenerative disease to proteinopathies. ALS Amyotrophic lateral sclerosis; BvFTD: Behavioral variant Frontotemporal Dementia; CDB= Corticobasal Degeneration; DLB= Lewy Bodies Dementia; EOAD= Early Onset Alzheimer's Disease; FvAD: Frontal variant Alzheimer's disease; LOAD= Late Onset Alzheimer's Disease; PCA= Posterior Cortical Atrophy; PD= Parkinson's disease;PPA= Primary Progressive Atrophy; PSP= Palsy Supranuclear Progressive. Source: author.

Alzheimer's disease was described as the typical cortical dementia; this phenotype includes amnesia alongside aphasia, agnosia and apraxia. The amnesic syndrome is characterized by poor episodic memory performance in both free recall and recognition plus intrusions and is associated with medial temporal atrophy (hippocampal atrophy). This typical phenotype in patients with mild cognitive impairment is considered to be at high risk of developing Alzheimer's disease (8). In recent years, several authors have described atypical variants of Alzheimer Disease, such posterior cortical atrophy, logopenic primary progressive aphasia, and behavioral variants (9).

Fronto-temporal dementia has been considered a disease, a syndrome, and a complex, going by several names such as Pick's disease, frontotemporal dementia, and frontal lobe dementia (2). Initially, the classic behavioral variant (Pick's disease) was considered, but in 1968, Rebeiz described corticobasal degeneration with a pathology like that of Pick's disease. In 1982, Marcel Mesulam described the primary progressive aphasia as a new entity (10) and finally considered to be associated with amyotrophic lateral sclerosis (10). Neuropathological findings in these phenotypes are diverse and include tau pathology, TDP-43, and FUS, as well as amyloid deposition (11).

The amnesic syndrome affects the hippocampus, the dysexecutive syndrome affects the frontal lobe; and the visuospatial syndrome affects the posterior parietal cortex. (12). Clinical phenotypes reflect the involvement of neuroanatomical systems, i.e., 'where' the disease is located. If a patient has primary progressive aphasia (PPA), the language system in the left hemisphere is affected. If the patient has non-fluent PPA, the left frontal lobe is the source. If the patient has semantic PPA, the left anterior temporal lobe is the site of origin (13).

Parkinson described the "Shaking Palsy" (Parkinson'disease), in which the senses and intellect remain intact. However, Charcot and Vulpian were the first to conclude that psychic faculties were impaired. (14). The presence of dementia in patients with idiopathic Parkinson's disease has been repeatedly demonstrated in epidemiological and neuropsychological studies (15). Albert et al. (1974) first proposed the term "subcortical dementia" (characterized by slowness, apathy, forgetfulness and defective ability to manipulate acquired knowledge) to describe the pattern in progressive supranuclear palsy (16). This subcortical profile could also be applied to dementia associated with Parkinson's disease (17). In 1976, Kosaka published the first case of diffuse Lewy body disease, and in 1980 he proposes the term "Lewy body disease" to encompass Parkinson's disease, Parkinson's disease with dementia and dementia with Lewy bodies (18).

The first diagnostic criteria for this condition were launched in 1996 (18). These conditions have the accumulation of the protein alpha-synuclein in vesicles called Lewy Bodies as a common characteristic. (6,19). In 1964 Steele, Richardson and Olszewski described a form of parkinsonism accompanied by dementia, which they termed progressive supranuclear palsy (PSP), characterized by a striking degree of atrophy of the midbrain and pontine tegmentum (20). As with Parkinson's disease, the substantia nigra was pale; however, this was not due to alpha synuclein, but tauopathies (21).

Tauopathies are a group of neurodegenerative diseases associated with tau inclusions in the central nervous system (22). These can be classified according to the tau protein isoform present in the inclusions. Primary tauopathies include Pick's disease, which has a 3R isoform, and corticobasal degeneration and progressive supranuclear palsy, which have 4R isoforms. Alzheimer's disease is a secondary tauopathy involving 3R+4R isoforms and neurofibrillary tangles. (23).

In the last year, a study found that 25% of patients with typical amnestic hippocampal Alzheimer's disease did not present Alzheimer's disease neuropathology but rather had TDP-43 deposition. For this population, the term "limbic-predominant age-related TDP-43 encephalopathy (LATE) has been proposed (24). One form of dysexecutive syndrome (frontal degeneration) has been linked to tauopathy, TDP-43 or even amyloidopathy. Amnesic hippocampal syndrome may be caused by either amyloidopathy or TDP-43 proteinopathy (24).

Proteinopathies: new insights

Based on the above descriptions several clinical phenotypes that were produced by the same neurodegenerative disease could be produced by different proteinopathies. Given the development of several antibodies against proteinopathies and their metabolic pathways, we need to shift the focus of nosology from classical neurodegenerative disease to proteinopathies. Current clinical dementia diagnoses recognize 'where' the pathology may be found, but not 'what' the underlying pathophysiology is. Degenerative dementias should be investigated based on molecular findings.

Today, Alzheimer's research cannot be considered without including biomarker results, which is challenging from a public health perspective, particularly in developing countries such as those in Latin American region.

The discovery and development of Alzheimer's disease biomarkers has led to a new paradigm in the study of neurodegenerative dementias. The biomarker assay enables the in vivo assessment of pathological disease traits.

Current biomarkers used in the clinic for Alzheimer's disease include (25):

1) Aβ1-42, total tau and phosphorylated tau assay in cerebrospinal fluid CSF.

2) Structural neuroimaging studies such as brain MRI and hippocampal volume analysis.

3) Functional neuroimaging of metabolic activity such as fluorodesoxyglucose (FDG) PET.

4) Protein-identifying neuroimaging using amyloid and tau PET .

The significant development has been the use of biomarkers. We can know identify the proteinopathy responsible for the symptoms in living subjects.

Since the original description of diagnostic criteria (NINCDS ADRDA) by McKhan et al. in 1984 (26), a diagnosis of dementia of Alzheimer's type was considered to be either probable or possible, with a definitive diagnosis only possible through neuropathological examination following the patient's death. While these criteria enabled the diagnosis of dementia, in the 1990 the concept of mild cognitive impairment (MCI) emerges as a stable between normality and dementia. MCI is a risk factor for dementia (27). More recently, it has become apparent that the disease begins biologically 15 to 20 years prior to the onset of clinical symptoms (28).

Based on this, a presymptomatic stage of the disease has been described (29). Thus, Alzheimer's disease has been recognized as having three stages: mild, moderate and severe dementia, a stage of mild cognitive impairment and a presymptomatic stage. Building on the success of using disease biomarkers two working groups made an initial effort to develop Alzheimer's disease diagnostic criteria. These were the international group (International Working Group - IGW) and the north american group comprising the National Institute on Aging (NIA) and the Alzheimer's Association of the USA (Alzheimer's Association - AA) (30).

In 2011, the NIA (National Institute on Aging) and the AA (Alzheimer's Association) published wider, more inclusive criteria based on AD biomarkers, establishing disease stages as a continuum from pre-symptomatic AD and mild cognitive impairment to dementia Jack et al (31,32). In 2014, Dubois et al. (33) expanded the diagnostic criteria to include typical (amnestic-hippocampal) and atypical (cortical posterior atrophy – CPA, PPA, frontal, and Down variants) forms, prioritizing amyloid markers in the diagnosis (12).

Finally, Jack et al (32) introduced a new A/T/N (Amyloid/Tau/ Neurodegeneration) classification based on biomarker. In this classification, "A" refers to the presence of a β-amyloid biomarker (detected using amyloid PET or by measuring the level of CSF Aβ42); 'T', refers to the value of a tau biomarker (measured in CSF using a phosphorylated tau assay, or tau PET); and 'N' refers to biomarkers for neurodegeneration or neuronal injury (evaluated using [18F]-fluorodeoxyglucose-PET, structural MRI atrophy, or total tau measurement in CSF). This classification system offers a clearer pathophysiological categorization and prediction of patient outcome (32).

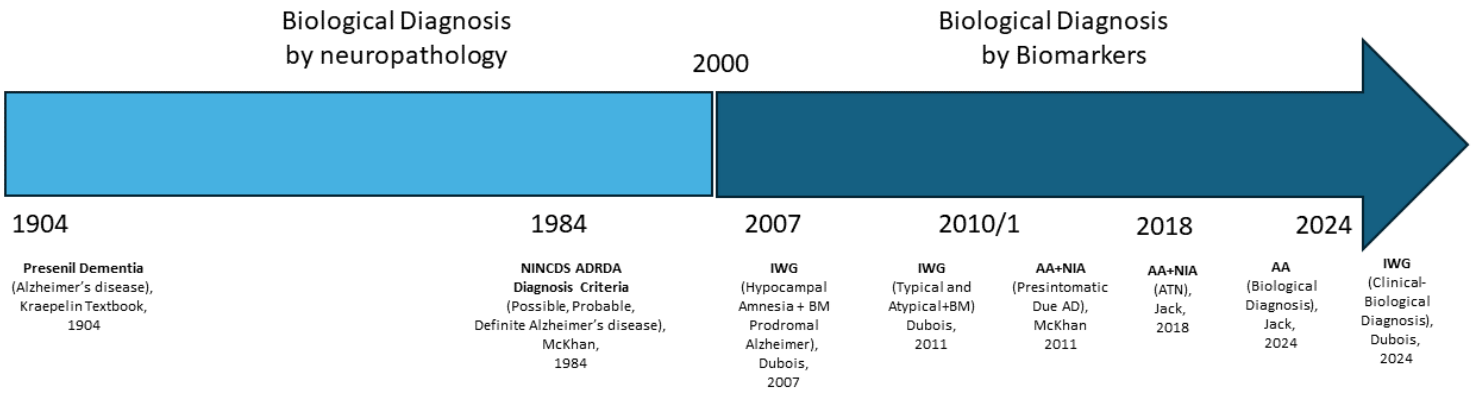

Figure 2. Evolution of diagnosis criteria for Alzheimer's disease. A=Amyloid; AA=Alzheimer's Association; AD=Alzheimer's Disease; BM=Biomarkers; IWG=International Working Group; MCI=Mild Cognitive Impairment; N=Neurodegeneration; NIA=National Institute of Aging; T=Tau. Source: author.

Following the approval of new anti-amyloid antibodies and the emergence of new biomarkers in 2024, criteria for diagnosing the disease were developed based solely on the biomarkers' biological aspects

(30). These constant changes demonstrate the rapid progress being made in the diagnosis and treatment of the disease.

The latest version (30) organized by the Alzheimer's Association, defines the disease biologically rather than syndromic. This oncology-based concept is being extended to all neurodegenerative diseases, moving away from syndromes and basing diagnoses on physiopathology and neuropathology. Following the publication of the diagnostic criteria by the American Alzheimer's Association (AA) group (30), the international group (33) is considering reviewing these criteria, which were solely biology-based and not clinically oriented.

They are proposing biological clinical criteria for practical clinical use. While both groups (AA and IWG) agree on the description of cases involving clinical cognitive impairment (mild cognitive impairment as well as mild, moderate and severe dementia) and the presence of biomarkers, but their concepts of cognitively normal subjects with positive biomarkers differ. The AA group considers these subjects to be part of Alzheimer's disease spectrum, whereas the IWG group considers them to be subjects "at risk" of developing the disease. Knowledge of the pathophysiology of Alzheimer's disease (AD) and its biomarkers has developed rapidly in recent years, leading to novel therapeutic approaches. Some of these have been approved by regulatory agencies such as the US Food and Drug Administration (FDA), including anti-amyloid antibodies such as lecanemab-2023 and donanemab-2024).

Conclusions

Ongoing research into proteinopathies is crucial for understanding the mechanisms behind these diseases and for finding more effective treatments to slow down or halt the progression of cognitive decline. In the coming years, we will therefore move from diagnosing "where" to diagnosing "what" disease produces these symptoms.

Conflicts of interest

The author declare no conflict of interest.

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Ethics statement

Not applicable.

Data, Materials, and Code Availability

This manuscript did not conduct data analysis.

Contributor roles

Ricardo F. Allegri: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

AI Usage Disclosure

This manuscript did not use artificial intelligence for information processing or writing.

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