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Commentary

Cogitations on a proteocentric lexicon

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Technical terms are the currency with which the business of science is conducted. Terminology provides the means to communicate complex ideas quickly and efficiently. This capability is maximized by agreement of the scientific community that a particular term means a particular thing. Terms may describe physicochemical entities, such as DNA, amino acids, or membranes; or processes, such as apoptosis, axonal transport, or mitosis. In each case, these terms incorporate many quanta of experimentally-determined chemical, biochemical, structural, or physiological information. In addition, implicit in the usage of scientific terminology are intangible elements, including prevailing assumptions and dogma. For example, the term amyloid originated from the tangible *observation* of abnormal deposition of a substance in the brain and the *assumption* that this substance was "starch-like." Combinations of tangible and intangible elements not only shape our definitions of scientific terms but create implicit intellectual and conceptual boundaries for scientific discourse and experimentation. These boundaries are at the same time inclusive and exclusive, and where these boundaries lie has profound effects on the manner in which science is conducted. If too narrow, academic consideration of certain scientific questions may exclude possible answers and explanations. If too broad, analysis of the question may become hopelessly complex due to the sheer breadth of information with apparent relevance.

In an accompanying article, Walker and LeVine argue, in essence, that recent new discoveries concerning the involvement of proteins in neurodegenerative diseases necessitate a reappraisal of the use of the term "amyloid." Their argument appears to rest upon two important observations. First, amyloid deposits are not composed of starch, a fact which has been known for many decades. Second, the pathobiology of a number of protein deposition diseases is not consistent with that of a typical amyloidosis, i.e., the formation and deposition of amyloid fibrils. Recent studies showing that nonfibrillar and protofibrillar protein assemblies can be cytotoxic support this second point [3,5]. These studies have raised the question of whether the proximate effectors of neurotoxicity in vivo are in fact soluble oligomers or protofibrils, and not typical amyloid-type assemblies. For these and other reasons, Walker and LeVine suggest that a more appropriate general term to define neurodegenerative diseases involving aberrant protein folding, assembly, or deposition would be "proteopathies." The classical amyloidoses, associated with Congo Red binding and cross-β structure, would be referred to as "β -proteopathies," while those proteopathies associated with the brain would be the "cerebral proteopathies."

In evaluating new terminology, two questions must be addressed: 1) Is there a need for the new term? and 2) Does the definition of the new term incorporate appropriate tangible and intangible elements? In the case of the term "proteopathy," it is unclear whether these questions can be answered in the affirmative. Language is malleable, and in fact, over time, the meanings of many words may change. Although some (I included) may find this objectionable and would instead prefer creation of new words, if the goal of language is to facilitate communication, then a gradual logoistic drift may not only be desirable, but essential. As discussed above, although "amyloid" clearly is a misnomer, scientists now understand well what this word means, both with respect to its implications of protein deposition within tissues and of biophysical characteristics including fibril formation, cross-β structure, and Congo Red staining. In addition, the word "amyloid," and its abbreviation "A," are part of an accepted paradigm for the naming of amyloid proteins [4]. Thus, it is not obvious that replacing this term with "β -proteopathies" is necessary or advantageous. This could be one reason why George Glenner's use of the term "β -fibrilloses," even in the context of an important review article in the *New England Journal of Medicine* [1,2], did not subsequently result in the use of this term rather than "amyloidoses." Even if the need for new terminology were compelling, implicit in the proposed definition of "cerebral proteopathy" are conceptual boundaries that result in the

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exclusion of important phenomena from the definition. For example, as correctly argued by Walker and LeVine, the potential involvement of nonfibrillar species in the pathogenesis of neurodegenerative disease must be considered. These species may not exist as polymers or as deposits in tissues and thus appear to be excluded by the definition of cerebral proteopathy as a "neurodegenerative disease in which abnormal protein polymerization and deposition are key features." On the other hand, if "proteopathy" were to include diseases of other organ systems that also involve protein deposition, such as AA amyloidosis or diabetes-related amyloidosis, it would appear appropriate to also include under this rubric sickle cell anemia or immune complex-associated syndromes such as rheumatoid arthritis and glomerulonephritis, which result from aberrant protein folding or deposition. From this perspective, "proteopathy" may be too inclusive a term.

From a didactic perspective, it is my view that one must consider at least four issues when attempting to explain key elements of diseases in which aberrant protein folding or assembly are implicated: 1) What is the primary anatomic site(s) affected by the disease (e.g., organ, local, systemic)? 2) What is the primary cellular site of protein action (intracellular or extracellular)? 3) How is the pathogenic effect of the protein related to its solubility or insolubility? and 4) What is the pathogenic form(s) of the protein (e.g., monomer, oligomer, protofibril, fibril, amorphous aggregate)? No single term can adequately incorporate all of these issues into its definition. It would thus be preferable to eschew the oversimplification of complex phenomena necessary to create a new term. Instead, consideration of the detailed mechanistic bases for diseases of protein folding or assembly should occur in the context of a discussion of the overall pathogenesis of the individual disease. In Alzheimer's disease, fibrillogenesis and amyloid formation are but two facets of this complex disorder. To refer to this disease as a cerebral proteopathy is to ignore the myriad other factors (e.g., genetic, hormonal, environmental) which figure prominently, and potentially seminally, in the pathogenesis of this disorder. As a protein chemist and structural biologist, I would like nothing better than to create a proteocentric lexicon. However, in the case of protein deposition diseases, this does not seem warranted.

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