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Open Commentary

Pathology's New Role: Defining Disease Process and Protective Responses

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Since inception, pathology has served as the indispensable link between basic science and clinical disease, encompassing the defining of disease processes and mechanisms through observation of structural alterations, as well as hypothesis-driven experimentation. The careful study of pathology has delivered an understanding of disease sufficient to guide effective treatment, and recognize ineffective treatment, so consequential to man's enhanced life expectancy in the past century. This paradigm has been particularly successful in providing insights for treatment of acute diseases; however, in the setting of chronic disease, where the relationship between basic pathology (typically end-stage) and patho-physiology is often misinterpreted, progress towards effective therapy has been slow, at best [1].

Here we consider the slow progress made in effectively understanding and healing Alzheimer disease (AD) by some of the most talented scientists of our time. At the root of the issue is the role of the pathologist, who may, in the setting of chronic diseases such as AD, assign too literal a meaning to the basic pathology. The pathologists' fascination with lesions, and in particular, lesions that can be visualized – in the case of AD, the senile plaque and neurofibrillary tangle – has proven a powerful and distracting a priori bias in his assessment of pathophysiology [1, 2].

Why is this distinction so important? The medicine-pathology partnership has made the most headway with acute disease (e.g., coronary artery thrombosis and myocardial infarction), where the body responds quickly and directly to a process that if not addressed rapidly leads to major morbidity and mortality. The structural changes of the disease are linked to processes at disequilibrium. In contrast, the pathological changes of AD develop over years, and it remains an open question whether such changes mark a movement toward health, i.e. an adaptive response to a chronic process, or death. Yet, studies addressing the pathogenesis of AD are dominated by the latter construct, something more akin to an acute infection than an age-related neurodegeneration, suggesting that removal of the microscopic lesion (infectious agent by analogy) will restore health [3, 4]. Such concrete thinking, we believe, represents a fundamental misconception of the relationship between pathology and chronic disease, one that has been propagated over the decades as scientists perseverate on the latest technologies rather than the clinico-pathological entities themselves. As such, a fundamental re-organization of the thought processes surrounding the pathology of chronic diseases is paramount, and a more open-minded view of pathology by pathologists themselves, we believe, is necessary to fulfill the ultimate goal of providing useful

Table 1 Technological advance and scientific discovery in AD

Technology	Discovery	References
Histological Stains	Senile plaques and neurofibrillary tangles	Alzheimer A [5]
Electron Microscopy	Amyloid fibers and paired helical filaments	Terry RD *et al* [15]
Immunohistochemistry	Linkage to the cytoskeleton	Iqbal K *et al* [16], Glenner GG *et al* [17], Perry G *et al* [18]
Protein Chemistry	Amyloid-β and tau	Glenner GG *et al* [19], Lee VM *et al* [20]
Molecular Genetics	Amyloid-β protein precursor, presenilin, apolipoprotein E	Strittmatter WJ *et al* [21], Goate AM [22], George-Hyslop PS *et al* [23]
Biophysics	Oligomers	Lacor PN *et al* [24]

information that would guide treatment efforts.

Last year marked the centennial of the clinical pathological discovery of AD, a dementia characterized by two pathological lesions [5]. Throughout this time, up to the present, the technology of the day continues to attempt to understand AD pathogenesis (**Table 1**). With each successive wave of technology, precision has increased, but the target – the pathological lesions or their surrogates – has remained essentially unchanged for those 100 years.

Even the hope of unbiased analysis through molecular genetics has disclosed genes that have all been related to AD through the pathology. Such a focus is not surprising, since pathological lesions have been effective avenues to therapeutics for over two centuries. Unfortunately, focusing on AD pathogenesis through the narrow prism of "lesion = disease," has not lead to a significant therapeutic advances [6]. Indeed, the most direct test of the pathology hypothesis, vaccine therapy, has led to pathology reversal at the cost of increased morbidity and mortality with no cognitive benefits [4]. This contradicted the prediction based on experimental models, where removal of amyloid-β (Aβ) or tau accumulation from genetically engineered animals effectively treats cognitive impairment and neuronal death. However, distinct from AD, these models are conditions produced by using an agent or gene to disturb normal metabolism; therefore, it might not be surprising that use of agents to remove/reverse the abnormal brings the system to normal. In this sense the models are much like infections, acute or genetic conditions where the linkage between pathology and mechanism is direct. Simple removal/reversal of the pathogen reverses disease.

AD fails the definition of a direct linkage between "pathology" and mechanism. Considering the pathological changes as primary may be highly analogous to consider the same for the inflammation of infection. Aspirin or steroids can modulate the inflammation, but not reverse the disease which requires eradication of the infectious agent. In AD and many other chronic diseases, we live with pathology for decades. Even more important, the pathology of AD is found to a similar extent in many of the normal aged [7]. Rather than viewing the lesions of AD as the traditional linkage of pathology and mechanism, they should instead be viewed as adaptive responses necessary for maintaining brain function in the face of earlier changes, e.g., oxidative stress, cell cycle reentry, and mitochondrial abnormalities [8-11]. In this light, removal of AD lesions could exacerbate the progression of disease by not protecting the brain from the primary, as yet unknown agent. In contrast, in cellular models and transgenic mice, Aβ is produced through exogenous intervention rather than through physiological response, and, as such, does not model the normal host response to chronic disease that should be required for any model of chronic disease to be considered relevant.

Genetic analysis has been used as the primary support for Aβ role in AD [12]. Numerous mutations in amyloid-β protein precursor (AβPP) and presenilin linked to AD modulate Aβ metabolism leading to increased Aβ1-42. Not emphasized is that absolute Aβ levels decrease with these mutations [13, 14]. Further, if viewed as a critical response to the unidentified cause of AD, Aβ alteration by mutations could be responsible for AD through abnormalities in the physiological response, as would therapeutics that alter critical physiological responses.

Instead of arguing that we are entering a post-pathology era, the complexity of responses in chronic conditions requires broader understanding of pathophysiology where the normal function of gene products is on-going as diseases develop. Without that understanding, the pathologist will continue to search for structural alternations and reflexively consider them maladaptive, without fully considering the body's responses and potential adaptive structural alternations that develop over decades. On the other hand, the thoughtful pathologist who maintains his priorities would continue to be in a unique position at the interface between basic science and clinical disease, and continue to contribute to these insights through careful understanding of both the strengths and limitations of the pathological basis of disease.

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