Immune responses are considered to be either humoral, resulting from cloning of B lymphocytes, or cell mediated, resulting from cloning of T lymphocytes. Autoimmune diseases occur when the cloned products attack host tissue. Inflammation is considered a nonspecific response to injury, characterized by exudation of serum into damaged tissue, and identified by the cardinal signs of rubor, calor, dolor, and tumor. However, these classic mechanisms do not fit pathological observations of Alzheimer disease (AD)—affected brain tissue. Although many of the components prominently associated with peripheral immunological and inflammatory states are present in AD lesions, there are no identifiable B lymphocytes or antibodies, and T cells are sparse. Furthermore, the blood-brain barrier is intact, excluding exudation of exogenous serum proteins. Although “neuroinflammation” is the term commonly used to describe the pathological changes, it fails to define adequately the process that is taking place. The reaction is neither a nonspecific response to injury, as classically implied for inflammatory reactions, nor an autoimmune reaction, despite the directed attack against plaques and extracellular tangles. It is most appropriately defined as an innate immunoreaction. The fact that such a reaction can be mounted by brain, an organ frequently described as being immunologically privileged, suggests that a reevaluation is required of the dimensions of the innate immune system, including how it operates at the tissue level. The innate immune system is primitive, while the adaptive immune system, which is directed by peripheral immune organs, is an invention of vertebrates. Even in vertebrates, however, the innate immune system is the first line of defense. Much more needs to be learned about the operation of the innate immune system in health and disease.

The reaction in Alzheimer disease (AD) is orchestrated by microglial cells. Metchnikoff identified their counterpart more than a century ago. He impaled starfish larvae with rose thorns, and named the cells mobilized to defend the tissue “phagocytes.” Del Rio Hortega, who originally identified microglia as cells that entered brain in late embryonic life, recognized their phagocytic function. Van Furth provided closure with his concept of the monocyte phagocytic system, through which all tissues are supplied with resident phagocytes from blood monocytes.

Highly activated microglia aggregate around the senile plaques and extracellular tangles of AD-affected brain. Their purpose is to phagocytose the lesions, but they fail to do so. Instead, the attack spills over, destroying neighboring neurons and their processes. The phenomenon can best be described as “autotoxicity” to distinguish it from classic autoimmunity that is directed by peripheral immune organs.

The methods by which microglia identify and attack their targets are still uncertain. However, opsonized complement is clearly one. The complement system is phylogenetically ancient, being traced back to sponges. Therefore, complement must be able to identify its targets in the absence of antibodies. For the classic pathway all that is required is binding of the C1q subcomponent of C1. The C1 complex then dissociates and the C1r and C1s esterases activate the further steps. While antibodies activate complement by binding to the globular head of C1q, β-amyloid protein, amyloid P- and C-reactive protein, all of which are found in senile plaques, activate complement by binding to the collagen tail. The end result of this collagen tail activation of complement is the same as if high levels of specific antibodies were present.
Downstream fragments of C4 and C3 covalently attach to hydroxyl and amino groups close to the C1q-binding site, opsonizing the target. Alzheimer disease lesions are richly decorated by these fragments. Moreover, the membrane attack complex, which is designed to destroy foreign invaders, is observed inserted into nearby neurites, damaging their viability. A process is called bystander lysis.

A surprising discovery was that the complement proteins are all made by resident brain cells. Neurons are a particularly abundant source, but astrocytes and microglia are also producers. Since complement is an important component of the innate immune response, the implication is that innate immunity operates in every organ of the body, with multiple cell types within that organ participating in the response.

A vigorous and sustained up-regulation of the complement system exists in AD-affected brain. The messenger RNA levels for the complement proteins are increased from 1.6- to 20-fold in affected areas of AD tissue. C1q, the component that initiates the complement cascade, and C9, the component that confers lytic activity to the membrane attack complex, show the greatest up-regulation.

In addition to the complement system, the brain produces a range of cytokines and chemokines known to be associated with classic immunological and inflammatory reactions. These include interleukin 1β, interleukin 6, tumor necrosis factor α, and macrophage inflammatory protein 1α, all of which are up-regulated in AD. Unlike the complement system, however, these cytokines and chemokines are nonspecific mediators. But they do intensify microglial activation.

Activated microglia express prodigious quantities of complement and immoglobulin receptors on their cell surface, thus facilitating their ability to bind to opsonized targets to phagocytose them. In addition, they generate products that are toxic to their targets, as well as to unaffected tissue in the surrounding region. In particular, they produce oxygen-derived free radicals that are powerful oxidizers. Although this respiratory burst system can be directly measured only in vitro, the products of attack, such as oxidized lipids, malondialdehyde, and glycated end products, can be identified post mortem and have all been found to be present in affected AD tissue.

Additionally, several acute-phase reactants are produced by brain tissue and are present in AD lesions. Acute-phase reactants are traditionally thought to be products of liver, which are stimulated by acute systemic reactions. C-Reactive protein, α1-antichymotrypsin, and α1-macroglobulin are 3 representatives. These are all chronically up-regulated in AD. All of these processes, which are present throughout the course of AD, are silent, because the brain has no pain fibers. However, pain fibers are present in joints, prompting individuals with arthritis to seek relief with anti-inflammatory agents. A test of whether these postmortem findings in AD are relevant to the in vivo situation is whether individuals taking anti-inflammatory agents for the symptomatic relief of arthritis will have a significantly lower odds ratio for developing AD than control subjects. Nonsteroidal anti-inflammatory drugs seem to be particularly effective, and, in one small, double-blind, clinical trial of indomethacin therapy seemed to halt the progression of established AD.

Since autotoxicity may be a general phenomenon, it can be anticipated that similar changes to those observed in AD will be documented for other neurological and peripheral conditions. For example, heart tissue injured by a myocardial infarct up-regulates its own complement production. The complement system becomes activated, with the membrane attack complex exacerbating damage to cardiomyocytes. Such autotoxic damage may continue over long periods. Autotoxicity may also contribute to diseases believed to be exclusively autoimmune in nature. If autoimmune and autotoxicity exist simultaneously, attempts to solve the etiology based on analyzing only adaptive immune components will fail.

Finally, the processes revealed by studies of AD pathological specimens may direct research toward drugs that will be more effective in inhibiting autotoxicity than current anti-inflammatory agents. Only mild interventions are possible through the use of cyclooxygenase inhibitors or steroids, while agents that interfere with such fundamental processes as nucleic acid activity (ie, methotrexate or cyclosporine) are highly toxic. A new therapeutic era can be anticipated when drugs are developed that influence more appropriate targets, such as the complement system and cytokine pathways influencing microglia or macrophage up-regulation.

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Corresponding author: Patrick L. McGeer, MD, PhD, Kinsmen Laboratory of Neurological Research, University of British Columbia, 2255 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 1Z3 (e-mail: mcgeerpl@interchange.ubc.ca).

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