An explosion of new techniques to explore DNA and protein biology during the last 2 decades has illuminated one of the most enigmatic and intractable subjects in biomedicine—neurodegeneration. Eponymic diseases of the nervous system that were until recently characterized by mechanistic ignorance and therapeutic nihilism are falling steadily to the power of molecular genetics, cell biology, biochemistry, and animal modeling. Alzheimer, Huntington, Creutzfeld-Jacob, and Parkinson diseases, as well as amyotrophic lateral sclerosis, spinocerebellar atrophies, frontotemporal dementia, and other previously obscure diseases, have all yielded rapid progress in the deciphering of their biochemical pathology and genetic underpinnings. This sea change in our understanding of a group of incurable diseases that confer enormous personal and societal burdens has brought us to the verge of rationally designed therapies and, in some cases, into actual human trials.

Perhaps the foremost example, both in terms of its impact on society and how far we have moved toward clinical application, is that of Alzheimer disease (AD). This most common of the late-life dementias is rising in prevalence with the aging of populations in developed countries and may now affect 20 to 30 million people worldwide. I will review the classic neuropathological lesions of AD that, despite some doubts along the way, turned out to provide a road map to the etiology and pathogenesis of the disease. Then, I will discuss how elucidating the genotype-to-phenotype relationships of certain genetic alterations linked to familial forms of AD has pinpointed molecular targets for treatment and prevention, some of which are now being addressed in clinical trials.

A WELL-DEFINED NEUROPATHOLOGY SPURRED THE QUEST FOR THERAPY

The successful attempts during the mid-1980s to develop methods for purifying microvascular and plaque amyloid deposits and neurofibrillary tangles from postmortem brains have enabled much of the further progress in this field. In particular, the isolation and partial sequencing of the amyloid β-protein (Aβ) by Glenner and Wong, followed by the recognition that amyloid plaques (but not neurofibrillary tangles) were composed of the same protein, led to the cloning of the β-amyloid precursor protein (APP) and the localization of its gene to human chromosome 21. The latter finding offered an explanation for the invariant development of the neuropathology of AD (often accompanied by cognitive decline) in patients with trisomy 21 (Down syndrome). It soon became clear that patients with Down syndrome begin to show immature Aβ deposits, known as diffuse plaques, as early as the second decade of life and later develop mature neuritic (amyloid) plaques and neurofibrillary tangles indistinguishable from those found in patients with AD. This information provided the first genetic evidence that Aβ build-up can precede and apparently initiate the typical neuropathology of AD. It was subsequently discovered that Aβ is naturally produced by all cells through-
out life,
protease.12 Mutations causing AD alter the conforma-
coveries in the disease and helped direct the search for
cauative genes. In accord, the first AD-causing gene to
classical and straight cytoplasmic filaments composed of

denormalities to the genetics of familial forms of AD.

**GENETIC DEFECTS THAT PREDISPOSE TO AD STRONGLY IMPLICATE Aβ**

The hypothesis that AD represents an amyloidosis of the
molecules in AD is a subject of active study, and several
viewpoint that the presence of Aβ deposits in the

The next 2 AD genes discovered were presenilin (PS)
and roughly 10 in PS2 confer an aggressive, early-onset phenotype. In cell culture, transgenic mouse
models, and the sera and brains of affected patients, it
has been shown that PS1 and PS2 missense mutations increase the production of Aβ42, the highly self-aggregation of paired helical filaments. These various assemblies—in particular, small
diffusible oligomers—appear to be able to induce synap-
amic and dendritic dysfunction and to activate microg-

Separate studies established the nature of the neuro-
the proteolytic processing of β-amyloid precursor protein (APP) and the fate of amyloid β-protein.

**TAU MUTATIONS LEAD TO FRONTOTEMPORAL DEMENTIA AND RELATED DISORDERS WITHOUT INDUCING Aβ DEPOSITION**

The long-standing debate about the primacy of tangles
vs plaques in AD pathogenesis has been largely resolved
by the exciting discovery of missense and splicing mu-
tations to date include frontotemporal dementia with
parkinsonism, progressive supranuclear palsy, and Pick
disease, but not AD. This knowledge indicates that a pri-
ary alteration of tau can cause severe neuronal degener-
ation, profound dementia, and the death of the host in
the absence of Aβ deposition. Alzheimer disease is de-

**ELUCIDATION OF THE PATHOGENIC PATHWAY PROVIDES MOLECULAR TARGETS AMENABLE TO BIOTECHNOLOGY**

Although numerous aspects of the detailed mechanism
of neuronal dysfunction in AD remain unsettled, a broad
consensus about some of the principal pathogenic events
has been reached by many investigators in the field. Ev-

den plaque deposition. The presence of Aβ-elevating APP
mutations augments the formation of tau deposits in neurons, rather than the converse.13 The precise way in which Aβ accu-
mulation induces a cascade of neuronal metabolic changes
that includes the hyperphosphorylation of wild-type tau
molecules in AD is a subject of active study, and several
kinases have been proposed as culprits.

Several other candidate genes are in the process of being
definitively confirmed as predisposing to late-onset AD.
Ultimately, a variety of genes will probably be determined to confer risk, each one responsible for only a rela-
tively small fraction of all cases.
lia and astrocytes (representing a local inflammatory reaction). Such changes, first subtle and then increasingly robust, are accompanied by an array of further cellular and biochemical alterations, including altered ionic homeostasis, free radical formation, oxidative injury, neutritic dystrophy, and, ultimately, neuronal death. Because the potential cellular responses to Aβ are myriad and complex, it has been argued that it would be more efficient to decrease the levels of Aβ42 in the brain than to attempt to interfere with 1 or more of these secondary effects of Aβ.

While intensive research into AD pathogenesis has occurred in large part in academic laboratories and enabled the field to move toward therapy, the actual discovery, preclinical validation, and clinical development of agents that lower Aβ are being conducted primarily by biotechnology and pharmaceutical companies. Indeed, the movement from basic research to the identification of treatments represents an important cooperative interaction between these 2 sectors. Many companies are now vigorously pursuing several well-defined molecular targets, the inhibition of which could allow not only treatment of active AD but perhaps also its prevention.

Based on the information reviewed herein, there is great interest in identifying small-molecule inhibitors of the β- and γ-secretases. The availability of a crystal structure for the active site of β-secretase (also known as BACE-1) is enabling medicinal chemists to systematically modify inhibitors arising from initial compound screens in ways that should enhance potency and still ensure specificity. Because genetic deletion of the BACE-1 gene in mice appears to have little or no adverse consequences, β-secretase inhibitors would be expected to have few mechanism-based adverse effects. Therefore, β-secretase inhibition represents a particularly attractive therapeutic target. On the other hand, the size and shape of the active site of this aspartyl protease present considerable challenges for the design of potent small-molecule inhibitors that can also achieve good brain penetration.

In the case of γ-secretase, the situation is more complex. Because its active site is intramembranous, and because PS requires 3 additional membrane proteins (nicastrin, Aph-1, and Pen-2) for proteolytic activity, the possibility of crystallizing γ-secretase is highly remote. Moreover, this unusual enzyme has numerous substrates besides APP, perhaps the most important of which is Notch. Notch comprises a family of cell-surface receptors that must undergo intramembranous cleavage by PS/γ-secretase to mediate cellular differentiation in multicellular organisms. Notch processing is thus required for life. It remains to be seen whether γ-secretase inhibitors can be found that lower the cleavage of APP to hinder sufficiently the release of Aβ but do not interfere with Notch cleavage to an extent that would produce adverse effects. Intriguingly, there is evidence that certain nonsteroidal anti-inflammatory drugs such as ibuprofen may subtly modulate γ-secretase cleavage to lower Aβ42 production without impairing Aβ40 production and Notch cleavage. Derivatives of certain anti-inflammatory drugs that can no longer inhibit cyclooxygenase activity but still lower Aβ42 production are currently being tested in patients with AD.

A different treatment approach to the Aβ problem in AD is to prevent the aggregation of the peptide and/or promote its clearance. One novel paradigm that appears to work by the latter mechanism is anti-Aβ immunotherapy. Two general approaches have been studied in AD mouse models: active vaccination with Aβ or fragments thereof and passive infusions of monoclonal antibodies to Aβ. Both have worked well to clear plaques and lower Aβ levels in mice, and they have decreased neutritic dystrophy and even ameliorated learning deficits in these models. A clinical trial of active vaccination with Aβ42 peptide plus an adjuvant led to the development of meningoencephalitis (apparently mediated by anti-Aβ T cells) in 18 (6%) of 300 study patients after just 2 vaccinations. Administration of the vaccine was halted, but all patients were followed up closely, and the 18 patients recovered to baseline status. Neuropsychological evaluations after 1 year suggested that some of the vaccine recipients had experienced stabilization of their cognitive decline and perhaps even some improvement on some measures of cognition regardless of whether they had experienced the adverse T-cell reaction—and this was correlated with their titers of anti-Aβ antibodies. Moreover, when study patients died of causes other than AD, a few autopsies revealed an apparent partial clearing of Aβ deposits in some cortical regions. All of this new knowledge has led to the continuation of the immunotherapy approach in a new phase 1 trial, this time in the form of passive administration of a humanized monoclonal antibody to Aβ. An alternative active approach that may carry a lower risk of adverse events is mucosal (nasal or oral) vaccination. This method has been tried in APP transgenic mice (but not in humans) and has led to significant decreases in plaque burden, Aβ levels, neutritic dystrophy, and gliosis.

WHERE DO WE GO FROM HERE?

There are, of course, numerous other prospective strategies to treat or prevent AD, including some directed against the amyloid problem (eg, antiaggregation compounds and metal chelators) and some directed against other features of pathogenesis (eg, neurotrophins, antioxidants, and free radical scavengers). But anti-Aβ immunotherapy represents the most advanced disease-modifying attempt so far, in terms of experience in humans. All of the various thrusts toward treatment and prevention should be pursued vigorously by both academic and biopharmaceutical investigators so that more than 1 approach ultimately becomes available for clinical use.

In the future, it is likely that middle-aged adults will commonly undergo a formal risk assessment for AD that will include detailed family history taking, brief neuropsychological assessment, screening for known genetic risk factors, measurements of plasma Aβ (and perhaps cerebrospinal fluid Aβ and tau), and quantitative assessment of brain β-amyloid burden by imaging procedures. Based on the results, patients would be offered 1 of the potentially disease-slowing therapies contemplated herein or others not discussed here. One can only hope that such a scenario comes into practice well be-
fore another generation of older humans succumbs to this devastating disease.

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