elevated on the lesioned side as compared to the control side when mitochondria are fueled with pyruvate (*21*). This would result in the activation of various calcium-dependent mechanisms and of proteolytic processes that could induce the dissolution of axoplasm and disruption of the cytoskeleton (*22*), as has been proposed for degenerative changes in peripheral neurons (*9*). The activation of these proteolytic processes might be responsible for the initial atrophy in the denervated dendrites, as well as the subsequent generation of appropriate sites for reinnervation (*1–3*).

Our results suggest that different forms of plasticity in the hippocampus might be initiated by similar biochemical mechanisms. The modification of the state of phosphorylation of α-PDH by high-frequency stimulation (*4*) or learning (*11*) and by hippocampal denervation might result in a decreased ability of mitochondria to rapidly eliminate excess cytosolic calcium, followed by an activation of calcium-sensitive proteolytic processes. In plasticity induced by high-frequency stimulation or learning, this activation could be limited in time and space and result in local membrane changes that cause the unmasking of neurotransmitter receptors (*23*) or a change in spine shape (*24*). With denervation, this activation would be more dramatic in extent and longer lasting, leading initially to a resorption of dendritic spines and later to reactive synaptogenesis. This raises the possibility that plasticity reflects the potential ability of synaptic connections to evolve from stability to instability to irreversible instability and degeneration.

MICHEL BAUDRY
JANNON FUCHS
MARKUS KESSLER
DENISE ARST
GARY LYNCH

Department of Psychobiology, University of California, Irvine 92717

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Cholinergic Innervation in Neuritic Plaques

Abstract. *Although several studies of Alzheimer's disease suggest that the frequency of neuritic plaques in the cerebral cortex is correlated with the severity of dementia and with reduction in presynaptic cholinergic markers in the cortex, the relationship between cholinergic cortical innervation and the pathogenesis of plaques is unknown. The hypothesis was tested that the neurites in the plaque consist, in part, of presynaptic cholinergic axons, many of which arise from neurons in the basal forebrain. This hypothesis was tested by analyzing the character and distribution of plaques in monkeys, aged 4 to 31 years, with staining for acetylcholinesterase and also with Congo red and silver stains. Immature and mature plaques were rich in acetylcholinesterase. As the plaques matured, the amount of amyloid increased, and the number of neurites and the activity of acetylcholinesterase decreased. End-stage amyloid-rich plaques lacked acetylcholinesterase. These observations indicate that changes in cortical cholinergic innervation are an important feature in the pathogenesis and evolution of the neuritic plaque.*

Alzheimer's disease (AD) and senile dementia of the Alzheimer's type (SDAT) are the most common causes of dementia in middle and late life (*1, 2*). The principal histological hallmarks of the disease are neurofibrillary tangles and neuritic plaques. The latter are composed of degenerating axonal terminals, amyloid, and reactive cells (*1, 3, 4*). Although not all reports agree (*5*), in studies utilizing systematic testing, patients with severe dementia showed the greatest number of neuritic plaques (*6*) and the most profound loss of the cortical cholinergic presynaptic markers, acetylcholinesterase (AChE) and choline acetyltransferase (CAT) (*7, 8*).

Our previous studies of AD/SDAT (*9*) have shown a severe loss of neurons in the nucleus basalis of Meynert (nbM), a nucleus of the basal forebrain (*10*) that projects directly and diffusely to neocortex (*11*). Neurons in the nbM provide the major source of cortical cholinergic innervation. The nbM shows high levels of CAT activity, and its large neurons are rich in AChE and stain with antibodies directed against CAT (*12–15*); undercutting the cortex or selective destruction of the neurons in the nbM is associated with reductions in cortical AChE and CAT levels (*13, 15*). These lines of evidence, in conjunction with the observation that some plaques in patients with AD/SDAT contain AChE (*16*), suggest that some of the dystrophic neurites in immature and evolving plaques may be degenerating intracortical branches of nbM axons. If this hypothesis is correct, the neurite-containing plaques

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should stain for AChE and, as the neurites disappear, AChE activity should decline and be virtually absent in compact plaques. Since rhesus monkeys develop neuritic plaques with increasing age (*4*), we examined representative samples of frozen and fixed frontal cortices of three 31-year-old, one 26-year-old, two 9-year-old, and two 4-year-old monkeys (*17, 18*). Frozen sections (25 or 40 μm) were thaw-mounted, fixed with 1 percent phosphate-buffered formaldehyde, and stained for AChE (*19*). They were also stained with Congo red to permit visualization of both amyloid (Congo red birefringence in polarized optics) and AChE activity (bright image in dark field). Quantitative estimates (*20*) of the type, number, and densities of plaques were made in comparable parts of fixed (*21*) and frozen cortex (Table 1). Each plaque was classified as immature, classical, or end-stage (amyloid-rich), depending on the numbers of large neurites and amount of amyloid (*5*).

In the frontal cortex of the four oldest monkeys, stains with silver or Congo red dye demonstrated varying numbers of plaques similar to those reported in humans (*22*); the 4- and 9-year-old monkeys did not have plaques in this part of the cortex. The AChE staining and the Congo red stains disclosed foci of the reaction product similar in size and distribution to the plaques demonstrated by the other techniques (Fig. 1). Immature plaques contained little amyloid and were rich in AChE activity that was often contained in neurite-like forms. Classical plaques contained large amounts of amyloid and showed marked AChE activity. End-stage plaques, more frequent in the 31-year-old monkeys, particularly in animals L and O (Table 1), showed abundant amyloid, relatively few neurites, and very little AChE activity. Only by combining Congo red stains with AChE histochemistry were we definitively able to recognize these foci that stained weakly for AChE as plaques.

Quantitative studies of plaques stained with silver impregnation methods showed that the percentage of compact plaques increased in parallel with an increasing density of plaques (Table 1). Conversely, staining for AChE was most intense in the animals with fewer plaques. Older monkeys, with many plaques, showed diffuse decrease of superficial cortical staining (layer 1) and patchy AChE staining in the deeper cortical layers.

Our study indicates that immature and mature plaques contain AChE-rich dystrophic axons. Many of the AChE-rich neurites in these cortical plaques probably arise from neurons in the basal forebrain, particularly those in the nbM, since the major AChE staining of the cortex is derived from the nbM (*15*), and AChE activity disappears with loss of neurites in the compact plaques.

Table 1. Quantitative estimates of plaques in the cortex. The ages for the 31-year-old animals are estimated because these monkeys were feral-born. The younger groups are not included since they showed no plaques in this part of cortex. All plaques were counted in the same parts of the cingulate, orbital, and rectal gyri by three independent observers; the scores were averaged. End-stage, amyloid-rich plaques were those lesions with an amyloid core containing fewer than two neurites.

Animal	Age	Plaques		
		Number per square millimeter	Mature (%)	End-stage (%)
M	26	0.80	59.4	5.9
N	31	1.24	36.4	38.0
L	31	2.83	29.4	70.2
O	31	2.33	24.9	74.5

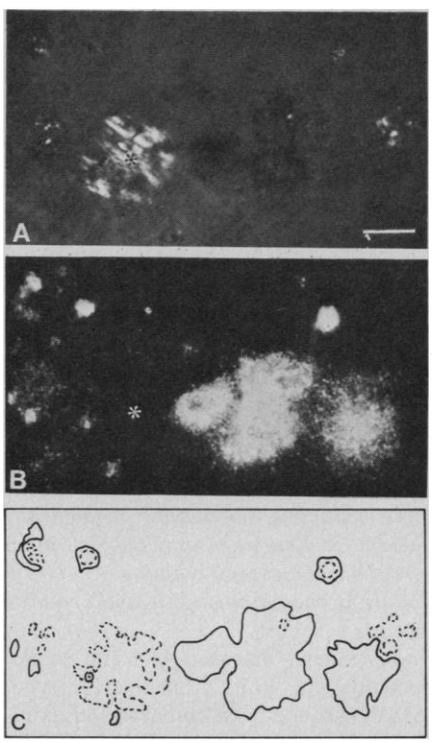

Fig. 1. (A and B) Photomicrographs of identical fields of a 25-μm-thick frozen section from a 31-year-old monkey. (A) Tissues stained for amyloid with Congo red. Cross-polarization optics discloses foci of amyloid deposition. (B) Tissues stained for AChE. The AChE reaction product is seen in dark-field illumination. Comparison shows that intense AChE activity is associated with little amyloid, whereas large accumulations of amyloid (*) are virtually devoid of AChE activity. (C) Drawing emphasizing the differences in distribution of AChE and amyloid. The regions showing the most intense AChE activity are indicated by solid lines; amyloid birefringence is outlined by broken lines. Some bright spots noted in (B) are not present in (C); bright-field examination disclosed these spots to be lipofuscin (*3, 4*). Magnification, ×160; scale bar, 20 μm.

Preliminary observations of the nbM in our monkeys have not shown neuronal loss of the magnitude identified in AD/SDAT (*9*), nor does the number of cortical plaques in these monkeys approach that seen in severe AD/SDAT (*3, 4*), but is more comparable to that reported in normal aged human brains (*22*). The six oldest monkeys in the Davis collection (*17*), four of which were used in this study, showed significant impairment of short-term memory with increasing age.

Our studies suggest the following sequence of plaque formation. The initial pathology of immature plaques appears to be enlargement of neurites, many of which are rich in AChE. As the disease progresses, some of these neurites degenerate; their constituents are liberated into the microenvironment of the neuropil and are acted on by microglial cells to form amyloid. Mature plaques, containing amyloid-rich cores, are argentophilic and contain neurites that stain for AChE. Eventually, the dystrophic axons in the plaque disappear; there is concomitant loss of AChE staining and CAT activity. The compact plaque, containing only amyloid, marks the site of degenerated terminals of axons from the basal forebrain. Since presynaptic cholinergic innervation represents a major input to the cortex, it is not surprising that the frequency of neuritic plaques is directly correlated with the loss of CAT activity and the degree of dementia (*6, 7*). This study provides evidence that changes in cholinergic cortical axons are an important component in the pathogenesis and evolution of the neuritic plaque.

ROBERT G. STRUBLE
Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205
LINDA C. CORK
Division of Comparative Medicine and *Department of Pathology, Johns Hopkins University School of Medicine*
PETER J. WHITEHOUSE
Department of Neurology, Johns Hopkins University School of Medicine
DONALD L. PRICE
Neuropathology Laboratory, Departments of Pathology and *Neurology, Johns Hopkins University School of Medicine*

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18. After the animal was given an overdose of pentobarbital, the brain was removed and transected through the upper mesencephalon. One hemisphere was immersed in 4 percent formaldehyde solution and processed for paraffin embedding; the other hemisphere was cut coronally into 1-cm-thick slabs and then frozen individually in liquid nitrogen (−70°C).
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20. Plaques were characterized as immature, mature, and end-stage amyloid-rich, depending on their content of neurites and amyloid. They were counted by three independent observers; scores are averages of three counts. The areas counted were computed using a Hewlett-Packard digitizer.
21. Fixed sections were stained with cresyl violet, hematoxylin and eosin, Luxol fast blue, Congo red and hematoxylin, and with silver by the Sevier-Munger silver method.
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Systemic Lupus Erythematosus-Like Syndrome in Monkeys Fed Alfalfa Sprouts: Role of a Nonprotein Amino Acid

Abstract. *Hematologic and serologic abnormalities similar to those observed in human systemic lupus erythematosus (SLE) developed in cynomolgus macaques fed alfalfa sprouts. L-Canavanine sulfate, a constituent of alfalfa sprouts, was incorporated into the diet and reactivated the syndrome in monkeys in which an SLE-like syndrome had previously been induced by the ingestion of alfalfa seeds or sprouts.*

Systemic lupus erythematosus (SLE) has been observed in monkeys fed alfalfa seeds (*1*, *2*). This primate model of SLE is characterized by an anemia that results from the occurrence of antibodies to red blood cells, by lowered complement components in the serum, by antibodies to nuclear antigens (ANA), antibodies to double-stranded DNA (anti-dsDNA), lupus erythematosus (LE) cells in peripheral blood smears, and the deposition of immunoglobulin and complement in the kidneys and skin (*2*). We have proposed the hypothesis that this syndrome may be triggered by L-canavanine found in alfalfa seeds (*3*). L-Canavanine, $H_2N\text{-}C(=NH)\text{-}NH\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH(NH_2)COOH$, is the guanidinoxy structural analog of arginine; it constitutes about 1.5 percent of the dry weight of alfalfa seeds and alfalfa sprouts (*4*) and is toxic to many organisms (*5*), including mammals (*6*).

Twelve adult female cynomolgus macaques (*Macaca fascicularis*), obtained in Indonesia, were randomly assigned to two groups of six animals each and fed, for 7 months, semipurified food (group 1) or similar food containing 40 percent (oven-dried) alfalfa sprouts (group 2). The percentage composition of semipurified food (group 1) was: casein, 18; sugar, 30; Alphacel, 12; honey, 10; banana, 10; butter, 3; coconut oil, 8.5; safflower oil, 2.5; cholesterol, 0.108; and additional vitamins and salts. The amount of 40 percent dried alfalfa sprouts added to the diet of animals in group 2 was based on isocaloric substitution of nutrients; that is, the percentage composition of oven-dried alfalfa sprouts was: moisture, 10; protein, 31.2; fat, 2.08; carbohydrate, 49.4; fiber, 16.1; and ash, 7.3. The caloric value was 270 kcal/100 g (*7*). Group 2 continued the alfalfa sprout diet for an additional 3 months. Venous blood was obtained before dietary manipulation and at monthly intervals thereafter. The following determinations were made: complete blood count and Technicon Sequential Multiple Analyzer Computer Chemistry Screen (SMAC); ANA test by indirect immunofluorescence with the use of 4-μm sections of frozen mouse kidney and the HEp-2 human cell line (Microbiological Associates) (*8*, *9*) as substrates; anti-dsDNA (*10*); C3 and C4 components of complement (*11*); direct antiglobulin test (Coombs' test) for the determination of antibodies to red blood cells (*12*, *13*).

Significant differences among animals ingesting food with or without alfalfa sprouts were not apparent for the following variables: body weight, food intake, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, calcium, phosphorus, total protein, albumin, triglycerides, total and direct bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), serum glutamate oxaloacetic transaminase (E.C. 2.6.1.1) and γ-glutamyl transpeptidase (E.C. 2.3.2.2). Plasma cholesterol values (averaged for the first 6 months of the diet) were 395 ± 101 mg/dl (mean ± S.D.) in monkeys on diet 1 (controls) and 186 ± 35 mg/dl in animals on the diet containing alfalfa sprouts ($P < .01$, Student's *t*-test). Additional hematologic and serologic values are shown in Table 1. Control animals and four monkeys ingesting alfalfa sprouts did not show hematologic or serologic abnormalities

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