Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Gadolinium enhancing lesions on T1-weighted MR images reflect abnormalities in the blood-brain barrier (BBB), and are used as measures of active inflammation. Enhancement has been found to precede the development of chronic lesions and clinical symptoms, suggesting that BBB breakdown may be linked to the demyelinating process. Recently, the process of atrophy in MS has begun to be evaluated using quantitative MRI. Studies have found significant atrophy of the spinal cord, corpus callosum, cerebellum, and cerebrum. The mechanism of atrophy in MS has yet to be elucidated but potentially involves multiple processes. It has been suggested that BBB breakdown is the seminal event in the pathogenesis of atrophy in MS. In this study, a semi-automated whole brain segmentation method based on high-resolution dual fast spin-echo was used to determine whether whole brain atrophy over a 2-year period is related to initial inflammatory activity.

SUBJECTS AND METHODS
Twenty-four relapsing-remitting MS patients were studied for 2-years. Patients were treated only with short courses of steroids for acute exacerbations; no other immunomodulating therapy was given before or within the interval of the study. MR imaging was performed using a 1.5-T unit, and 3-mm contiguous, interleaved axial dual-echo fast spin echo (PD- and T2-weighted) images were acquired before and after injection of Gadolinium-DTPA at 0.1 mmol/kg. Lesion volume calculations were performed using a validated semiautomated computerized method based on the concept of fuzzy connectedness using two image sets (PD and T2). This method has demonstrated intra- and inter-operator variability less than 1% for total T2 lesion volume. For enhanced lesion assessment, the system has no inter- or intraoperator variability, with only one missed enhancing lesion out of 38 true lesions. Brain parenchymal volume was calculated using the following method. The extracranial contents are excluded based on segmentation of fuzzy connected 3D objects (gray matter, white matter, and CSF) to obtain the extracranial contents including brain parenchyma and CSF. Each of the segmented sections are then reviewed and any residual extracranial components manually excluded, if needed. An angle image of CSF is created from segmented T2- and PD-weighted data sets. This method creates a voxel-by-voxel image using the formula: $\theta = \tan^{-1}(I_{\text{angle}})$, where $I_{\text{angle}}$, $I_{\text{PD}}$, and $I_{\text{T2}}$ are the intensities of the voxels from the angle and from the T2 and PD-weighted images. The resulting angle image has relatively homogeneous CSF intensity values which can be easily thresholded to produce a CSF-only image and volume. The total brain parenchymal image and volume are obtained by subtracting the CSF from the intracranial contents. To normalize for baseline differences in volume of brain parenchyma among patients, an additional parameter, the percent brain parenchymal volume (PBV) was calculated as the percentage of brain volume within the volume of the intracranial contents. This method of brain parenchymal volume determination has previously shown less than 1% variability after a one week repeat scan.

RESULTS AND DISCUSSION
A disease duration dependent decrease in percent brain parenchymal volume was observed at baseline ($r = -0.64, p = 0.0007$). Mean brain volume significantly decreased by 34.6 ml ($p = 0.0001$), and mean PBV decreased by 1.84% ($p = 0.0003$) over the course of the study. Neither baseline nor change in enhanced T1 lesion number or volume correlated with change in PBV (atrophy) over the 2-year period. This lack of correlation can be interpreted as evidence for the insignificance of MR visible inflammation, as manifest by gadolinium enhancing lesions, in the pathogenesis of atrophy in multiple sclerosis. This suggests that other more global processes underlie atrophy, and that the blood-brain barrier abnormality associated with inflammation is merely an easily observed epiphenomenon. The results of this study have implications for the designing and monitoring of therapeutic interventions for multiple sclerosis. Drugs targeting the blood-brain barrier abnormality and therapies that succeed in reducing the frequency of enhancing lesions may not truly affect the course of disease progression and atrophy in MS.

REFERENCES