reversal of hypovolemia. Even as novel antagonists of antidiuretic hormone become available, the treatment of specific cause of the syndrome of inappropriate antidiuretic hormone secretion should remain the treatment of choice.

Besides studying the spectacular cases in which a reversal of hyponatremia followed treatment of hypoalbuminemia, we also examined the possibility that milder hyponatremia is due to hypoalbuminemia. In a random series of 3852 patients at the Royal Free Hospital, we found 111 who had plasma sodium concentrations of less than 130 mmol per liter. In this group of 111 patients, plasma albumin was measured in 41 who had no evidence of renal or hepatic dysfunction; 17 (42 per cent) had albumin concentrations of less than 32 g per liter. In contrast, only 11 patients (4.7 per cent) had an albumin concentration of less than 32 g per liter among 232 consecutive patients who had plasma sodium concentrations above 130 mmol per liter. This difference is significant ($P<0.01$), and although it does not establish a causal relation between plasma albumin and sodium concentrations, it provides the framework for further investigation indicated strongly by the case histories presented above.

P. Dandona
V. Fonseca
D.N. Baron
Royal Free Hospital and
School of Medicine
London NW3, 2QG, U.K.

## FOCAL SIGNS AND BRAIN CT SCANS IN PSYCHIATRIC PATIENTS

*To the Editor:* In a 1981 report, Larson and colleagues[1] surveyed 123 psychiatric patients who underwent CT scanning of the brain; they found that 6 patients had "true positive" studies, all of whom had concurrent focal neurologic signs. Another 81 patients with "normal" or "normal except for atrophy" CT results were entirely free of focal neurologic signs. This study, with its emphasis on using focal neurologic signs as a guide for using CT scans in psychiatric patients, has formed the basis for institutional policy in many hospitals; often a neurologist's approval, presumably to document focal signs, is required before a CT scan can be performed in a psychiatric patient.

Roberts and Lishman[2] provided tentative data questioning the usefulness of "neurologic examination," when they reported that 12.0 per cent of patients with positive examinations (24 of 201) had positive CT findings, whereas a larger percentage — 19.7 per cent — had abnormal CT scans but no clinical neurologic abnormalities. Similarly, Tsai and Tsuang[3] found that abnormal neurologic examination was associated with positive CT results in only 26 per cent of positive CT cases. Neither group commented on focal findings in their samples. We specifically addressed the usefulness of focal neurologic signs in predicting meaningfully positive CT-scan results among psychiatric inpatients. We reviewed 156 CT scans of the brain (3.5 per cent of all psychiatric admissions) that were requested over a 2½-year period. A total of 16 patients presented with focal neurologic signs; only 7 of these patients had a positive CT scan. Conversely, 18 patients without focal signs had positive scan results. Although percentage differences favor the association of focal signs and CT results (43 per cent vs. 15.5 per cent), the absolute numbers of patients with positive CT scans with and without focal signs (7 vs. 18) in our sample suggest that these percentage rates are of little use in guiding clinical practice. For the 16 patients with focal signs on examination, the statistical association with focal CT findings was no greater than chance (chi-square = 3.6, 1 df). From this experience we suggest that no empirical evidence currently exists validating the use of focal signs in ordering CT scans for psychiatric inpatients. In our series, a psychiatrist's mental-state examination eliciting impaired cognition was the best predictor of a positive CT scan, with a 49.3 per cent yield. The association between cognitive impairment and positive CT-scan results was greater than chance (chi-square = 17.3, $P<0.001$). It appears that careful assessment of mental status offers a more reliable guide to CT scanning than do focal neurologic signs in this population.

Thomas P. Beresford, M.D.
Frederic C. Blow, Ph.D.
Linda O. Nichols, Ph.D.
James W. Langston, M.D.
Veterans Administration Medical Center
University of Tennessee
Memphis, TN 38104 Center for the Health Sciences

Richard C.W. Hall, M.D.
Orlando, FL 32803 The Florida Hospital

1. Larson EB, Mack LA, Watts B, Cromwell LD. Computed tomography in patients with psychiatric illnesses: advantage of a "rule-in" approach. Ann Intern Med 1981; 95:360-4.
2. Roberts JKA, Lishman WA. The use of the CAT head scanner in clinical psychiatry. Br J Psychiatry 1984; 145:152-8.
3. Tsai L, Tsuang MT. How can we avoid unnecessary CT scanning for psychiatric patients? J Clin Psychiatry 1981; 42:452-4.

## ALZHEIMER'S DISEASE: DOES NEURON PLASTICITY PREDISPOSE TO AXONAL NEUROFIBRILLARY DEGENERATION?

*To the Editor:* Gajdusek hypothesizes that disruption of neurofilaments is the basis for several dementing diseases (March 14 issue).[1] To explain why some neurons in the brain are affected and not others, he suggests that cells with large axonal trees, because of their great demands for axonal transport, are especially vulnerable to axoskeletal damage. Gajdusek's hypothesis is attractive, but fails to account for the observation that large motor neurons are minimally affected in Alzheimer's disease.

We suggest that cell plasticity as well as the size of the axonal tree may impose demands on axonal transport. The plasticity of neural cells has been related to a variety of trophic factors,[2] some of which involve axonal transport. A pertinent example is the axon sprouting seen in septal norepinephrine terminals,[3] presumably accompanied by a sizable influx of new neurofilaments.

Neurons showing a high degree of plasticity probably form the substrate of memory and learning; both are impaired in Alzheimer's disease. Norepinephrine pathways have been associated with reward-related learning,[4] and the norepinephrine cells of the locus ceruleus are destroyed in some cases of Alzheimer's disease.[5] Alzheimer degeneration also damages the locus of origin of serotonin cells in the midbrain raphe,[6] and serotonin has been proposed as the mediator of classic conditioning.[7] Acetylcholine pathways projecting from the nucleus basalis of Meynert to the cortex may have the role of latchkey in complex memory storage and retrieval,[8,9] and as is well known, Alzheimer's disease is associated with loss of these cell bodies as well as their enzymes.[10] At the cortical level Alzheimer-type deterioration preferentially affects neurons in associative areas, most strikingly the hippocampus and amygdala,[11] both of which play a major part in memory.[12] Furthermore, neurofibrillary degeneration occurs selectively in neurons with axons connecting the hippocampus with the entorhinal cortex.[13] Since neurons from each of these groups form connections associated with the encoding of information,[14] which requires a high degree of plasticity, their deterioration supports the inference that cells showing considerable plasticity are prone to neurofibrillary disruption.

The disruption of the slow axonal-transport mechanism in neurons with a high degree of plasticity may lead to pervasive memory dysfunction, the core symptom of dementia regardless of the cause. This axonal-filament dysfunction may provide a micropathological basis for the previously postulated link between a microtubular diathesis and Alzheimer-type dementia[15,16] and tie together a subclass of dementing diseases.

J. Wesson Ashford, M.D., Ph.D.
Lissy Jarvik, M.D., Ph.D.
Los Angeles, CA 90024 UCLA Neuropsychiatric Institute

1. Gajdusek DC. Hypothesis: interference with axonal transport of neurofilament as a common pathogenetic mechanism in certain diseases of the central nervous system. N Engl J Med 1985; 312:714-9.
2. Kandel ER, Spencer WA. Cellular neurophysiological approaches in the study of learning. Physiol Rev 1968; 48:65-134.
3. Raisman G. Neuronal plasticity in the septal nuclei of the adult rat. Brain Res 1969; 14:25-48.
4. Stein L, Wise CD. Release of norepinephrine from hypothalamus and amygdala by rewarding medial forebrain bundle stimulation and amphetamine. J Comp Physiol Psychol 1969; 67:189-98.
5. Bondareff W, Mountjoy CQ, Roth M. Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. Neurology (NY) 1982; 32:164-8.
6. Ishii T. Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. Acta Neuropathol (Berl) 1966; 6:181-7.
7. Kandel ER, Schwartz JH. Molecular biology of learning: modulation of transmitter release. Science 1982; 218:433-43.
8. Deutsch JA. The cholinergic synapse and the site of memory. Science 1971; 174:788-94.
9. Drachman DA. Memory and cognitive function in man: does the cholinergic system have a specific role? Neurology (NY) 1977; 27:783-90.
10. Coyle JT, Price DL, DeLong MR. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 1983; 219:1184-90.
11. Brun A. An overview of light and electron microscopic changes. In: Reisberg B, ed. Alzheimer's disease: the standard reference book. New York: Free Press, 1983:37-47.
12. Mishkin M. A memory system in the monkey. Philos Trans R Soc Lond [Biol] 1982; B298:85-95.
13. Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science 1984; 225:1168-70.
14. Ashford JW. The electrophysiology of visual encoding in the monkey. (Ph.D. dissertation).
15. Heston LL. Alzheimer's disease, trisomy 21, and myeloproliferative disorders: associations suggesting a genetic diathesis. Science 1977; 196: 322-3.
16. Jarvik LF, Matsuyama SS. The philothermal response: diagnostic test for Alzheimer disease? In: Wertheimer J, Marois M, eds. Senile dementia: outlook for the future. New York: Alan R Liss, 1984:283-9.

## SHARED ANTIGENS ON ACETYLCHOLINE RECEPTOR AND BACTERIAL PROTEINS

*To the Editor:* The report by Stefansson et al. (Jan. 24 issue) describes the sharing of antigenic determinants between the nicotinic acetylcholine receptor and three bacterial proteins.[1] Their conclusion is based on the analysis of 22 IgG and 4 IgM rat monoclonal antibodies directed against the acetylcholine receptor, and the authors point to the possibility that the primary event in myasthenia gravis is the induction of antibacterial antibodies.

This hypothesis may well turn out to be correct, but there is one problem that needs more discussion. In the study by Stefansson et al., the two cross-reactive monoclonal antibodies were both of the IgM class. Since only 4 of the 26 monoclonal antibodies were of the IgM class, this indicates a selection.

Secreted IgM molecules are pentameric and thus contain more binding sites than IgG. This results in an increased avidity (total binding strength), as compared with IgG molecules, provided that sufficient antigenic determinants are available.[2,3] Since in the study reported by Stefansson and colleagues homogenates of bacteria were electrophoretically separated, this should have resulted in sufficient concentrations of antigens, possibly even higher concentrations than those originally observed on the bacterial membrane.

Analysis of monoclonal antibodies from patients with tumors of the B-lymphocyte lineage has demonstrated an overrepresentation of IgM as compared with IgG antibodies directed against self-antigens,[4] possibly reflecting the avid binding properties of IgM molecules.

Thus, although the results of the study by Stefansson et al. provide an interesting possible clue, an analysis of more control IgM monoclonal antibodies is warranted in order to ascertain whether there is a statistically significant increase in bacterial cross-reactivity of anti-acetylcholine receptor IgM monoclonal antibodies, as compared with IgM antibodies directed against other antigens.

C.I. Edvard Smith, M.D., Ph.D.
Lennart Hammarström, M.D., Ph.D.
Karolinska Institute
S-141 86 Huddinge, Sweden Huddinge University Hospital

1. Stefansson K, Dieperink ME, Richman DP, Gomez CM, Marton LS. Sharing of antigenic determinants between the nicotinic acetylcholine receptor and proteins in *Escherichia coli, Proteus vulgaris,* and *Klebsiella pneumoniae:* possible role in the pathogenesis of myasthenia gravis. N Engl J Med 1985; 312:221-5.
2. Metzger H. Structure and function of γM macroglobulins. Adv Immunol 1970; 12:57-116.
3. Steward MW, Steensgaard J, eds. Antibody affinity: thermodynamic aspects and biological significance. Boca Raton, Fla.: CRC Press, 1983; 1-170.
4. Dighiero G, Guilbert B, Fermand J-P, Lymberi P, Danon F, Avrameas S. Thirty-six human monoclonal immunoglobulins with antibody activity against cytoskeleton proteins, thyroglobulin, and native DNA: immunologic studies and clinical correlations. Blood 1983; 62:264-70.

*To the Editor:* The paper by Stefansson et al. is very interesting. However, I must sound a word of caution. The authors tested over 25 monoclonal antibodies prepared against the acetylcholine receptor from *Torpedo californica* for cross-reactivity with bacterial antigens. Only two of the antibodies tested (77F and BK57, both IgM) cross-reacted with bacterial proteins. It is unfortunate that the authors did not discuss in their paper the pertinent binding characteristics of the monoclonal antibodies they tested. Elsewhere, they have shown that 77F does not bind to muscle acetylcholine receptor[1] and that neither 77F nor BK57 causes experimental myasthenia gravis in rats.[2] Because these two monoclonal antibodies do not bind to muscle acetylcholine receptor (i.e., they are not true autoantibodies), it is very misleading to imply that such antibodies may be involved in the initiation of myasthenia gravis. Furthermore, in their paper, the authors do not specify what type of acetylcholine receptor was used for the studies; this is an important point, because many antigenic determinants found on torpedo acetylcholine receptor do not have a counterpart on muscle acetylcholine receptor. The proposed link between bacterial infection and myasthenia gravis requires that the cross-reactive bacterial determinant be present on muscle acetylcholine receptor as well. Yet, published binding characteristics of 77F and BD57 show that this cannot be the case.

In summary, the data presented by Stefansson et al. demonstrate an interesting cross-reaction between a bacterial protein and torpedo acetylcholine receptor. However, these findings do not provide the basis for suggesting that myasthenia gravis is due to an immune response against a bacterial protein that shares an antigenic determinant with muscle acetylcholine receptor.

Donard S. Dwyer, Ph.D.
Birmingham, AL 35294 University of Alabama at Birmingham

1. Gomez CM, Richman DP, Burres SA, Arnason BGW. Monoclonal hybridoma anti-acetylcholine receptor antibodies: antibody specificity and effect of passive transfer. Ann NY Acad Sci 1981; 377:97-109.
2. Richman DP, Gomez CM, Berman PW, Burres SA, Fitch FW, Arnason BGW. Monoclonal anti-acetylcholine receptor antibodies can cause experimental myasthenia. Nature 1980; 286:738-9.

The above letters were referred to the authors of the article in question, who offer the following reply:

*To the Editor:* In response to Drs. Smith and Hammarström, the fact that the IgM often has greater avidity than IgG is of interest. It is also interesting that autoreactive human monoclonal antibodies are more often of the IgM than the IgG isotype. However, if the experiments are properly controlled, neither one of these observations implies that a demonstration of the sharing of epitopes using an IgM monoclonal antibody is any less convincing than if the sharing is shown with an IgG monoclonal antibody. Indeed, it is more difficult to control for unspecific binding of IgM than IgG.