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## INSIDE



# What Causes Normal Aging?

ABSTRACT & COMMENTARY

**Source**: Trifunovic, et al. Premature aging in mice expressing defective mitochondrial DNA polymerase. *Nature.* 2004;429:417-423.

THE CAUSE OF NORMAL AGING HAS BEEN WIDELY STUDIED, AND a large number of nuclear factors have been implicated in normal aging including DNA polymerase, P53, and klotho. Some mutations result in defective repair of nuclear DNA. It has also been demonstrated that a progeroid syndrome in mice is caused by defects in A-type lamins. Mice with these defects develop a marked reduction in growth rate and death by 4 weeks of age with pathology in the bone, muscle and skin that are consistent with progeria (Mounkes, et al., *Nature.* 2003 423:298-301). Another major theory of aging is that mutations in mitochondrial DNA may speed up the aging process. It has long been known that mitochondrial deletions and point mutations accumulate with normal aging. This has been demonstrated in a large number of species. The mitochondria have their own genomes, which encode a few mitochondrial proteins. It has been speculated that the mutations which accumulate with age, might lead to impaired energy generation as well as increased amounts of reactive-oxygen species, resulting in cellular damage. The association between mitochondrial mutations in aging however, could be merely correlative. The numbers of mutations, which are commonly observed, are below the threshold which is observed in diseases of the mitochondrial genome. A definitive answer to this conundrum has been lacking. One argument has been that the smaller number of mutations observed may only be a tip of the iceberg phenomenon.

Larsson and colleagues put cause and effect together to address whether mitochondrial point mutations directly contribute to normal aging. Trifunovic and colleagues genetically engineered mice to carry mutations in an enzyme called DNA polymerase polg A. This enzyme is encoded by nuclear genes and then transported to mitochondria. It is involved in both copying and proofreading mitochondrial DNA, eliminating errors that it makes during replication. It is also thought to participate in DNA repair processes. Mitochondria are replaced in all cell types throughout life. New mitochondria also must be made when cells divide. This requires the replication

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of mitochondrial DNA. Trifunovic et al rendered the mitochondrial DNA polymerase error-prone by eliminating its proofreading activity, while maintaining its catalytic potency. The idea is that this will then lead to accumulation of mitochondrial DNA mutations.

Trifunovic et al then wanted to know whether this would accelerate normal aging. They observed that the somatic tissues of mice bearing 2 mutant copies of DNA polymerase gamma gene showed extensive mitochondrial DNA mutations largely comprising deletions and point mutations. The percentage of mitochondria bearing deletions was similar in different tissues and did not vary with age, suggesting that the deletions had occurred early in development. Point mutations were common in several enzymes. For instance, cytochrome-b had a 3-5 fold increase in single-base substitutions which were widely disbursed throughout the gene. For example, by 8 weeks, mutant animals had about 9 mutations per 10 kilobases of DNA, while normal mice had less than 1. But, it was the physiology of the animals that was most pronounced. At first they looked normal, but by about 25 weeks of age (that's early adulthood to a mouse), they started to show signs of premature aging. The animals stopped gaining weight and became bald. Low bone mineral density curved their spines in a sign of clinical osteoporosis. Half of the animals were dead by 48 weeks and 61 weeks, respectively, much sooner than the typical lab mouse, which lives about 2 years. The mutant animals showed a decrease in the activity of enzymes involved in the respiratory chain and in the production of ATP, which may be a result of the mutations in the mitochondrial DNA encoded components of the respiratory complex. These findings strongly support the idea that mutations in mitochondrial DNA, which might be acquired during normal aging, can contribute to the aging process.

## COMMENTARY

Trifunovic et al have made a very novel and important observation, which strongly links the accumulation of mitochondrial DNA mutations to normal aging. The data from their transgenic mouse model, the strongest data to date, show that the accumulation of these mutations does have functional relevance. It is likely that they contribute to the production of reactive oxygen species consistent with the oxidative damage theory of aging. This is the theory that aging is caused by an increase in levels of reactive oxygen species, which largely arise from the mitochondrial electron transport chain. Normal aging is likely to be multifactorial however, the contribution of mitochondrial impairment to it appears now to be well established based on the observations of the present authors. It is likely that this mitochondrial impairment which accompanies normal aging may contribute to the pathogenesis of age-related neurodegenerative diseases.

**— M. FLINT BEAL**

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# Electrodiagnostic Update 2004

### Carpal Tunnel Syndrome

**Source**:Witt JC, et al. Carpal tunnel syndrome with normal, nerve conduction studies. *Muscle Nerve.* 2004;29:515-522.

How valuable are nerve conduction studies (NCS) in the diagnosis and management of carpal tunnel syndrome (CTS)? Over a 7-month period, patients who both met CTS diagnostic criteria and were referred to the Mayo Clinic Electromyography (EMG) laboratory for suspected CTS, were voluntarily enrolled in a study designed to address this question. Criteria included 1) hand paresthesiae in a median and/or ulnar nerve distribution which were 2) aggravated by activity; 3) relieved by shaking; and 4) awoke the patient from sleep; 5) sub-

jective hand weakness; 6) clumsiness; or (7) Tinel or Phalen sign. For enrollment, patients had to have criteria #1 and at least 1 (possible CTS) or 2 (definite CTS) other criteria. Patients with confounding neurological conditions were excluded, including prior CTS surgery or other potential cause for paresthesiae (eg, radiculopathy, polyneuropathy, ulnar neuropathy, myelopathy, stroke). All patients underwent electrodiagnostic studies encompassing NCS of the median and ulnar motor and sensory nerves, performed using standard technique, as well as needle EMG study of relevant muscles. Statistical analysis included the Pearson chi-square test, Fisher exact test, two-sample t-test, one-way analysis of variance, and multiple logistic regression analysis.

Among 99 eligible CTS patients, NCS were abnormal in 74 and normal in 25 (25%). Only 84 agreed to participate, including 60 of 74 normals and 24 of 25 abnormals. Patients categorized as definite CTS were more likely to have abnormal NCS compared to the possible CTS group (78% vs 47%) but, in both groups, the frequency of mild, moderate, or severe NCS abnormalities was similar. Normal NCS were more likely in patients with bilateral symptoms (83% vs 57%; $P = 0.02$), while patients with abnormal NCS were more likely to be older ($P < 0.001$), heavier ($P = 0.015$), and have higher body mass index ($P = 0.002$). Treatment outcome, whether conservative or surgical, did not differ between the definite and possible groups and, similarly, nonsurgical outcome did not differ between the normal or abnormal NCS groups. NCS are of diagnostic value, particularly when clinical clues are scarce, but they are not predictive of nonsurgical treatment outcome.

### Ulnar Neuropathy

**Source**: Shakir A, et al. Which motor nerve conduction study is best in ulnar neuropathy at the elbow. *Muscle Nerve*. 2004;29:585-590.

Ulnar neuropathy at the elbow (UNE) is often difficult to localize electrodiagnostically. Slowing of ulnar motor nerve conduction velocity (MNCV) across the elbow provides supportive evidence, but controversy remains on how best to determine its presence. Two methods include comparing the across-elbow ulnar MNCV to that of an adjacent segment of the ulnar motor nerve (either the forearm or above-elbow segment) or comparing the across-elbow MNCV to an absolute normal standard. Which yields optimal results?

Receiver operator characteristic (ROC) curves, a statistical tool which graphically depicts the relationship between sensitivity and specificity of a measurement as a function of normal cut-off values, were used in this study to compare the 2 methods for determining across-elbow slowing. In a retrospective 8-year review of ulnar MNCS performed for suspected neuropathy in an arm (n = 1703), UNE was the referring diagnosis in 283 and the final diagnosis in 165. Of these, 99 had ulnar MNCS with recording from both the first doral interosseous and the abductor digiti minimi muscles, of which 85 yielded a recorded response from both muscles and were not repeat studies. These 85 served as the true-positive UNE group and were compared to 77 carpal tunnel syndrome patients without UNE who had similar electrodiagnostic studies. NCS were performed in the standard fashion, ROC curves were plotted as sensitivity against 1, minus specificity for all cut-off points, and 95% confidence intervals were calculated.

Across-elbow MNCV, as an absolute measure, was significantly more sensitive in determining the presence of UNE than comparing the across-elbow segment to an adjacent segment. This was true both when recording from the first doral interosseous (sensitivity, 80% vs 51%) and the abductor digiti minimi (sensitivity, 77% vs 38%), and was even more pronounced, though not significantly so, when ulnar evoked compound muscle potential amplitudes were very low. Across-elbow ulnar MNCV, compared to a normal standard, is preferred to adjacent segment comparison for diagnosing UNE.

### Demyelinating Polyneuropathy

**Source:** Van Den Bergh PYK, et al. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve*. 2004;29:565-574.

Acquired demyelinating neuropathies are eminently treatable. Timely diagnosis has significant ramifications on patient management and outcome. Both intravenous immune globulin and plasma exchange are effective in the appropriate setting but costly, occasionally requiring in-patient hospitalization if only to satisfy third-party payers. Accurate diagnosis of demyelination is crucial to the patient, doctor, and insurance carrier.

Ten sets of published criteria for demyelinating neuropathy were compared, retrospectively, in 53 Guillain-Barre syndrome (GBS) and 28 chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients to establish an 11th set of criteria with greatest specificity, without significant loss of sensitivity. Patients with amyotrophic lateral sclerosis (ALS) and diabetic polyneuropathy (DPN) served as disease control groups. Diagnosis of GBS and CIDP was based on published clinical criteria, including cerebrospinal fluid analysis and response to immune therapy in most. Exclusionary criteria included drug or toxin exposure, family history

of neuropathy, HIV infection, lupus, gammopathy, or central nervous system demyelinating disease. ALS patients all satisfied Airlie House criteria (revised El Escorial criteria) and DPN patients had long-standing diabetes mellitus with chronic symmetric sensorimotor polyneuropathy. Nerve conduction studies were performed using standard technique. Statistical analysis included chi-square 4-fold tables and calculation of Pearson's goodness-of-fit chi-square with *P*-values for all sets of criteria.

For the 10 published sets of criteria, sensitivity ranged from 24% to 83% for GBS and 39% to 89% for CIDP. Specificity for 9 of the sets completely excluded ALS, but up to 9% of DPN patients satisfied demyelinating criteria in half the sets. As little as 20% motor conduction block (drop of amplitude on proximal compared to distal stimulation) was specific for GBS and CIDP, being present in at least 1 nerve in 70% and 93%, respectively. Increased temporal dispersion was specific but of low sensitivity.

Based on these findings a new set of criteria is proposed:

1. Motor distal latency prolonged by > 150% above upper limit of normal;
2. Motor velocity slowed to < 70% below lower limit of normal;
3. F wave latency prolonged by > 125% above upper limit of normal if motor amplitude is > 80% of normal, or > 150% if motor amplitude is < 80% of normal;
4. Abnormal temporal dispersion by > 30% in at least 2 nerves.

Compared to the original 10 sets of criteria, GBS and CIDP were diagnosed with 72% and 75% sensitivity, respectively, with 100% specificity in differentiating them from DPN or ALS. Validation of these results in other databases is warranted and awaited.

### Myasthenia Gravis

**Source:** Rubin DI, et al. Trigeminal nerve repetitive stimulation in myasthenia gravis. *Muscle Nerve.* 2004;29:591-596.

A 10% decrement or more, of the compound muscle action potential amplitude (CMAP) on repetitive nerve stimulation (RNS), is the electrodiagnostic hallmark of myasthenia gravis (MG). Positivity of response varies from 41% to 95%, with higher positivity correlating not surprisingly with more muscles being tested. Distal muscles are less sensitive but technically more reliable than proximal muscles. Bulbar muscles, being most proximal, should provide the highest sensitivity and, in bulbar myasthenia, may be the only muscles to yield a decremental response. Facial nerve testing in generalized MG is positive in 62%. What about trigeminal nerve RNS?

Twenty-one MG patients, 2 with ocular involvement and 19 with weakness affecting other than ocular muscles, were compared to 26 normal controls. All underwent 2 Hz RNS of the trigeminal nerve, using percutaneous monopolar needle stimulation of the masseteric branch, with surface recording of the CMAP over the masseter muscle. MG patients additionally underwent transcutaneous ulnar, spinal accessory, and facial nerve RNS, recording from the abductor digiti minimi, trapezius, and nasalis muscles, respectively. 2 Hz stimulation was used, rather than 3-4 Hz, due to its relative comfort level, preferable artifact profile, and technical ease. RNS was thrice repeated at rest to ensure reproducibility, and repeated immediately after exercise and at 1, 2, and 3 minutes.

Trigeminal RNS was positive in 43% of MG patients compared to 57% of facial, 20% of ulnar, and 48% of spinal accessory RNS. Trigeminal RNS was better tolerated than facial RNS in all patients. Though less sensitive, trigeminal RNS may be added to the electrodiagnostic armamentarium in the evaluation of patients suspected of MG.

### Quantitative Sensory Testing

**Source:** Chong PS, et al. AAEM Practice Topic in Electrodiagnostic Medicine. Technology literature review: quantitative sensory testing. *Muscle Nerve.* 2004;29:734-747.

Quantitative sensory testing (QST) non-invasively measures function of both large diameter nerve fibers (Aa and Ab) mediating light touch and vibration, and small diameter nerve fibers (Ad and C) mediating temperature and pain sensation. QST is often used in peripheral neuropathy clinical drug trials as a method of documenting progression or improvement, and its use in clinical practice is increasing as well. Yet, as a psychophysical test, it requires an honest, alert, and cooperative patient for results to be meaningful. No method exists to reliably differentiate subjects who wish to manufacture or magnify their impairment, although variability on repeat testing is likely to be greater in this group. How the stimulus is presented to the patient, how the subject's response is obtained (yes-no or forced-choice method), and how the response is used to determine sensory threshold vary between sites, investigators, and computers used. Reproducibility varies among studies reported and is better among normal persons than in neuropathy patients. Given these issues, just how useful is QST?

Based on a Medline search and review of the litera-

ture from 1966 to 2001 dealing with this topic, the following conclusions are drawn: QST is a reliable psychophysical test of peripheral large and small nerve fibers, testing the entire sensory neuraxis from periphery to brain without localization value, and requiring complete patient cooperation and integrity. Reproducibility appears to be satisfactory during short-term studies, cold threshold testing moreso than warm threshold, and vibration perception threshold testing moreso than thermal. However, strict calibration and testing protocols must be followed. No one instrument may be recommended over another based on the literature, and the degree of allowable experimental error remains unknown for the individual patient. — **MICHAEL RUBIN**

# Old and New Options for Rasmussen Encephalitis

ABSTRACT & COMMENTARY

**Sources**: Jonas R, et al. Cerebral hemispherectomy: Hospital course, seizure, developmental, language, and motor outcomes. *Neurology*. 2004;62:1712-1721; Duchowney M. Hemispherectomy for epilepsy: When is one half better than two? [Editorial] *Neurology*. 2004;62:1664-1665; Bien CG, et al. An open study of tacrolimus therapy in Rasmussen encephalitis. *Neurology*. 2004;62:2106-2109.

JONAS AND COLLEAGUES HAVE COLLECTED THE largest series of cases of unilateral hemispherectomy (UH) and assessed outcomes for the parameters listed in the title of their manuscript. In 21 of 115 patients (18%), the indication for surgery was Rasmussen encephalitis (RE). Other indications included hemimegalencephaly and hemispheric cortical dysplasia. Among these disorders, patients with hemimegalencephaly had the worst post-operative outcome. Regardless of underlying pathology, shorter seizure duration, better seizure control, and higher preoperative developmental quotients (DQ) predicted better postoperative DQ.

In the realm of non-surgical treatment of RE, Bien and colleagues administered tacrolimus to 7 patients with histopathologically proven RE. They compared seizure outcome, neurologic function (NIH Stroke Scale Motor Item score), and progression of cerebral hemiatrophy by MRI planimetry in these patients versus 12 historical controls (RE patients not exposed to tacrolimus). Tacrolimus-treated patients displayed slower progression of hemiparesis and hemiatrophy than controls. Unfortunately, seizure outcome was no different between tacrolimus patients and controls.

## COMMENTARY

RE is a catastrophic neurological disorder of early childhood. The initial presentation is commonly focal seizures, often evolving into epilepsia partialis continua, a form of focal motor status epilepticus. Eventually, RE evolves to include progressive neurological decline, with hemiparesis, and cognitive dysfunction and concordant contralateral cerebral hemiatrophy on neuroimaging. What makes RE unique is that the ultimate decision to treat with UH requires that the disease has progressed to the point that the clinical diagnosis is certain and that the neurologic deficit includes hemiplegia. After all, only the particularly brave (or cocksure) neurologist and neurosurgeon will recommend UH for "probable" RE, or undertake a procedure that will convert a child who has mild or moderate hemiparesis into one with complete hemiplegia.

The current studies address surgical and non-surgical treatments for RE that may help to settle the issue of when to treat. Jonas et al, along with accompanying editorial by Duchowney, indicate that UH is a relatively safe and effective procedure for RE and can render almost 60% of operative patients seizure-free. Of the RE patients we have encountered, seizure-freedom is the most important factor in affording these patients any neurologically meaningful quality of life. The UH study does indicate that diagnosis and referral for surgery is being made in increasingly younger patients, and, although the data are not specifically analyzed as far as age at surgery relative to outcome, the fact that seizure duration was inversely correlated with post-operative developmental quotient suggests that the trend towards earlier referral is a favorable one. Moreover, functional recovery from UH will also be enhanced if performed at a young enough age to take advantage of developmental plasticity.

While treatment with tacrolimus does not significantly alter seizure frequency, as acknowledged by Bien and colleagues, this limited study is very intriguing. Alert is encouraged that new treatment options (ie, a well-established suppressor of T-cell activation) are again being explored that build upon the initial insights regarding the pathophysiology of RE. This particularly involves antibodies directed towards the R3 sub-unit of the glutamate receptor in RE patients (*Science*. 1994;265:648-651) and cytotoxic T-cells (*Ann Neurol*. 2002;51:311-318). Prior studies of immunomodulatory therapies (eg, plasmapheresis, intravenous immunlobulin, corticosteroids) founded on the basis that either outcome data were equivocal or the therapy was impractical given the

chronic progressive nature of RE vs the short duration of benefit. Perhaps currently approved chemotherapeutic agents might work where other non-surgical treatments have failed. It is certainly worth a randomized controlled trial (even with such a low-incidence disorder) to prove the point.

Certainly, the tacrolimus study is flawed. The most obvious flaw is the study design employing historical controls. Given that this was an open study, and thus more prone to investigator bias, it is all the more disappointing that tacrolimus, unlike UH, led to no improvement in seizure outcome. Since RE patients usually have medically intractable seizures, functional debilitation on an ictal basis is expected to continue regardless of "superior outcome" for neurological function in tacrolimus-treated patients. As has been emphasized many times by *Neurology Alert*, the call goes forth for earlier diagnosis and treatment of various epileptic conditions. In the case of RE, further exploration of diagnosis and treatment is bound to provide insight into both epileptogenesis and immune-mediated neurological disease. **— ANDY DEAN**

# Plasma Aß Levels and Cerebrovascular Disease in Nondemented Carriers of an E4 Allele

ABSTRACT & COMMENTARY

**Source:** Van Dijk EJ, et al. Plasma Amyloid ß Apolipoprotein E, lacunar infarcts, and white matter lesions. *Ann Neurol.* 2004;55:570-575.

CEREBRAL WHITE MATTER LESIONS (WML) AND lacunar infarcts frequently are observed on MRI scans in elderly subjects. They are considered to be caused by disease of small vessels, with hypertension, advanced age, and cerebral amyloid angiopathy (CAA) as the most important risk factors. In CAA, amyloid ß peptide (Aß) is deposited in small and medium-sized cerebral arteries. The Aß peptide consists of either 40 (Aß 1-40) or 42 (Aß 1-42) amino acids derived from the proteolytic processing of the amyloid precursor protein.

Van Dijk and colleagues investigated whether plasma Aß levels were associated with lacunar infarcts and WML in the general population, and whether the apolipoprotein E (APOE) genotype modified this association. They studied more than 1000 participants in the Rotterdam Scan Study[1] who were 60 to 90 years of age and not demented. Cross-sectional associations were analyzed with adjustments for age, sex, creatine level, and hypertension.

**Table**
**Characteristics of Participants**

| Characteristic | n=1026 |
|---|---|
| Age, yrs. mean (SD) | 72 (7) |
| Women, % | 52 |
| Hypertension, % | 72 |
| Ever Smoked, % | 66 |
| Diabetes, % | 7 |
| APOE E4, % | 29 |
| Lacunar Infarcts only, % | 22 |
| Other Brain Infarcts, % | 24 |
| Aß 1-40 (pg/ml) mean (SD) | 205 (58) |
| Aß 1-42 (pg/ml) mean (SD) | 20 (8) |

*modified from Van Dijk, et al.

In APOE E4 carriers, plasma Aß levels were positively associated with lacunar infarcts and WML. Plasma Aß 1-40 and Aß 1-42 levels increased with age and creatine levels (*see Table above*).

Aß 1-40 levels were higher in hypertensives and Aß 1-42 levels were lower in APOE E4 carriers. Gender, smoking, and diabetes were not associated with plasma Aß levels.

Van Dijk et al offer several speculative explanations for the association between higher plasma Aß levels and cerebral small vessel disease in APOE E4 carriers, but not in noncarriers. It may be that fibrillary deposits of Aß in the vessel wall lead to obliteration of the vessel lumen and subsequent lacunes and WML. Alternatively, soluble Aß may alter cerebral autoregulation by enhancing endothelium-dependent vasoconstriction. Another possibility is that higher Aß levels result from cerebral hypoperfusion and might, in turn, via vascular deposition of Aß, make hypoperfusion worse. The possible role of the APOE E4 allele in all 3 scenarios would be to facilitate transport of Aß from the CSF into vascular smooth muscle cells.

## COMMENTARY

The observation that APOE E4 in combination with elevated plasma Aß levels is associated with cerebral small vessel disease is new but not surprising. APOE E4 has been linked to pathologic changes in several brain diseases from Alzheimer's Disease to multiple sclerosis.[2] The possible mechanisms whereby APOE E4

influences disease progression include, among others, impaired neuronal repair and plasticity, accelerated neuronal degeneration and direct tissue damage via oxidative inflammatory and neurotoxic mechanisms. Given the impact of APOE E4 on the course of several disease processes, it may be that in the near future, APOE testing will become a routine screening test. **— JOHN J. CARONNA**

### References


1. Hofman A, et al. *Eur J. Epidemiol.* 1991;7:403-422.
2. Enzinger C, et al. *Ann Neurol.* 2004;55:563-569.


## New Alzheimer's Blood Markers?

ABSTRACTS & COMMENTARY

**Sources**: Englehart M, et al. *Arch Neurology.* 2004;61:668-672; Squitti R, et al. *Arch Neurology.* 2004;61:738-743.

Inflammation in the brain is one of the established features of the neuropathology of Alzheimer's Disease (AD). A large case-control study now indicates that patients with elevated serum markers of inflammation have an increased risk of developing AD. The study was based on a prospectively evaluated sample of 727 unaffected individuals and 188 AD cases culled from a larger cohort in the Netherlands. Relative to controls, levels of alpha-1-antichymotrypsin, interleukin-6 and to a lesser extent, C-reactive protein, were found to be elevated in patients who were cognitively intact at baseline but later developed AD. The increase in risk was statistically significant but amounted to less than 50% for each marker. These findings suggest that specific markers of inflammation in the blood may rise before patients develop AD, and might therefore be useful for identifying patients in the general population who are at increased risk of developing AD.

Elevated serum copper levels have been reported in association with AD. Squitti and colleagues previously reported that serum copper levels can be used to distinguish AD from normals and from other forms of dementia. They now report that the AD-affected member of a monozygotic twin pair discordant for dementia had elevated copper levels and indicators of oxidative stress. The twins were 73 years of age when initially studied by cognitive testing, brain imaging, and blood tests. The unaffected twin was documented to remain free of dementia over a 4-year period of follow-up. They found a greater than 40% increase in serum copper and peroxide levels in the affected twin, but no differences in iron, transferrin or homocysteine levels between the 2. The authors believe that the observed elevation in serum copper provides supportive evidence for an abnormality in biometals in AD, and provides encouragement for pursuing further studies of copper levels as a possible diagnostic marker for AD.

### COMMENTARY

Blood tests useful for detection of Alzheimer's have long been sought by AD researchers. Clinical applicability of any such assay requires there be validation and adequate sensitivity and specificity when applied in practice. Neither inflammatory markers in blood or serum copper levels have met these standards, and are unlikely to become stand-alone AD diagnostic tests. These reports provide useful information nevertheless. The elevations observed in blood markers of inflammation could be indicative of inflammation in the brain or of a more generalized systemic process in patients at risk for AD. Elevations in copper speak to the possible involvement of metals in the disease process. Moreover, both inflammation and copper levels can be reduced by available interventions, which could provide new inroads for development of future treatments for AD. While these biomarkers are not ready for general clinical use, they could prove useful in the future. **— NORMAN R. RELKIN**

## What is the Risk of Recurrent Intracerebral Hemorrhage After a Lobar Hemorrhage?

ABSTRACT & COMMENTARY

Source: Greenberg S, et al. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. *Stroke.* 2004;35:1415-1420.

This paper carried out a clinical study to use gradient-echo MRI to determine prior evidence of microhemorrhages relating to cerebral amyloid angiopathy after patients had presented initially with lobar intracranial hemorrhage. Green-

berg adn colleagues attempted to determine whether microhemorrhages, detected at the time of lobar intracranial hemorrhage, predicted recurrent intracranial hemorrhage or declines in cognition and function. The authors studied 94 consecutive survivors of primary lobar intracranial hemorrhage with gradient-echo MRI at presentation. They were studied prospectively for 32.9 ± 24.0 months. A subset of 34 patients had a second MRI after a stroke-free interval of 15.8 ± 6.5 end points. Greenberg et al found that the number of hemorrhages at baseline predicted the risk of future symptomatic intracranial hemorrhage. The 3-year cumulative risks were 14%, 17%, 38%, and 51% for subjects with 1, 2, 3 to 5, or > 6 baseline hemorrhages. These were significant differences. The higher numbers of hemorrhages at baseline also predicted increased risks for subsequent cognitive impairment, loss of independence, or death. These were in subjects who were not previously demented or dependent. In the subjects who were followed after the second MRI, new microhemorrhages appeared in 17 of 34 and predicted increased risk of subsequent symptomatic intracranial hemorrhage. The increased risk was similar to that observed in the initial part of the study. The 3-year cumulative risks were 19%, 42%, and 67% for subjects with 0, 1 to 3, or > 4 new microhemorrhages.

## COMMENTARY

These findings are of interest. They suggest that it may be possible to predict the risk of recurrent intracranial hemorrhage. Patients who have cerebral amyloid angiopathy are at high risk for this. It is clinically important to identify them to make sure that they are not receiving antiplatelet or other anticoagulating drugs, since this can worsen the risk. Interestingly, patients with either ApoE2 or E4 genotypes are at higher risk of developing cerebral amyloid angiopathy. Eventually, clinical trials are going to be designed to try and prevent these cerebral amyloid angiopathy and, therefore, knowing the risk of subsequent intracranial hemorrhage is important in designing these studies as well as in assessing risk benefit calculations in specific clinical situations. — **M. FLINT BEAL**

# CME Questions

**1.Potential repetitive nerve stimulation tests in the workup of a suspected myasthenia gravis patient include**
a. median nerve stimulation
b. ulnar nerve stimulation
c. facial nerve stimulation
d. trigeminal nerve stimulation
e. all the above

**2. In the localization of ulnar neuropathy to the elbow**
a. the across-elbow ulnar motor nerve conduction velocity is best compared to that of the forearm segment of the ulnar motor nerve
b. the across-elbow ulnar motor nerve conduction velocity is best compared to that of the above-elbow segment of the ulnar motor nerve
c. the across-elbow ulnar motor nerve conduction velocity is best compared to a normal absolute standard
d. the across-elbow ulnar motor nerve conduction velocity is best compared to that of the contra-lateral ulnar nerve
e. all the above are equally sensitive

**3. A new set of criteria are proposed for improved diagnosis of demyelinating neuropathy. These include:**
a. Motor distal latency prolonged by > 150% above upper limit of normal
b. Motor velocity slowed to < 70% below lower limit of normal
c. F wave latency prolonged by > 125% above upper limit of normal if motor amplitude is > 80% of normal, or > 150% if motor amplitude is < 80% of normal
d. Abnormal temporal dispersion by > 30% in at least 2 nerves
e. all the above

**4. In carpal tunnel syndrome**
a. Normal NCS were more likely in patients with bilateral symptomatology
b. Patients with abnormal NCS were more likely to be younger
c. Patients with abnormal NCS were more likely to be marfanoid
d. Patients with abnormal NCS were more likely to have lower body mass index
e. NCS are of diagnostic value and are predictive of nonsurgical treatment outcome.

**5. Quantitative sensory testing**
a. tests the entire sensory neuraxis from periphery to brain
b. has significant localization value
c. may be done on an unconscious patient
d. has poor reproducibility particularly during short-term studies
e vibration perception threshold testing shows less reproducibility than thermal

**Answers:** 1 (e) ; 2. (c); 3. (e); 4. (a); 5. (a)

## In Future Issues:

**Parkinson's Disease: A New Mutation Leads to Potential New Insights Into Disease Pathogenesis**

# PHARMACOLOGY WATCH

**Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.***


## Britain to Allow Over-the-Counter Sales of Zocor

The British government will soon allow over-the-counter (OTC) sales of Merck's simvastatin (Zocor), marking the first time any country has allowed the OTC sale of a statin. The drug lost its patent protection in England last year, and Merck is eager to make up for some lost revenues by entering the lucrative OTC market. It is likely the drug will be available in an OTC dose of 10 mg. Pharmacists will be asked to carry out a simple screening questionnaire on the spot to screen for appropriateness and safety. Not everyone is happy about the OTC switch however. An editorial in the British journal *Lancet* stated that there is insufficient evidence to justify the OTC switch and implied that the British government is simply trying to save money by defraying prescription drugs costs. Currently over 1.8 million patients in England take statins at a cost of over $1.1 billion per year.

### *FDA Rejects Plan B Bid*

FDA regulators have rejected a bid from Barr Pharmaceuticals to market their "morning after pill" as an OTC. The product, called Plan B, contains 0.75 mg of levonorgestrel, a progestin commonly used in birth control pills. Plan B is marketed as an emergency contraceptive that can be used up to 72 hours after unprotected intercourse or suspected contraceptive failure. The decision by the FDA was somewhat surprising as it went against the recommendation the agency's own advisers who, last December, voted overwhelmingly in favor of the over-the-counter switch for Plan B. The decision prompted some groups to suggest that political pressure from the Bush administration was responsible for the denial. The FDA, however, stated in its rejection letter that they were concerned about the safety of the product for younger women, and kept the door open by suggesting that more data may prompt a reconsideration. In the meantime, Plan B is still available by prescription.

### *Recombinant Erythropoietin Products May Stimulate Tumor Growth*

Two recent studies have raised the question of whether recombinant erythropoietin products may stimulate tumor growth in cancer patients. One study, published in the October 2003 *Lancet*, reviewed 351 adult patients with head neck cancer who were randomized to subcutaneous erythropoietin or placebo 3 times weekly prior to radiation therapy and continuing throughout radiation therapy. Patients treated with erythropoietin had improved hemoglobin concentrations, but otherwise had poor outcomes. Median locoregional progression-free survival was 745 days with placebo and 406 days with erythropoietin (relative risk, 1.62; [95% CI, 1.22-2.14]; $P$ = .0008). Overall,


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over the 4 years of study, 52% of placebo-treated patients died, compared to 61% of erythropoietin treated patients (RR 1.39; [95% CI, 1.05-1.82]; $P$ = .02). A second study in Europe of erythropoietin in breast cancer patients was terminated early because patients receiving the drug had lower 12 month survival rates than patients receiving placebo (70% vs 76%; $P$ = .0117). An editorial in the December 17th Journal of the National Cancer Institute reviewed this issue and raised the plausibility of the findings. The authors noted that erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. They also noted that the preliminary data suggest that some of these cancers may proliferate in the presence of erythropoietin.

The editorial concluded by calling for more research into the possible relationship between erythropoietin and poor outcomes in the treatment of cancer patients. The FDA's Oncologic Drugs Advisory Committee recently met in May, and backed a proposal by Johnson & Johnson (makers of Procrit) and Amgen (makers of Aranesp) to study this issue. The exact design of these studies is still to be delineated, but both companies have pledged to collaborate on such research.

## Rosuvastatin: Market's Most Potent Statin

Rosuvastatin (Crestor-Astra Zeneca) appears to be the most potent statin currently marketed. In a study of 3140 patients with CAD, atherosclerosis, or type 2 diabetes, patients were randomized to rosuvastatin 10 mg, atorvastatin 10 or 20 mg, simvastatin 20 mg, or pravastatin 40 mg for 8 weeks. Patients either remained on these treatments or were switched from other statins to rosuvastatin. The primary pinpoint was a LDL cholesterol of < 116 mg/dL. Significant improvement in LDL cholesterol goal achievement was found for patients who were switched to rosuvastatin 10 mg compared with patients who remained on atorvastatin 10 mg (86% vs 80%; $P$ < 0.5), simvastatin 20 mg (86% vs 72%, $P$ <.001), and pravastatin 40 mg (88% vs 66%, $P$ < .0001). For patients who were switched from atorvastatin 20 mg to rosuvastatin 20 mg, the rate at goal was 90% vs 84% ($P$ < .01) (*Am Heart J*. 2004;147:705-712). But while rosuvastatin appears to be the most potent statin, it may carry a higher dose related risk of muscle toxicity including myositis and rhabdomyolysis. Astra Zeneca has recently acknowledged 4 cases of rhabdomyolysis in patients who were taking 40 mg of rosuvastatin, and has urged physicians in England to avoid initial high dose therapy with the drug, instead starting at 10 mg and titrating with appropriate follow-up.

## FDA Actions

Immunex Corp.'s etanercept (Enbrel) has been approved for use in patients older than the age of 18 with moderate-to-severe plaque psoriasis. Enbrel is currently marketed for use in patients with ankylosing spondylitis, psoriatic arthritis, moderate to severe rheumatoid arthritis, and juvenile rheumatoid arthritis. The expansion of indications to treat psoriasis was expected after 2 phases.

All studies showed improvement with treatment up to 1 year. Etanercept, which is a tumor necrosis factor inhibitor, joins the biologics alefcept (Amevive) and efalizumab (Raptiva) in the suddenly rather crowded market for the treatment of psoriasis.

The FDA has approved Indevus Pharmaceutical's trospium chloride (Sanctura), for the treatment of overactive bladder with symptoms of the urge urinary incontinence, urgency and frequency. The drug is a muscarinic receptor antagonist, and as such, has side effects that include dry mouth and constipation. It is, however, relatively well-tolerated with fewer drug-drug interactions than currently available medications.

Fondaparinux (Arixtra-Fonda BV), the synthetic selective factor Xa inhibitor, has been given the expanded indication for treatment of acute pulmonary embolism and acute deep venous thrombosis without PE when coadministered with warfarin. Previously, the drug had been approved for prevention of DVT in the setting of orthopedic surgery.

Salix Pharmaceuticals has received approval to market rifaximin (Xifaxan) for the treatment of travelers diarrhea caused by noninvasive strains of *Escherichia coli*. The drug is unique in that it is minimally absorbed (< 0.5%) after oral administration, and exerts its action only in the gut. It is not for use in patients with diarrhea associated with fever or bloody stools, or pathogens other than *E. coli*. The drug is approved for patients age 12 and older and appears to be well-tolerated. ■