NEW RESEARCH CONNECTS MERCURY TO ALZHEIMER’S DISEASE

Scientists at the University of Calgary have demonstrated that trace amounts of mercury can cause the type of damage to nerves that is characteristic of the damage found in Alzheimer’s Disease (AD). The level of mercury exposure used was well below those levels found in humans with mercury/silver amalgam dental fillings. [Leong, CCW; Syed, NI; Lorschieder, FL. Retrograde Degeneration of Neurite Membrane Structural Integrity of Nerve Growth Cones Following In Vitro Exposure to Mercury. NeuroReport, 12(4):733-737, 2001.]

The exposure to mercury caused the formation of “neurofibrillary tangles,” which are one of the two diagnostic markers for AD. The scientists found that a number of other materials, including aluminum, did not cause the characteristic damage.

The research, published in a peer-reviewed medical journal, is accompanied by a dramatic video visual presentation. Utilizing digital time-lapse photography, this video shows the rapid damage to the nerve cells after the introduction of minute amounts of mercury.

Upon introduction of the mercury, the stripping away of the protein tubulin from the nerve can be seen. The tubulin forms the skeletal structure for the nerve. When the tubulin is stripped away, the bare nerve fiber is left unsupported, resulting in the “neurofibrillary tangles” characteristic of Alzheimer’s Disease. The video also contains an animated description of this process.

Public Awareness

It is important to the public health that the information from this study is widely revealed through the media. An addendum to this newsletter provides the details for members of
the media to obtain the video for use in their outlet. This new study provides a dramatic culmination of years of research investigating a possible connection between mercury and Alzheimer’s Disease. Abstracts of the following studies are provided in the “Science” section of this newsletter.

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Human Autopsy Studies on AD and Mercury
Scientists at the University of Kentucky began a series of autopsy studies in the 1980's. They conducted autopsy studies on AD victims and compared the levels of various heavy metals and other elements in the brain tissue to that of controls.

In the first study, bulk gray- and white-matter specimens were investigated. [Ehmann, WD et al. 1986.] The most significant differences between AD victims and controls were large elevations of mercury and bromine and depletion of rubidium in the AD brain.

Next, the scientists determined the element levels in the specific brain areas involved in AD. [Thompson, CM et al, 1988.] These were the hippocampus, amygdala, and the nucleus basalis of Meynert (nBM). The elevation of mercury in AD nBM as compared to controls was the largest element imbalance found. Mercury levels in the amygdala of AD brain were also much higher. The authors stated (page 5): “The source of the Hg in brain is not known, although environmental pollution and dental amalgams have been widely suggested.”

Finally, element levels in subcellular fractions (nuclei, mitochondria, microsomes) were examined. [Wenstrup, D et al, 1990.] Again, elevations of mercury and bromine and depletion of rubidium were found. The mercury elevation was found in all fractions of AD brain, although it was significantly elevated in the microsomal fraction. Again, the authors stated (page 130): “The source of the brain Hg in AD is not known although dental amalgams and environmental sources such as seafoods are potential sources.”

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Molecular Studies on AD and Mercury
Another team of researchers at the University of Kentucky and other scientists at the University of Calgary, then began investigating the pathology of Alzheimer’s Disease at the molecular level. It had been previously demonstrated that the formation of neurofibrillar tangles in Alzheimer’s Disease (AD) was a result of an interruption of tubulin polymerization.

Molecular experimentation at the University of Kentucky on rats found that this same type of lesion could be produced by exposure to mercury, and that this damage was irreversible. [Duhr, EF et al, 1991; Duhr, EF et al, 1993.]

Next, scientists at the University of Calgary conducted an in vitro and in vivo (rats) study that confirmed the findings that mercury inhibited the neuronal proteins tubulin and actin. This resulted in loss of the skeletal structure of the neurons, which is the characteristic of neurofibrillar tangles. [Palkiewicz, P; Zwiers, H; Lorscheider, FL, 1994.]

To date, the research had utilized ionic mercury. Now the two groups of scientists joined together to investigate the effects of inhaled mercury vapor (the major exposure route of dental amalgam mercury). [Pendergrass, JC et al, 1997.]

The mercury vapor exposure levels used were consistent with the levels experienced by many humans with mercury/silver amalgam dental fillings.

The effect on the tubulin of nerve structure was even more dramatic. The average mercury concentrations in rat brains increased 11-47 fold with the duration of exposure to mercury vapor. These levels were similar to the levels found in human AD victims. The identical neural lesion to that found in human AD victims was seen in the rat brains, at an occurrence of 41-74% compared to control tissues.

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Mercury and Beta Amyloid in AD
Alzheimer's Disease (AD) cannot be accurately
diagnosed in the living human. AD can only be distinguished from other dementia disorders on autopsy, with the finding of the two characteristic AD markers - neurofibrillary tangles and amyloid plaques. There is considerable controversy in the scientific community as to which of these two markers is the more significant.

Further indication of a relation between mercury and AD was provided by a study published in 1998. [Hock, D et al, 1998.] The study found that victims of AD had blood mercury levels more than two-fold higher than did controls. In early onset AD patients, the blood mercury levels were almost three-fold higher than in controls. The blood mercury levels were significantly correlated to the levels of amyloid beta-peptide in the cerebrospinal fluid.

In 2000, scientists in Switzerland published a study that demonstrated that extremely low levels of mercury could cause the formation of amyloid plaques on nerve tissue. [Olivieri, G et al, 2000.] The authors concluded (abstract): "These results indicate that mercury may play a role in pathophysiological mechanisms of AD."

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**Dental Journals Contradict Mercury/Alzheimer Connection**

In the face of all of this published research, the dental profession continues to try to contradict a connection between dental amalgam mercury and Alzheimer’s Disease.

One study, published in the journal *General Dentistry*, compared mercury urine concentrations from AD victims to controls. [Fung, YK et al, 1996.] They concluded that AD victims do not have a greater body burden of mercury than controls. Of course, they failed to mention that even the American Dental Association has formally acknowledged that "the distribution of mercury into body tissues is highly variable and there appears to be little correlation between levels in urine, blood or hair, and toxic effects." [JADA, 109, page 470, Sep 1984.]

Two additional studies were published in the *Journal of the American Dental Association*. [Saxe, SR et al, 1995; Saxe, SR et al, 1999.] These studies both concluded that mercury from amalgam dental fillings are not connected to AD. Actually, the latter study even concluded that there was no correlation between the presence of amalgam fillings and brain mercury levels in the subjects, a conclusion that is contradicted by a number of other published studies.

It should be noted that all three of these studies, commonly referred to by organized dentistry as "The Nun Study," were published in dental journals. Their findings and conclusions are contradictory to studies published in peer-reviewed medical scientific journals.

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**Summary on Mercury and AD**

Alzheimer’s Disease is a devastating disorder that has an immeasurable impact on the lives of its victims and their loved ones. Nobody that has encountered the disease can deny its horror. Presently, the cause of Alzheimer’s Disease is "unknown" and, worse yet, there is no cure. Diagnosis of the condition cannot be accurately made on the living. On autopsy, two diagnostic markers are characteristic of the disease: 1) neurofibrillary tangles, and 2) amyloid plaques. The medical community is uncertain as to which of these two is more significant if, indeed, either is more significant than the other.

Research conducted by reputable medical scientists and published in valid peer-reviewed medical scientific journals has demonstrated that mercury, in extremely small quantities, can cause both of these characteristics.

Several facts are acknowledged by all involved in the controversy over the safety of mercury/silver amalgam dental filling: 1) the fillings are circa 50% mercury, 2) the amalgam mercury exits the fillings continuously, 3) stimulation of the fillings
(chewing, heat, brushing, etc.) greatly increases the release of mercury from the fillings, 4) dental amalgam mercury enters the body of the patient and builds up with time, 5) amalgam mercury from mothers has been scientifically traced to the brain tissues of unborn babies and into newborns from nursing mothers, and 6) the amount of human exposure to mercury vapor that is without harm is unknown.

The amount of published research demonstrating that mercury can cause the type of damage found in Alzheimer’s Disease is absolutely compelling. The three studies in contradiction were all published in dental journals, rather than appropriate medical scientific journals. Action on this issue must NOT be delayed any longer! Every congressman in the United States and Member of Parliament in Canada must be made aware of this evidence, and urged to take immediate action to protect their citizens!

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SCIENCE

Hg2+ Induces GTO-Tubulin Interactions in Rat Brain Similar to Those Observed in Alzheimer’s Disease.

Duhr, E; Pendergrass, JC; Kasarskis, E; Slevin, J; Haley, B.


ABSTRACT: The pathogenesis of Alzheimer’s Disease (AD) is unknown. Using SDS-PAGE & autoradiography our laboratory has shown: (I) that the tubulin in AD brain is less photolabeled by [32P] 8N3GTP than is tubulin from control brain(Ann Neurol., 26:210-5, 1989) and (II) that low microM levels of preformed Hg2+EDTA specifically blocked interactions of tubulin-[32P]8N3GTP in control human brain homogenates giving a photolabeling profile identical to AD brain (FASEB J, 4:A2151, 1990).

Elevated levels of Hg2+ have been reported in AD brain by others (Neurotoxicol, 9:1-7, 1988). Earlier work using [32P]8N3GTP with Al3+

treated rat & rabbit brain showed no differences from control with regards to tubulin photolabeling (Neurotoxicol, 9:429-42, 1988). However, our latest data show that brain samples from Hg2+ fed rats display an abolished GTP-
tubulin interaction similar to AD brain samples as determined by [32P] 8N3GTP photolabeling profiles. Removal of Hg2+ from treated rats did not reverse the effect.

These results suggest that certain complexed forms of Hg2+ must be considered as a potential source for the etiology of AD.

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HgEDTA Complex Inhibits GTP Interactions With the E-Site of Brain Beta-Tubulin.

Duhr, EF; Pendergrass, JC; Slevin; J, Haley, BE.


ABSTRACT: We have found that EDTA and EGTA complexes of Hg2+, which conventional wisdom has assumed are biologically inert, are potentially injurious to the neuronal cytoskeleton. Tubulin, a major protein component of the neuronal cytoskeleton, is the target of multiple toxicants, including many heavy metal ions. Among the mercurials, inorganic mercuric ion (Hg2+) is one of the most potent inhibitors of microtubule polymerization both in vivo and in vitro. In contrast to other heavy metals, the capacity of Hg2+ to inhibit microtubule polymerization or disrupt formed microtubules cannot be prevented by the addition of EDTA and EGTA, both of which bind Hg2+ with very high affinity. To the contrary, the addition of these two chelating agents potentiates Hg2+ inhibition of tubulin polymerization. Results herein show that HgEDTA and HgEGTA inhibit tubulin polymerization by disrupting the interaction of GTP with the E-site of brain beta-
tubulin, an obligatory step in the polymerization of tubulin. Both HgEDTA and HgEGTA, but not free Hg2+, prevented binding of [32P] 8N3GTP, a photoaffinity nucleotide analog of GTP, to the E-site and displaced bound [32P]
8N3GTP at low micromolar concentrations. This complete inhibition of photoinertion into the E-site occurred in a concentration- and time-dependent fashion and was specific for Hg^2+ complexes of EDTA and EGTA, among the chelating agents tested. Given the ubiquity of Hg^2+ in the environment and the widespread use of EDTA in foodstuffs and medicine, these mercury complexes may pose a potentially serious threat to human health and play a role in diseases of the neuronal cytoskeleton.

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**Brain Trace Elements in Alzheimer's Disease.**
Ehmann, WD; Markesbery, WR; Alauddin, M; Hossain, TIM; Brubaker, EH.
ABSTRACT: Instrumental neutron activation analysis has been used to determine the concentrations of 16 elements in selected brain regions and separated gray- and white-matter specimens from histologically verified Alzheimer's disease (AD) and age-matched control patients.
Significantly different (p<0.05) mean concentrations of Br, Cl, Cs, Hg, N, Na, P, and Rb were observed in AD bulk brain samples compared to controls, while no significant differences were observed for Ag, Co, Cr, Fe, K, Sb, Sc, and Se. The differences that are most persistent and largest in magnitude for the pooled bulk samples, males and females, left and right hemispheres, and separated gray and white matter are the elevation of Br and Hg and the depletion of Rb in AD compared to controls.
Significant interelement correlations for the latter elements in both AD and control brains are also documented.
Based on these studies, the possibility of an etiological role for trace elements in AD clearly deserves further investigation.

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**Mercury Determination in Nursing Home Patients With Alzheimer's Disease.**
Fung, YK; Meade, AG; Rack, EP; Blotcky, AJ; Claassen, JP; Beatty, MW; Durham, T.
General Dentistry, 74-78, Jan-Feb 1996.
ABSTRACT: Trace element neurotoxicity contributing to the development of Alzheimer's disease (AD) may be an important etiologic factor for this disorder. This clinical study was conducted to determine the urine concentrations of mercury (Hg) from patients with AD disorders. Within the confines of a nursing home, all subjects were exposed to the same environment and a diet that excluded seafood. The results of this study do not indicate that subjects with AD have a greater body burden of Hg, according to urinary excretion. This can be further evidence that Hg from amalgam restorations or diet is not related to etiology and pathogenesis of AD.

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**Increased Blood Mercury Levels in Patients With Alzheimer's Disease.**
Hock, C; Drasch, G; Golombowski, S; Muller-Spahn, F; Willerhausen-Zonnchen, B; Schwarz, P; Hock, U; Growden, JH; Nitsch, RM.
ABSTRACT: Alzheimer's disease (AD) is a common neurodegenerative disorder that leads to dementia and death. In addition to several genetic parameters, various environmental factors may influence the risk of getting AD. In order to test whether blood levels of the heavy metal mercury are increased in AD, we measured blood mercury concentrations in AD patients (n=33), and compared them to age-matched control patients with major depression (MD) (n=45), as well as to an additional control group of patients with various non-psychiatric disorders (n=65).
Blood mercury levels were more than two-fold higher in AD patients as compared to both control groups (p=0.0005, and p=0.0000, respectively). In early onset AD patients (n=13), blood mercury levels were almost three-fold higher as compared to controls (p=0.0002, and
p = 0.0000, respectively). These increases were unrelated to the patients’ dental status.

Linear regression analysis of blood mercury concentrations and CSF levels of amyloid beta-peptide (A beta) revealed a significant correlation of these measures in AD patients (n = 15, r = 0.7440, p = 0.0015, Pearson type of correlation). These results demonstrate elevated blood levels of mercury in AD, and they suggest that this increase of mercury levels is associated with high CSF levels of A beta, whereas tau levels were unrelated.

Possible explanations of increased blood mercury levels in AD include yet unidentified environmental sources or release from brain tissue with the advance in neuronal death.

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Mercury Induces Cell Cytotoxicity and Oxidative Stress and Increases B-Amyloid Secretion and Tau Phosphorylation in SHSY5Y Neuroblastoma Cells.
Olivieri, G; Brack, Ch; Muller-Spahn, F; Stahelin, HB; Herrman, M; Renard, P; Brockhaus, M; Hock, C.

ABSTRACT: Concentrations of heavy metals, including mercury, have been shown to be altered in the brain and body fluids of Alzheimer’s disease (AD) patients. To explore potential pathophysiological mechanisms we used an in vitro model system (SHSY5Y neuroblastoma cells) and investigated the effects of inorganic mercury (HgCl2) on oxidative stress, cell cytotoxicity, B-amyloid production, and tau phosphorylation.

We demonstrated that exposure of cells to 50 microgram/L (180 nM) HgCl2 for 30 min induces a 30% reduction in cellular glutathione (GSH) levels (n = 13, p < 0.001). Preincubation of cells for 30 min with 1 microM melatonin or premixing melatonin and HgCl2 appeared to protect cells from the mercury-induced GSH loss. Similarly, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxicity assays revealed that 50 microgram/L HgCl2 for 24 h produced a 50% inhibition of MTT reduction (n = 9, p < 0.001).

Again, melatonin preincubation protected cells from the deleterious effects of mercury, resulting in MTT reduction equaling control levels. The release of B-amyloid peptide (AB) 1-40 and 1-42 into cell culture supernatants after exposure to HgCl2 was shown to be different: AB 1-40 showed maximal (15.3 ng/ml) release after 4 h, whereas AB 1-42 showed maximal (9.3 ng/ml) release after 6 h of exposure to mercury compared with untreated controls (n = 9, p < 0.001). Preincubation of cells with melatonin resulted in an attenuation of AB 1-40 and AB 1-42 release.

Tau phosphorylation was significantly increased in the presence of mercury (n = 9, p < 0.001), whereas melatonin preincubation reduced the phosphorylation to control values.

These results indicate that mercury may play a role in pathophysiological mechanisms of AD.

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ADP-Ribosylation of Brain Neuronal Proteins is Altered by In Vitro Exposure to Inorganic Mercury.
Palkiewicz, P; Zwiers, H; Lorscheider, FL.

ABSTRACT: ADP-ribosylation is an essential process in the metabolism of brain neuronal proteins, including the regulation of assembly and disassembly of biological polymers. Here, we examine the effect of HgCl2 exposure on the ADP-ribosylation of tubulin and actin, both cytoskeletal proteins also found in neurons, and B-50/43-kDa growth-associated protein (B-50/GAP-43), a neuronal tissue-specific phosphoprotein.

In rats, we demonstrate, with both in vitro and in vivo experiments, that HgCl2 markedly inhibits the ADP-ribosylation of tubulin and actin.

This is direct quantitative evidence that HgCl2, a toxic xenobiotic, alters specific neurochemical
reactions involved in maintaining brain neuron structure.

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Mercury Vapor Inhalation Inhibits Binding of GTP to Tubulin in Rat Brain: Similarity to a Molecular Lesion in Alzheimer Diseased Brain.
Pendergrass, JC; Haley, BE; Vimy, MJ; Winfield, SA; Lorscheider, FL.
ABSTRACT: Hg2+ interacts with brain tubulin and disassembles microtubules that maintain neurite structure. Since it is well known that Hg vapor (Hg0) is continuously released from “silver” amalgam tooth fillings and is absorbed into brain, rats were exposed to Hg0 4 h/day for 0, 2, 7, 14 and 28 d at 250 or 300 microgram Hg/m3 air, concentrations present in mouth air of some humans with many amalgam fillings. Average rat brain Hg concentrations increased significantly (11-47 fold) with duration of Hg0 exposure. By 14 d exposure, photoaffinity labeling of the beta-subunit of the tubulin dimer with [alph32P]8n3GTP in brain homogenates was decreased 41-74%, upon analysis of SDS-PAGE autoradiograms.
The identical neurochemical lesion of similar or greater magnitude is evident in Alzheimer brain homogenates from approximately 80% of patients, when compared to human age-matched neurological controls. Total tubulin protein levels remained relatively unchanged between Hg0 exposed rat brains and controls, and between Alzheimer brains and controls. Since the rate of tubulin polymerization is dependent upon binding of GTP to tubulin dimers, we conclude that chronic inhalation of low-level Hg0 can inhibit polymerization of brain tubulin essential for formation of microtubules.

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Dental Amalgam and Cognitive Function in Older Women: Findings From the Nun Study.
Saxe, SR; Snowdon, DA; Wekstein, MW; Henry, RG; Grant, FT; Donegan, SJ; Wekstein, DR.
ABSTRACT: The authors determined the number and surface area of occlusal dental amalgams in a group of 129 Roman Catholic sisters who were 75 to 102 years of age.
Findings from this study of women with relatively homogenous adult lifestyles and environments suggest that existing amalgams are not associated with lower performance on eight different tests of cognitive function.

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Alzheimer’s Disease, Dental Amalgam and Dental Mercury.
Saxe, SR; Wekstein, MW; Kryscio, RJ; Henry, RG; Cornett, CR; Snowdon, DA; Grant, FT; Schmitt, FA; Donegan, SJ; Wekstein, DR; Ehmann, WD; Markesbery, WR.
ABSTRACT: Background: Mercury, or Hg, is a neurotoxin that has been speculated to play a role in the pathogenesis of Alzheimer’s disease, or AD. Dental amalgam releases low levels of Hg vapor and is a potential source of Hg for a large segment of the adult population.
Methods: The authors studied 68 subjects with AD and 33 control subjects without AD to determine Hg levels in multiple brain regions at autopsy and to ascertain the subjects’ dental amalgam status and history. The subjects were from central Kentucky and Elm Grove, Wis. The authors conducted dental amalgam assessments during the lives of the majority of subjects and in some subjects at the time of autopsy only. The authors also determined three dental amalgam index scores - Event (placement, repair or removal of amalgam); Location and Time in Mouth - in addition to the numbers of and surface area of occlusal amalgam restorations. The authors determined Hg levels in multiple brain regions and performed full neuropathologic evaluations to confirm the normal status of the brain or the presence of AD.
Results: The authors found no significant association of AD with the number, surface area or history of having dental amalgam restorations. They also found no statistically significant differences in brain Hg level between subjects with AD and control subjects. Clinical Implications: Dental amalgam restorations, regardless of number, occlusal surface area or time, do not relate to brain Hg levels.

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Regional Brain Trace-Element Studies in Alzheimer’s Disease.
Thompson, CM; Markesbery, WR; Ehmann, WD; Mao, Y-X; Vance, DE.
ABSTRACT: Alzheimer’s disease (AD) brain trace-element imbalances in the amygdala, hippocampus and nucleus basalis of Meynert (nBM) are found in most cases to be consistent with those previously reported in samples derived principally from AD cerebral cortex (Ehmann et al., 1986). The elevation of mercury in AD nBM, as compared to age-matched controls, is the largest trace-element imbalance observed to date in AD brain.
In addition to the general confirmation of imbalances for Cs, Hg, N, Na, P, and Rb noted previously in cerebral cortex samples, imbalances for Fe, K, Sc, and Zn were observed in two regions and one region also exhibited imbalances for both Co and Se. Persistent imbalances for the univalent cations Na, K, Rb and Cs support arguments for a membrane abnormality in AD.
The data presented here also provide the first comprehensive simultaneous multi-element determinations in both control and AD nBM.

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Trace Element Imbalances in Isolated Subcellular Fractions of Alzheimer’s Disease Brains.
Wenstrup, D; Ehmann, WD; Markesbery, WR.
ABSTRACT: Concentrations of 13 trace elements (Ag, Fr, Co, Cr, Cs, Fe, Hg, K, Na, Rb, Sc, Se, Zn) in isolated subcellular fractions (whole brain, nuclei, mitochondria, microsomes) of temporal lobe from autopsied Alzheimer’s disease (AD) patients and normal controls were determined utilizing instrumental neutron activation analysis.

Comparison of AD and controls revealed elevated Br (whole brain) and Hg (microsomes) and diminished Rb (whole brain, nuclear and microsomes), Se (microsomes) and Zn (nuclear) in AD. The elevated Br and Hg and diminished Rb are consistent with our previous studies in AD bulk brain specimens. Comparison of element ratios revealed increased Hg/Se, Hg/Zn and Zn/Se mass ratios in AD. Se and Zn play a protective role against Hg toxicity and our data suggest that they are utilized to detoxify Hg in the AD brain. Overall our studies suggest that Hg could be an important toxic element in AD. Whether Hg deposition in AD is a primary or secondary event remains to be determined.

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FORUM
IAOMT 2001 MID-YEAR MEETING
DATE: Friday-Saturday, 7-8 September 2001.
SITE: Oakbrook (Chicago), Illinois.
HOTEL: The Lodge (Hyatt). 2815 Jorie Blvd., At McDonald’s Office Campus, Oakbrook, IL 60523. T: 630-990-5800 or 800-233-1234. Specify IAOMT.
Room rate: $130/night s/d, Deadline: 9 August!
MEETING REGISTRATION: IAOMT, P.O. Box 608531, Orlando, FL. 32860-8531. T: 407-298-2450; F: 407-298-3075. Registration (U.S.): Members: $495, non-members: $595; spouses/staff with registrant: $175 each. Includes continental breakfast and lunch on Friday and Saturday, Saturday night Awards Banquet. Cancellation fee after 1 September: 10%.
WELCOME RECEPTION (Cash bar): Thursday, 6 September 2001, 7:30pm.