



"Dedicated to improving the health, well-being and quality of life of patients and their caregivers."

QUARTERLY

Who do we address this to? Thoughts from the publisher.

Names and labels matter. When the government collects more money is that "revenue enhancement" or a "tax increase?" The answer depends on how steamed you get over the 16th Amendment to the Constitution.

What about the people who come to the Memory Disorders Clinic? Are they patients? Persons with a condition? What about the family members and friends who come to clinic with them: caregivers, carers, or knowledgeable informants? No one term seems complete. No one term misses offending some concept of dignity and self-respect.

The rise of "mild cognitive impairment" makes these problems all the more significant (see next article). To label a person who has cognitive problems not significant enough to interfere with every day activities a patient overextends the concept of being a patient. The concept of "caregiver" simply makes no sense too.

Language reflects ideas. As long as our ideas of what is dementia, normal aging, and living with someone with cognitive impairment change, our language will play catch-up. We risk sounding rude or foolish. But still we must speak.

This quarterly goes out to patients and carers who attend the Memory Disorders Clinic, leaders in dementia research and care, friends of the Alzheimers Disease Center, interested strangers, donors. My parents too. We make out the address label to both the patient and carer. We address it to both recognizing that both may not read this. But we consider this a minor error to the greater mistake of not respecting both of the persons who come to a clinic visit, however they are labeled.

Mild Cognitive Impairment: Pushing the diagnostic threshold

by Jennifer Klocinski, MA and Jason Karlawish, MD

As physicians and researchers have become better at diagnosing Alzheimer's disease and diagnosing it at earlier and earlier stages a new entity has emerged, Mild Cognitive Impairment or MCI.

MCI describes a person with impairments that exceed normal age related cognitive changes but are not severe enough to meet criteria for dementia. As we age cognitive changes do occur. For the most part it is the speed and not the accuracy of cognitive processes that are affected by age. This means that while it may take an older adult longer to answer questions as compared to a young adult those answers are generally correct. The older adult functions well in their usual and every day activities.

The criteria for dementia is that the person must have impairments in at least two domains of cognition, for example, difficulties with memory, language or executive function (the abilities to plan and organize) and these impairments interfere with the person's ability to

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Mild Cognitive Impairment... *Continued from page 1*

perform usual and everyday activities. Mild cognitive impairment describes someone with impairment in only one domain of cognition or minor impairments in more than one domain of cognition.

MCI is new and it is evolving. Many physicians may not be familiar with the term. Some experts believe that a variant of MCI called MCI amnesic variant is the earliest sign of Alzheimer's disease. Table 1 shows

Table 1. Criteria for MCI-amnesic variant

1. Memory complaint
2. Normal activities of daily living
3. Normal general cognitive function
4. Abnormal memory for age
5. Not demented

Taken from Petersen RC, et al. Mild Cognitive Impairment: Clinical Characterization and Outcome. *Arch Neurol.* 1999; 56:303-308.

the criteria for MCI amnesic variant. The key issue here is that despite the complaints of memory loss and the measured impairment in memory function, the person performs as usual in their everyday activities such as managing their money and driving. In other words, they are not demented.

Research has shown that individuals with MCI amnesic variant have an increased risk of developing Alzheimer's disease. In well-classified groups of persons whose impairment is in memory, 12 to 15% per year convert to Alzheimer's disease.

But some people with MCI never progress to Alzheimer's disease or a related dementia. The challenge researchers face is how to distinguish those with MCI who will progress to dementia from those who will not. This will become more important as researchers develop treatments to prevent, halt and significantly slow Alzheimer's disease.

But MCI also challenges society. So far in this article, we have avoided calling it a "diagnosis." In other words, we are hesitant to call it a disease. Mild cognitive impairment as a diagnosis raises a series of questions. Some of which were mentioned on page 1 in the "Thoughts from the Publisher" article. The broad contours of these challenges are that we maybe transforming the way we think about Alzheimer's

disease. MCI amnesic variant may simply be Alzheimer's disease. In sum, we may be on the threshold of a revolution whose outcome will be that you do not have to be demented to have Alzheimer's disease. But using the language of Alzheimer's disease for persons with MCI seems plainly silly. A person who has memory problems that they can manage with a few notes and reminders is a "patient" because he is "at risk?" Their family member is not a "caregiver." They are a "knowledgeable informant."

Disease or not, the more MCI is the concern of medicine, the more the people who carry that label transform into some kind of patient. This opens an unexplored territory of questions. First, how well can physicians make this "diagnosis?" MCI is not easy to

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Dementia Care Conference: Webcast Available

On October 18th the Alzheimer's Disease Center hosted it's first conference, "Dementia Care: Living for Today and Planning for Tomorrow." Over 75 family carers, persons with mild cognitive impairment or early stage dementia, and healthcare professionals attended the full-day event. Through a partnership with ULiveandLearn.com, Inc. and WHYY's Wider Horizons and with funding through the Novartis Foundation for Gerontology the conference was broadcast live over the Internet. The internet broadcast allowed people around the country and overseas to participate in the conference. The webcast is archived and available through the ADC's website, www.uphs.upenn.edu/ADC.

The conference was made possible through generous grants from the National Institutes of Health/National Institutes on Aging, John A. Hartford Center of Geriatric Nursing Excellence, Natestch Pharmaceutical Company, Inc., and The University of Pennsylvania Health System's Board of Women Visitors. We welcome your comments about the conference and suggestions for future conferences. Please send comments and suggestions to Jennifer Klocinski via the postal mail or email address found on the back of this Quarterly.



How a urine test might one day help in diagnosing Alzheimer's Disease

by Jennifer Klocinski, MA and Jason Karlawish, MD

Results of research conducted at the Alzheimers Disease Center.

The ability to diagnose Alzheimer's disease and related illnesses as accurately and early as possible is extremely important. Early diagnosis means access to treatments to slow or even halt the disease progression. Patients and families who attend the Memory Disorders Clinic have been key participants in research that moves the field closer to this test: an oxidative stress test. This article is not simply a summary of exciting research results. It is a testament to the contribution patients made in giving samples of blood, urine and spinal fluid.

Oxidative stress occurs when the body is unable to destroy oxygen-free radicals. These are chemicals produced as a part of normal metabolic process and are also used to fight bacteria. These chemicals are unstable and quickly degrade. But when they come into contact with other molecules in the body they cause damage. The same mechanism that can destroy a bacteria cell can destroy a nerve cell. .

Oxidative stress has been implicated in a variety of disease processes including heart disease and cancer. Evidence also suggests that it has a role in Alzheimer's disease. The brain is considered to be at a high risk for damage due to oxidative stress for a number of reasons. Its has a high oxygen consumption and metabolic rate and abundance of polyunsaturated fatty acids which are highly susceptible to oxidative damage, but compared to other organs it has few defenses against oxidative stress. Further support of the role of oxidative stress in Alzheimer's disease is the clinical trial that showed vitamin E, a vitamin that reduces oxidative stress, may slow the progression of Alzheimer's disease.

Measuring oxidative stress has been difficult. The markers of oxidative stress disappear quickly. Therefore, they are difficult to measure. But Dr. Dominico Pratico of the Center for Experimental Therapeutics and Department of Pharmacology at the University of Pennsylvania has identified a molecule that can measure oxidative stress. His research focuses on isoprostanes. Isoprostanes are produced when oxygen-free radicals interact with polyunsaturated fatty

acids. His research measures and compares isoprostane levels in people with normal cognitive function, mild cognitive impairment, and Alzheimer's disease.

The two keys to his research were coming up with an easy way to measure isoprostanes and showing that isoprostane levels differ in persons with AD versus those without it. Dr. Pratico measured isoprostane levels in study participant's urine, blood and cerebrospinal fluid (CSF). He found that isoprostane levels in urine, blood and CSF were correlated. This means that the measure of oxidative stress in urine or blood reflects oxidative stress levels in the brain. This is a significant finding. It means that a simple urine sample can get the same kind of information as a hassle filled and more costly spinal tap.

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ADC STAFF HIGHLIGHTS:

- Patients, families and our staff are delighted that Dr. Clark and Dr. Arnold have returned to the clinic from one-year sabbaticals.
- Farewell to Drs. Marjorie Marenberg and Christian Kohler who cared for MDC patients during Drs. Clark and Arnold's sabbaticals. Dr. Marenberg has returned to her geriatrics practice in the Ralston-Penn outpatient practice. Dr. Kohler has returned to his practice in the psychiatry department but will continue working with the Memory Disorders Clinic through his research into emotion recognition in dementia.
- A Warm welcome to Hannah McCoubrey and Gerri Anselmo. Hannah has joined our team as a psychometrician. She received her BA from the University of Pennsylvania. Gerri Anselmo has joined our team as a psychometrician and research coordinator working with Dr. Kohler. She graduated from Pennsylvania State University with a B.S. in Counseling and Rehabilitation Services.
- Dr. John Q. Trojanowski, Director of Penn's ADC, has been named Director of Penn's Institute on Aging. He has also been elected to the Institute of Medicine, one of the National Academies which provides scientific advice to the Nation.
- Dr. Jason H.T. Karlawish was named a Greenwall Foundation Faculty Scholar in Bioethics. This award will help to fund Dr. Karlawish's work on research ethics which will examine research advance planning.



Finding meaning in the age of memory:

Book Reviews of "Memories are made of this: How memory works in humans and animals," "Searching for memory: the brain, the mind and the past," and "Losing My Mind: An intimate look at life with Alzheimer's" by Jason Karlawish, M.D.

Diseases kindle discussions of the meaning of the things they harm: TB inaugurated a dialogue on the meaning of infectiousness, cancer on death, schizophrenia on the notion of normal behavior. Alzheimer's disease has inaugurated a dialogue on the meaning of memory. What is it? What does it mean to lose it? How does memory shape our selves and how does its loss unmake ourselves?

Memory is no longer the academic interest of educators and psychologists. It is of interest to all who ponder the nature of the self and its loss by a disease such as Alzheimer's disease.

Alzheimer's disease always was. But it is like the New World of Columbus and Vespucci. It was out there waiting to be discovered. Only in the last 25 years have we begun to figure out how to get there. As we understand Alzheimer's disease, we begin to understand the map of memory. We are discovering our home.

Where can a nonscientist learn about memory? Two recent books offer excellent introductions to the topic. Both authors are scientists. Bourchouladze is a molecular biologist at Columbia University and Schacter a psychologist at Harvard. Both have succeeded in writing books accessible to the nonscientist. Their difference lies in their focus and style. Bourchouladze's is an overview of memory: its history, categories, measurement and how brain cells "make it." Schacter's is a more thorough treatment of these subjects.

These books are not self-help books to "beat memory loss" or "stop brain aging." They are thoughtful efforts to answer the question "What is memory?" It is, after all, only sensible that you have to know what something is before you set about doing something about it.

A key lesson is that memory has a history. Our understanding of what is memory has changed and

will continue to change. Memory and the way we learn about it changes the way we understand it. A model of associations cued to emotions replaces initial theories that memories are like photographs etched in our brains. The implications of this model are significant. Our minds make and unmake memories. Hence, we are constantly recreating the substance of what makes us ourselves: our memories.

Bourchouladze's book is a shorter read than Schacter's. In fact, it quotes from Schacter's. The key differences are their perspective and the direction of their narrative. Bourchouladze starts with people and ends with mice and sea slugs. Her chapters suggest there is a linear narrative to the science of memory. The science is leading to something: unlock-

ing the molecular origins of memory. Schacter's focus is people and he is more circumspect in his lessons. The more we learn of what is memory, the more we learn about ourselves and in turn change. He is not leading to an end of the story because as long as there is memory, there is no end.

Bourchouladze and Schacter are professionals. Their books are an objective treatment of memory. The third book by Thomas DeBaggio is a story of the loss of memory. Once upon a time, at the end of a doctor's visit, he mentioned he was having trouble with his memory. Several doctor visits later, he got a diagnosis: AD.

Unlike Charlton Heston's and Abigail Van Buren's sterile and highly manufactured narratives, DeBaggio tells a fever pitched story. He is in a race against his failing memory. His story is a narrative that reaches backward and forward and weaves together three stories: his life with the disease, his life before the disease and the story of AD. What is extraordinary about the book is its apparent ordinariness. DeBaggio

Memories are made of this: How memory works in humans and animals. by Rusiko Bourchouladze. 2002. Columbia University Press. 208pp., \$25.00

Losing my mind: An intimate look at life with Alzheimer's. by Thomas DeBaggio. 2002. The Free Press, 207pp. \$24.00

Searching for memory: The brain, the mind, and the past. by Daniel L. Schacter. 1996. Basic Books. 398pp. \$16.50

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Support the MDC

Private support enables our physicians and researchers to pursue novel research initiatives. These funds also provide for creation and circulation of this Quarterly to over 700 persons, website development, and production of the annual Dementia Care Conference.

We are truly grateful for your generosity and continued support of the Memory Disorders Clinic. For example,

- The Memory Disorders Center has been chosen by some families as the recipient of holiday donations.
- Many families are electing to designate the Memory Disorders Clinic as an in memoriam or in lieu of flower donation recipient upon the death of a loved one.
- Several of our families have provided funding for specific projects such as the Reminiscent Video project.

To send a gift, make the check payable to the "Trustees of the University of Pennsylvania" and indicate Memory Disorders Clinic" in the memo line. Send the check to:

Memory Disorders Clinic
Attention: Program Administrator
University of Pennsylvania
3615 Chestnut Street, Room 212
Philadelphia, PA 19104

Contributions are tax deductible. To find out more about our program needs please contact our main office at (215) 662-7810 or visit our website at www.uphs.upenn.edu/ADC.

Meaning in the age of memory... *Continued from page 4*

is a retired herb grower and failed leftist journalist. But out of this ordinary life, he tells a story of a failing mind writing about the experience of having a failing mind. He is at the same time both the knower and the known. It is a dance with the loss of self.

I recommend all three books. Start with Bourtchouladze and then read Schacter. Bourtchouladze's is a linear narrative of the science of memory. Schacter's is a thorough treatment of the subject of memory, including false memories, recovered memories – he's willing to show that the science remains incomplete and is not necessarily leading to a

finish. DeBaggio's story amply debunks the myth that a patient has no insight and their cognition is empty thinking. This is a textbook for clinicians. It is also a clarion call to inaugurate a candid and thoroughgoing discussion of what it means to live with a failing brain. It is a story of suffering.

Research Update:

Can reducing Homocysteine levels slow the rate of progression in Alzheimer's Disease?

Homocysteine is an amino acid normally produced by the body. Among other things it is involved in changing cholesterol to the harmful LDL form. There is recent evidence to suggest that high levels of homocysteine may increase the risk of developing AD and for those with AD speed disease progression. The Memory Disorders Clinic is expecting to participate in a clinical trial which will examine whether high doses of dietary supplements will reduce homocysteine levels and slow the rate of decline in people with mild to moderate AD. The study being planned is sponsored by the Alzheimer's Disease Cooperative Study group.

Can Simvastatin slow the progression of Alzheimer's disease?

Studies have suggested that high levels of cholesterol influence Alzheimer's disease through a variety of pathways. Epidemiological studies have demonstrated that individuals taking statins, a class of cholesterol lowering drugs, have a reduced risk of developing AD. Based on these findings the Memory Disorders Clinic will be participating in a national study to examine whether or not a specific statin, Simvastatin, can slow the rate of decline in people with mild to moderate AD. The study being planned is sponsored by the Alzheimer's Disease Cooperative Study group.

Interested in learning more about studies? Please contact Kris Gravanda, clinical study coordinator by email at krisg@mail.med.upenn.edu or phone at 215-349-5903.



Meet the Leaders of Penn's ADC: An Interview with Christopher Clark

by Jennifer Klocinski, MA

The Alzheimer's Disease Center (ADC) at the University of Pennsylvania is one of 29 ADC's and 3 affiliates in the country. Every five years we compete with other medical institutions around the country for one of these multimillion dollar AD center grants. This is the second in a three part series that will introduce you to each of the ADC's core leaders and director. The first part featured John Q. Trojanowski, Director of Penn's ADC.

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ADC Associate Director and Clinical Core Leader, Christopher M. Clark, M.D.:

Dr. Clark is a board certified neurologist. He received his MD from Jefferson Medical College in 1973. He completed his Internship at Pennsylvania Hospital and his Residency and a Research Fellowship at Columbia Presbyterian Medical Center in New York. Dr. Clark returned to Philadelphia in 1977 and joined Penn's Neurology Department. In 1986, Dr. Clark became an Assistant Professor of Neurology at Duke University and directed their Memory Disorders Clinic and the clinical core of Duke's ADRC. In 1990 he returned to the University of Pennsylvania, established the Memory Disorders Clinic and became Leader of Penn's ADC clinical core. Dr. Clark serves on local and national committees including the Medical and Scientific Advisory Panel for Alzheimer's Disease International, Director of New Program Development and member of the Board of Directors for the local chapter of the Alzheimer's Association. Dr. Clark is consistently cited in *Philadelphia Magazine* as a "Top Doc" for Alzheimer's disease care.

Conversation with Christopher M. Clark, M.D.:

JK: How did you become interested in dementia care and research?

CMC: I was doing neuromuscular disease clinical research at Pennsylvania Hospital working on a collaborative study that included Alan Roses at Duke. In 1985 he put in an application for an Alzheimer's Disease Center at Duke and asked me if I wanted to organize the clinical core. I really hadn't thought about dementing illnesses and up until that point I had only taken care of a handful of patients with dementing illnesses. I met some good people and the more I got involved the more interesting it became and it was probably the best career move I ever made.

JK: What do you see as the most important finding in AD research over the last several years?

CMC: There are two from my standpoint. Unraveling the molecular pathology of amyloid is I think critical in understanding AD and critical to opening up potential therapeutic targets. And the other is the definition and

recognition of the prodromal states of AD because that opens up the potential for starting therapy much earlier in the pathological process. We were stuck when we didn't know how to recognize and reliably diagnose mild cognitive impairment (*see related article on page 2*).

JK: What do you see as the most promising avenue of research for emerging therapies?

CMC: Five years ago most people would have said getting rid of the amyloid that forms plaques is the appropriate target and there is a small group of people who would have said getting rid of the neurofibrillary tangles is the right thing to do. Now it's a little unclear on whether getting rid of the amyloid plaque is really going to help. I don't know actually what the most promising therapy is going to be but my guess is that it's going to have something to do with the way that amyloid is processed, whether that's changing the way that it's folded or changing the way abnormally folded amyloid is gotten rid of or how fast that process is. I'm not terribly optimistic that it's just going to be cleaning up the debris after the problem occurs.

JK: What do you see as the most important contribution that Penn's ADC clinical core has made?

CMC: I think we've made progress in biomarkers with measuring the Tau protein in cerebrospinal fluid (CSF) and Dr. Pratico's oxidative stress marker, isoprostone (*see related article on page 3*). Isoprostones are I think well enough established as very important in the aide in early diagnosis, and in clinical situations in muddled diagnoses they can be very helpful and even in the differential diagnosis. And they have the potential as efficacy markers for treatment. I think these are good contributions from the clinical side.

Next issue: Dr. Jason Karlawish, Leader of Penn's ADC education core and Associate Director of the Memory Disorders Clinic.



Alzheimer's Disease Test... *Continued from page 3*

But what does that urine test mean? The key findings are that AD patients have significantly higher levels of isoprostanes than cognitively normal individuals and that isoprostane levels increase as Alzheimer's disease progresses. Finally, Dr. Pratico compared isoprostane levels in people with mild cognitive impairment (MCI), normal cognition and AD. He found that people with mild cognitive impairment had isoprostane levels that were higher than normal individuals but lower than individuals with AD. Taken together, these data suggest that isoprostane levels can serve as both a diagnostic test and that isoprostane levels may indicate the severity of brain cell damage.

One finding that is especially provocative is the results in persons with MCI. People with certain kinds of MCI are at a high risk for developing AD (see page 1). For some, MCI may be the earliest phase of AD. But not all people with MCI go on to develop AD. Isoprostane levels may help to identify people in the earliest stage of AD before they develop symptoms and significant damage to brain cells. This could remove much of the ambiguity and judgement in the labeling of MCI.

This is a story of research results. It could not be told without the efforts of the patients who volunteered their time and effort.

Further reading:

Praticò D, Clark CM, Liun F, Lee VM-Y, Trojanowski, JQ. Increase of brain oxidative stress in Mild Cognitive Impairment: A possible predictor of Alzheimer disease. *Archives of Neurology*. 2002; 59:972-976.

Praticò D, Commentary: Alzheimer's disease and oxygen radicals: new insights. *Biochemical Pharmacology*. 2002; 63(4): 563-567.

Praticò D., Clark CM, Lee VM-Y, Trojanowski JQ, Rokach J, FitzGerald GA. Increased 8, 12-iso-iPF₂a-VI in Alzheimer's disease: correlation of a noninvasive index of lipid peroxidation with disease severity. *Annals of Neurology*. 2000; 48:809-812.

Sano M. et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *The Alzheimer's*



Thank you!



The University of Pennsylvania's Memory Disorders Clinic thanks individuals and organizations for their generous contributions:

In Memory of Joseph Bologna

In Memory of George Strong Jr.

The Previti Family Foundation



Research Made Possible Through The Participation of People Who Attend the MDC:

People who attend the Memory Disorders Clinic have made possible the research conducted at the Alzheimer's Disease Center. The following are selected, recent publications that resulted from that research:

Casarett D, Takesaka J, Karlawish J, Hirschman K.B., Clark CM: How should clinicians discuss hospice for patients with dementia? Anticipating caregivers' preconceptions and meeting their information needs. *Alzheimer's Disease and Associated Disorders*. 2002; 16:116-122.

Duda JE, Giasson BI, Mabon ME, Lee VM, Trojanowski JQ: Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. *Annals of Neurology*. 2002 Aug;52(2):205-10.

*Karlawish JHT: The search for a coherent language: The science and politics of drug testing and approval. In: Kapp M.B., ed. *Ethics, Law and Aging Review*. New York, NY: Springer Publishing Company 8;2002:39-56.

Karlawish JHT, Casarett DC, Propert KJ, James B, Clark CMC: The relationship between dementia severity and

Alzheimer's disease patients' participation in decisions about their medical care. *Journal of Geriatric Psychiatry and Neurology*. 2002;15(2):68-72.

Kung MP, et al.: Radioiodinated styrylbenzene derivatives as potential SPECT imaging agents for amyloid plaque detection in Alzheimer's disease. *Journal of Molecular Neuroscience*. 2002 Aug-Oct;19(1-2):7-10.

Zhukareva V., et al.: Sporadic Pick's Disease: A Tauopathy Characterized by a Spectrum of Pathological τ Isoforms in Gray and White Matter. *Annals of Neurology*. 2002;51:730-739.

**This paper is a critical history of AD drug development that examines how scientific, political, and regulatory interests attempt to construct a valid and valuable language of treatment. Please write Doctor Karlawish for a reprint.*



ADC QUARTERLY



"Dedicated to improving the health, well-being and quality of life of patients and their caregivers."

Mild Cognitive Impairment... *Continued from page 2*

identify. The memory tests take skill and time not available to the typical physician.

The second question is what does it mean to have this label? Do these people suffer? What symptoms bother them? Can a treatment effectively relieve these symptoms? These questions are not ivory tower concerns devoid of real world meaning. Studies suggest that persons with MCI experience marked degrees of anxiety and depression and that these symptoms attenuate as they pass into dementia (that is, AD). This has implications for the value of the current strategy of clinical trials, which is to delay the time to progression into AD. As valuable as this is, does it also prolong a period of suffering?

Further reading about MCI controversies and questions.

On March 13-14, 2001, the Food and Drug Administration held a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee. Experts discussed the strengths and limits of current research and clinical trials that involve persons with MCI. The transcript of the meeting is a lively affair and is available on the internet at the FDA's Center for Drug Evaluation and Research website (<http://www.fda.gov/ohrms/dockets/ac/cder01.htm#PeripheralCentralNervous>) or through the freedom of information act. You may contact the Philadelphia District Information Officer, Anitra D. Brown-Reed, at 215 597-4390 (ext. 4202 or 4548) for assistance.

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