News for the VA research community **Vol. 2, No. 3/March 2002**

VA Research Currents

Update from the Medical Research Service

MRS offers array of career-development opportunities for new investigators

By Paul M. Hoffman, MD, Director

The Medical Research Service (MRS) funds scientific research focused on disease etiology, pathogenesis, diagnosis and treatment. A primary goal of MRS is to foster the careers of the next generation of VA clinician scientists and researchers. The recruitment and training of promising new scientists is critical to our success.

MRS training programs are designed so that a trainee works together with a senior mentor to develop the necessary skills and resources to eventually succeed as an independent scientist. The available pool of potential mentors is vast, representing more than 1,400 ongoing, individually funded research programs at 75 VA medical centers. In addition, MRS-supported Research Enhancement Award Programs (REAPs) and Centers provide exceptional training environments, where early-career scientists interact regularly and collaboratively with peers and senior investigators in exploring diverse aspects of important biomedical problems.

Three training programs provide entry points for investigators to initiate a career in the VA immediately upon completion of their MD or PhD. MRS regularly monitors the progress of all trainees to ensure that program goals are being met.

The **Associate Investigator** program provides training for both clinician and non-clinician scientists with little or no prior research experience. Mentors may be senior scientists individually funded through the Merit Review program, or investigators associated with REAPs or Centers.

The **Career Development** program provides salary and mentored research support to a fully-trained clinician who is entering a research career. MRS administers an entry-level and an advanced-level Career Development award.

The **Merit Review Entry Program** is a mentored program open to both clinician and non-clinician scientists. Three-year awards provide research and salary support (the latter for non-clinicians). It is intended to facilitate the transition from mentored trainee to independent scientist.

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20th annual HSR&D meeting

Secretary Principi to HSR&D:

'Your studies have revolutionized health care'

Speaking at the 20th annual meeting of VA's Health Services Research and Development (HSR&D) Service, held Feb. 13 – 15 in Washington, D.C., Secretary of Veterans Affairs Anthony Principi told health-services researchers their work is vital in helping VA improve veterans' quality of life.

"Compassion is not how much money we throw at a problem—it's measured by results and outcomes. And you are helping us measure those results," Mr. Principi said.

The secretary traced the growth of the service over the 25 years from its inception—when its budget was $3.6 million and it funded seven projects—to 2001, when HSR&D investigators worked on 143 projects, with total funding from HSR&D and other sources of more than $107 million. He described HSR&D's impact in impressive terms: "The men and women of this service have revolutionized the practice of medicine in VA, in America, and throughout the world."

Mr. Principi cited specific HSR&D research to illustrate this impact, such as a recent cooperative study led by Denise Hynes, PhD, RN, showing that subcutaneous, rather than intravenous, administration of the drug erythropoietin for end-stage renal disease—

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3rd national RR&D meeting

Keynote speaker Krauthammer: 'God's work' found in everyday adaptive technology, not just in sensational cures

Speaking as a Washington insider, medical doctor, and spinal cord injury patient, Charles Krauthammer, the keynote speaker at the national VA Rehabilitation Research meeting held Feb. 10 – 12 in Arlington, Va., offered attendees this hard-boiled assessment of how research funding often works:

"When you offer the cure, the magic, the great revolution, you get media attention, the funding, the hearings. When you offer the ameliorative work, which you are doing, and which I believe is God's work, you get in some ways left behind."

The Pulitzer Prize-winning newspaper and television commentator took exception to those who instill false hopes for an impending cure among patients with spinal cord injury, blindness and other disabilities.

"It's a cruel hoax to let people think [a cure] is around the corner," he said, referring even to well-meaning advocates for the disabled. Dr. Krauthammer, trained as a psychiatrist, said it is harmful to focus patients on preparing for a cure when they'd be better off learning how to maximize their remaining abilities.

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"I don't think three hours a day of exercising paralyzed muscles is the best use of your time," said Dr. Krauthammer, who suffered a spinal cord transection when he was in medical school 30 years ago. "You ought to be learning new skills, developing your mind, your talents, working with the function you have left as a result of the accident, preparing for your new life. If you exercise those muscles in moderation, as a way to maintain cardiovascular health, that's OK. But if you're doing it to run the marathon in 2015, that's a mistake."

Medical training shielded him from 'illusions' about life with SCI

Dr. Krauthammer said his class at Harvard was studying the anatomy of the spinal cord on the day of his life-changing accident. And this provided him with a realist's view of his injury from day one.

"I have no doubt that [one day] spinal cord injuries will be as unknown … as polio is today. But I believe that is 50 or 100 years from now. And I knew that from the day I was injured. And in many ways that insulated me from the illusions, the disappointments, the frustrations of having hope that would not be realized."

Dr. Krauthammer urged VA rehabilitation investigators to continue making strides in developing technologies to help patients maximize their remaining function.

"For this generation, the way to help people with injuries like mine is to do precisely what you are doing. Accepting the injury and working with it, by using high technology, by using whatever residual function is there, by using training—by using your genius—to make life better, to make function higher, to make one able to achieve more."

Rehabilitation–research advocates needed in Washington

He said more voices are needed in Washington to enlighten policymakers, who are often swayed by hype, about the benefits of rehabilitation research.

"I think it's important for people in my position, who have been on the receiving end of this technology, and also who have some involvement in the public policy debate, to try to emphasize how absolutely critical in the lives of real, living people is the work of rehabilitation, using technology to make life the best that we can have. And that is what you do. And I think you should be honored, respected and supported."

In response to a question on how to commercialize products that serve only a small number of patients, Dr. Krauthammer, who was a science advisor to President Carter, suggested that researchers look to the "orphan drug" market as a model and seek subsidies from the federal government.

"The way to sell it is to say that by dramatically changing the lives of this small population, you many change them from people who are dependent on public aid, to people who are productive and who pay taxes."

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20th annual HSR&D meeting

Health services research in 2027: 'Nothing about me without me'

What will health-services research look like 25 years from now?

"In 2027, proposed studies that don't involve all stakeholders are considered amusing—but they're not funded," was the wry assessment of Carolyn M. Clancy, MD, of the Agency for Healthcare Research and Quality (AHRQ), in her keynote talk at the HSR&D meeting. Dr. Clancy is acting director of AHRQ's Office of Priority Populations Research.

Taking listeners on a fanciful but purposeful voyage to 2027, she described a health-services enterprise that fully involves patients—as well as managers and policymakers—in every phase of research. She invoked the catch phrase "Nothing about me without me," coined at an international meeting of health professionals in Austria in 1998, proposing it as an apt slogan for the next generation of health-services researchers.

In addition, Dr. Clancy stressed the AHRQ tenet that publication of findings is only the first level of impact for research. Ideally, study results should then affect healthcare policy and clinical practice, leading to what she called the "Holy Grail" of research: meaningful impact on patient outcomes.

In 2027, she said, the only studies that will receive funding will be those that "include an explicit and compelling plan for incorporation into practice."

Having learned how to consistently incorporate all stakeholders and effectively disseminate study findings, health services researchers will enjoy status equal to that of biomedical scientists in the eyes of policymakers, envisioned Dr. Clancy.

"It's become incredibly clear [in 2027] that the tsunami of advances in medical science will not be successful, and are unlikely to be delivered to the patients most likely to benefit, without a very robust clinical evaluation

> "[In 2027] policymakers finally get it—the return on investment for biomedical research is significantly enhanced by a robust health-services research enterprise."

enterprise," said Dr. Clancy. "Policymakers finally get it—the return on investment for biomedical research is significantly enhanced by a robust health-services research enterprise."

Dr. Clancy pointed to VA's Quality Enhancement Research Initiative (QUERI) program as a model for translating research into practice and improving patient outcomes. "I think frankly the healthcare system has a lot to learn from how QUERI is working." She described a future healthcare system in which the boundaries between research and quality improvement have disappeared.

"Throughout the U.S., thankfully, after a long struggle, the question, 'What's the evidence?' is as routine as the question, 'What are the patient's vital signs?'" ■

VA, AHRQ to make joint funding easier

At the HSR&D meeting, VA and AHRQ officials announced new steps to facilitate joint funding of studies by the two federal agencies. Until now, research administrators at VA and AHRQ have had to grapple with different regulations, formats and language in trying to draft joint program announcements. And researchers seeking joint funding have had to negotiate two sets of deadlines and application procedures. Now, as a starting point for increased cooperation, the organizations will unify their deadlines and integrate their review boards.

"What we've agreed to do is collapse that," said Dr. Clancy. "So the timeline will be the same, and the review group will be composed of VA and AHRQ reviewers."

John Demakis, MD, director of HSR&D, cited strong support and encouragement from AHRQ director Dr. John Eisenberg, who died March 10 after a yearlong illness, in pushing toward partnership between the two agencies. Dr. Demakis said there are "endless possibilities" for joint projects between VA and AHRQ.

3rd national RR&D meeting

Krauthammer challenges VA investigators to continue focusing on maximizing function

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Dr. Krauthammer also reminded researchers that high-tech is not always the best solution for a patient, and that new adaptive devices must represent a major improvement for patients to be willing to invest the time and energy to adjust to them. He portrayed himself as the quintessential "patient who doesn't want to change," pointing to his decade-old wheelchair and the gel cushion that he only recently adopted in place of his longtime foam pad.

He told of a low-tech modification to his wheelchair that enabled him to easily propel it by turning a crank with his hands, and that allowed his then four-year-old son to sit behind him on a wooden platform, so the two could enjoy rides through the park. "That little piece of wood created memories that will last for him and for me for a lifetime," said Dr. Krauthammer. ■

RR&D's Dr. Aisen: 'We are unimpressed by hype'

Dr. Krauthammer's keynote talk was preceded by remarks from Chief R&D Officer John R. Feussner, MD, MPH, who cited several "markers of success" for VA's rehabilitation research program, including "a baker's dozen of superlative centers of excellence that are highly competitive and remarkably productive" and a number of winners of the Presidential Early Career Awards for Scientists and Engineers.

In her remarks, Mindy Aisen, MD, director of RR&D, urged investigators to take advantage of the size and scope of the VA research enterprise to forge innovative collaborations. "I believe rehabilitation researchers will be more effective working collaboratively than competitively," said Dr. Aisen. "That's a difficult level of 'karma' to achieve in this work that we do, since the very nature of scientific research is competitive." As a model for collaborative projects within the service, she cited how engineers in Pittsburgh and vision-impairment experts in Atlanta are working together to evaluate low-vision navigation aids.

Dr. Aisen also responded to Dr. Krauthammer's views on the power of media hype to influence funding, assuring the members of her service that VA funding is determined only by evidence. "We are unimpressed by hype. We are impressed by data that show the impact on quality of life, that shows if there is something about this technology that is different from what's on the market."

Another highlight of the meeting was the presentation of the 2002 Paul B. Magnuson Award to prosthetics pioneer Dudley Childress, PhD, a rehabilitation engineer with the VA Chicago Healthcare System (see coverage in last month's *VA Research Currents*).

Wanted: Hard evidence of efficacy

In a series of 20-minute plenary sessions at the annual RR&D meeting, directors from rehabilitation-related clinical areas, both at the national and local level, outlined for investigators what they see as priority research areas.

Barry Goldstein, MD, of the Spinal Cord Injury Service at the VA Puget Sound Healthcare System, talked about the prevalence of SCI side effects such as chronic pain and pressure ulcers, and lamented the lack of hard evidence for effective therapies.

"Lots of people with spinal cord injury have chronic pain. The question is, What hasn't been tried? We've tried narcotics, anti-seizure medications, antidepressants. What evidence do we have for using these medications? The answer is, not much. We have fundamental questions we need to address in these areas."

Dr. Goldstein also cited pressure ulcers as a condition requiring research. "We don't know what to do with pressure ulcers. Surgery or no surgery? There are 2,000 products on the market now for pressure ulcers. Which one do you use?"

Barbara Bates, MD, VA's national director of Physical Medicine and Rehabilitation, echoed the call for evidence to support—or reject—what clinicians are doing in the field.

"A lot of the techniques, treatments, modalities and processes that we use in rehab have very little evidence to back them up. We provide care based on old knowledge, tradition, what we think works best, what somebody

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PRINCIPI (cont. from pg. 1)

already the standard at most VA hospitals—could save the Medicare system as much as $142 million each year.

Said the secretary: "Let's see: improved quality of care; a more efficient way to provide that care; improving the quality of life for thousands of sick veterans; reducing VA's costs; and saving the American taxpayers millions of dollars every year. Dr. Hynes has hit a grand slam."

Mr. Principi praised HSR&D's Quality Enhancement Research Initiative (QUERI), quoting from a recent Institute of Medicine report that called QUERI "one of the strongest examples in America of synthesizing the evidence base and applying it to clinical care."

He challenged HSR&D investigators to ask three questions about their work: Will it reduce the cost of care to veterans? Will it improve the quality of care? Will it increase access to care?

"These are not mutually exclusive propositions," he said. "They're inextricably woven to make us a world-class health-care system." ■

Under Secretary's Award to Dr. Fihn of Seattle, leader in improving chronic–disease care

Stephan D. Fihn, MD, MPH, of the VA Puget Sound Health Care System, received the 2002 Under Secretary's Award for Outstanding Achievement in Health Services Research. The award was presented at the HSR&D meeting by Dr. Frances Murphy, VA's Acting Under Secretary for Health.

Dr. Fihn directs VA's Northwest Center for Outcomes Research in Older Adults, one of 13 HSR&D centers of excellence. His team studies ways to improve the diagnosis and management of chronic diseases such as heart disease, diabetes and depression.

In addition, Dr. Fihn has played a major role in training more than 140 physicians and scientists to conduct health-services research, and provided critical guidance to VA decision-makers on issues of health-care delivery.

In his acceptance remarks, Dr. Fihn offered an unusual perspective on health-services research: Having spent a recent sabbatical in the Netherlands, he showed slides of works by the Dutch masters, such as Rembrandt, and compared their landmark achievements to those of today's health-services researchers:

"[These painters] adopted new paradigms of looking at life, of looking at thinking. … They had a system of training—their apprenticeships—which, I would argue, very much resembles our career-development pathway. They were innovative, iconoclastic, original and daring in their creative techniques—and they found beauty in the mundane."

Dr. Fihn lavishly acknowledged his colleagues in Seattle and expressed gratitude for "the opportunity to work in an environment where caring for patients, caring for one another, the pursuit of knowledge, and intellectual honesty are esteemed."

EVIDENCE (continued from previous page)

taught you. A lot of those treatments have become entrenched. Unfortunately, what we see is wide variation in the services that are provided to veterans with disabilities, who happen to be in different parts of the country.

"We have no way of knowing if [these] treatments are effective—and as a result, we may be out there providing very ineffective treatments, wasting our veterans' time."

Dr. Bates put forth a set of broad questions she said investigators could apply to almost any area of rehabilitation: "What's effective? When is it effective? How much of it should we be providing to patients—and how much is too much? Where should we be treating? And what are those practices that we need to give up?" ■

R&D Hotline Conference Calls
are scheduled for May 13, July 8 and Sept. 9,
12 – 12:50 p.m. (EST).
Dial (800) 767-1750, code 17323

VA team and colleagues develop first oral drug to treat smallpox infection; drug also useful for herpes viruses

An oral drug that halts the deadly action of smallpox and related pox viruses in lab tissue culture cells and in pox-infected mice has been developed by researchers at the VA San Diego Healthcare System and the University of California, San Diego (UCSD) School of Medicine.

Called hexadecyloxypropyl-cidofovir (HDP-CDV), the antiviral drug blocks the activity of a variety of smallpox strains, halting their ability to replicate and spread.

Developed as part of a national research effort to design antiviral drugs for people infected by smallpox, HDP-CDV is not yet available for human use. The drug must still undergo additional testing in animals and safety trials in healthy people.

Announced March 20 at the 15th International Conference on Antiviral Research in Prague, HDP-CDV is a potent derivative of an existing compound, cidofovir, which is a weak inhibitor of smallpox virus replication. However, cidofovir must be administered intravenously, thus limiting its fast application in the event of a bioterrorism attack or widespread epidemic.

Found to be 100 times more potent then cidofovir alone, HDP-CDV was developed by Karl Y. Hostetler, MD, and James Beadle, PhD, both of VA and UCSD.

The VA/UCSD work was done in collaboration with research groups headed by John Huggins, PhD, of the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID), in Fort Detrick, Maryland, and Earl Kern, PhD, of the University of Alabama at Birmingham. The effort was initiated in 1999 when the National Institute of Allergy and Infectious Diseases (NIAID) asked the VA/UCSD team to develop an oral version of cidofovir. NIAID, the Army and the Atlanta-based Centers for Disease Control (CDC) oversee most of the country's efforts to develop antiviral therapies for smallpox.

After screening hundreds of existing compounds for activity against smallpox, the Army and CDC identified cidofovir, which is currently used in AIDS patients to treat retinal infections caused by cytomegalovirus.

> The new compound, HDP-CDV, was 100 more active than its parent drug, cidofovir, in slowing smallpox reproduction.

"Cidofovir's drawback is poor oral bioavailability. It can only be given intravenously," Dr. Hostetler said. "If you've got thousands of people exposed to smallpox, a drug that needs to be injected would be difficult to use widely."

If continuing studies support HDP-CDV's effectiveness and safety, the drug could be given in pill or capsule form over 5 to 14 days for the prevention and treatment of smallpox in persons exposed to the disease.

Also presented at the conference were Dr. Huggins' results of HDP-CDV therapy in mice infected with cowpox, a poxvirus closely related to smallpox. Working in collaboration with Dr. Hostetler's group, the USAMRIID team found that five daily oral doses of HDP-CDV given after infection prevented death from cowpox infection.

The Huggins group also found that virus levels in the lungs of infected animals was reduced to nearly undetectable levels by oral administration of HDP-CDV, but not by intravenous administration of comparable amounts of the parent drug, cidofovir.

In additional research presented at the conference, HDP-CDV was found to be active in lab tissue cultures against infections caused by cytomegalovirus, herpes virus, varicella zoster virus, and Epstein Barr virus, raising the possibility that the compound might be useful for a variety of more common viral infections.

Smallpox, however, continues to be a top concern.

"Until now, the eradication and control of smallpox relied upon vaccination," Dr. Hostetler noted. "Our results suggest that antiviral drugs given orally in a regimen consisting of as few as five doses might be used as an alternative to treat and contain a future outbreak of smallpox."

Smallpox is fatal in about 30 percent of cases. The virus spreads through saliva or respiratory droplets, and through infected clothing and linens. After infection, it takes about two weeks for the disease to become contagious, and for symptoms to

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Cooperative Studies Program marks retirement of Dr. Henderson

William G. Henderson, PhD, director of the Hines (Ill.) VA Cooperative Studies Program (CSP) Coordinating Center, retired last month after a 26-year career with VA. Prior to joining VA, Dr. Henderson was a mathematical statistician at the National Institute of Neurological Diseases and Stroke and a professor of biostatistics at the University of Iowa.

Dr. Henderson was attracted to the VA CSP by the opportunity to conduct large clinical trials that could have a major impact on clinical practice. He helped design, implement, conduct, and analyze more than 40 VA multi-center clinical trials in wide variety of disease areas: hypertension, heart disease, cancer, diabetes, arthritis, prostate disease, kidney failure, dental disease, cochlear implants, hearing aids, Gulf War illness.

In the early 1980's, Dr. Henderson helped to develop the Vietnam Era Twin Register (VETR) in response to a call for research on Agent Orange. Beginning in 1988, he served as director of the Register, which was opened to researchers throughout VA. VETR-related grants have generated more than $30 million in NIH funding.

Dr. Henderson collaborated with Dr. John Demakis in 1990 to create the Center for Cooperative Studies in Health Services Research, which coordinated major trials in areas such as hospital-based home care, primary care, cardiac surgical care, and schizophrenia. Dr. Henderson was a co-founder of the VA's National Surgical Quality Improvement Program (NSQIP), which has helped to improve surgical outcomes in VA. He also nurtured a relationship with the Chicago-based American College of Surgeons, which led to important clinical trials in surgery for hernia repair and Parkinson's disease.

In recent years, Dr. Henderson developed a five-day course on clinical research methods, now offered to as many as 70 VA researchers from around the nation.

Dr. Henderson was recently elected to a two-year term on the board of directors of the Society for Clinical Trials, and serves as a member of several data and safety monitoring boards and the Research and Methodology Committee of VA's Quality Enhancement Research Initiative (QUERI) program. He has authored or co-authored more than 190 articles in the scientific literature.

Dr. Henderson is retiring to south central Colorado with his wife, Sharon, and will serve as a part-time faculty member at the University of Colorado Health Outcomes Program. He will also take part in a three-year project sponsored by the Agency for Healthcare Research and Quality to expand the NSQIP into non-VA hospitals. ■

SMALLPOX (continued from previous page)

appear. These include fever, breathing problems and a severe rash.

Vaccination for smallpox ceased in the United States in the early 1970s. The World Health Assembly declared the disease eradicated in 1980. But today, the smallpox virus looms as a serious bioterrorism threat.

The United States still has a limited supply of potent smallpox vaccine left over from the 1970s, which could be used in an emergency. New lots are being produced and should be available by 2004. According to the CDC, Americans vaccinated 30 or more years ago probably have no remaining immunity.

The CDC also says that vaccination against smallpox carries risks of adverse reactions, such as brain inflammation, and is not recommended to prevent the disease in the general public. ■

Middleton Award to Dr. Butcher, immune researcher in Palo Alto

VA on March 11 presented the Middleton Award, one of its highest scientific honors, to Eugene C. Butcher, MD, of the Palo Alto VA Medical Center.

Dr. Butcher, whose work has been funded by VA's Medical Research Service and the National Institutes of Health since the early 1980s, has made important contributions to the understanding of lymphocyte "homing"—the process whereby these white blood cells move through the blood and tissues to find the "targets" where they initiate immune responses. He has also mentored numerous young scientists.

The Middleton Award was established in 1960 to honor William S. Middleton, a distinguished physician, educator and scientist who was chief medical director for VA from 1955 to 1963.

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The overall goal for each trainee is to compete successfully for independent funding following the training period. Within the VA, the primary independent funding mechanism is the Merit Review program. A follow-up analysis of Merit Review Entry Program (MREP) and advanced Career Development (ARCD) award holders shows that these training programs have been highly successful: 41 percent of MREP and 38 percent of ARCD awardees have obtained independent Merit Review funding.

The top five sites for MRS trainees are the VA Greater Los Angeles Healthcare System, the San Francisco VA Medical Center, the Charleston VA Medical Center, the Denver VA Medical Center, and the VA San Diego Healthcare System.

For more information on career development opportunities with MRS, contact Sara Clark at (202) 408-3605 or sara.clark@hq.med.va.gov. ■

How many veterans are in the U.S.?

A team led by Stephen Meskin, VA's Washington-based chief actuary, has developed a population model that estimates and projects veteran population data. The first release, VetPop2000, was the official VA estimate and projection of U.S. veterans as of Sept. 30, 2000. It was the first revision of official estimates and projections since 1993. An updated version, VetPop2001, is scheduled for release in the near future.

The VetPop2000 model is based on the 1990 Census—data from the 2000 Census are not yet available—and other sources, such as the Veterans Benefits Administration's Compensation & Pension (C&P) master file and records from the Social Security Administration and Department of Defense. According to the data, there were 25,498,000 veterans in the United States in 2000, with a median age of 57.4.

VetPop2000, along with user manuals and background information, is available at the following websites: http://www.va.gov/vetdata OR http://www.virec.research.med.va.gov/VETPOP2000%20MODEL/VETPOP2000_INTRO.HTM. It can also be obtained on CD-ROM, at no charge to VA researchers, by e-mailing a request to VetPop.2000@mail.va.com.

The Office of the Actuary is working with VHA's Office of Policy and Planning (OPP) to also produce veteran population data broken down by priority levels and smaller geographic regions, such as counties and zip codes. The VetPop 2000 data by these subcategories should be available within the next few months on the OPP Web site at the following site: http://vaww.va.gov/vhaopp.

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