Flat growths that elude colonoscopy may account for many cancers

A study including more than 1,800 patients at the VA Palo Alto Health Care System suggests that flattish abnormal growths in the colon—considered until recently to be rare in the U.S. and generally ignored during colonoscopies—are more common than previously thought. Moreover, they are nearly 10 times more likely to be cancerous than polyps—the small raised knobs of tissue that often contain or signal cancer and are the main target for detection and removal during colonoscopies.

The research is published in the March 5 Journal of the American Medical Association, accompanied by an online video showing the VA team’s innovative detection methods.

Alzheimer’s-caregiver study results being implemented at 20 VA sites

An individualized approach to helping family caregivers of older veterans with Alzheimer’s disease, shown successful in earlier research, is now being rolled out in community-based VA programs in 20 cities. VA investigators will further test the approach, known as REACH VA, to see if it boosts the health and well-being of the caregivers and patients and reduces their need for healthcare services.

REACH stands for “Resources for Enhancing Alzheimer’s Caregiver Health,” and was the title of two earlier trials sponsored by the National Institutes of Health and conducted by investigators with VA, NIH and several universities. An economic analysis of the program published this month in the Journal of the American Geriatrics Society shows that it costs only about five dollars a day to give caregivers about an extra hour in their day, free from the stress and burden of caring for their relative.

Large trial links fitness to longer life

If you need one more reason to start exercising, here it is: A study involving 15,660 veterans has confirmed that those who are the fittest tend to live the longest.

The results appeared in the Feb. 2008 issue of Circulation, published by the American Heart Association. Researchers at the Palo Alto and Washington, DC, VA medical centers tracked mortality among 6,749 black and 8,911 white veterans who took a treadmill test for various reasons, ranging from annual check-
Study reveals ‘selective publication’ of research on antidepressants

Prozac, Zoloft, Lexapro—these and other antidepressants make up the most widely prescribed class of drugs in the U.S. According to the 2008 book Comfortably Numb, cited in the March 2 Washington Post, “In 2006, 227 million antidepressant prescriptions were dispensed to Americans, more than any other class of medication.”

Do these drugs work as well as people think—or at least as well as it would appear from reports in medical journals? The answer is no, according to Erick Turner, MD, a psychiatrist at the Portland VA and former clinical reviewer for the Food and Drug Administration (FDA).

Turner and colleagues reported in the Jan. 17 New England Journal of Medicine that clinical trials showing negative results for antidepressants are far less likely to get published than trials showing positive results. In a few of the unpublished studies, the drugs being tested didn’t even match up to placebo treatments.

‘A matter of degree’

Turner, whose study focused only on effectiveness and not safety, admits that on the whole, all the drugs have proved to be effective—that is, they work better than placebo. Otherwise, they wouldn’t have gotten FDA approval.

“The matter of how enthusiastic we should be about these drugs. Maybe doctors and patients shouldn’t be quite so starry-eyed, and should not be shocked when the drugs don’t hit a home run the first time.”

His team looked at a total of 74 FDA-registered trials of 12 drugs—all widely prescribed antidepressants. The studies were conducted between 1987 and 2004, and included more than 12,000 patients.

Of the 38 studies viewed by the FDA as positive, all but one found their way onto the pages of medical journals. However, of the remaining 36 trials, which produced results viewed by the FDA as either negative or questionable, only three were published in a straightforward manner, says Turner. The others were either never published (22 studies) or published in a way that conveyed a positive outcome (11 studies)—for example, by highlighting a secondary result as if it were the main outcome.

A doctor surveying the literature would get the impression that 94 percent of the antidepressant trials were positive, when in fact only 51 percent were positive, based on the more balanced information the FDA receives from drug companies seeking approval to market their drugs in the U.S.

New FDA law may boost access to drug-trial results

The new findings aren’t entirely surprising, given past reports of publication bias across a variety of drug classes. But the new study is the most thorough analysis to date of a particular drug class. What the VA study doesn’t address is where the blame lies: Is it the fault of the drug companies that sponsor research but don’t submit negative results for publication, or the journals that receive such articles but turn them down? Both play a role in the complex process whereby research results get transmitted to the public. And in the eyes of a cynic, both might be seen as having a stake in featuring positive results more than negative ones.

Turner, who in 2004 published an essay in PLoS Medicine advocating for FDA data to be made more accessible to the public (http://dx.doi.org/10.1371/journal.pmed.0010060), is hoping a recently passed law, the FDA Act of 2007, will further that goal. The bill provides for a greatly expanded FDA database of clinical-trial results that will presumably be posted online, as the agency now does on a more limited basis. One downside, though, is that the law won’t apply retroactively to drugs approved in the past, even though these medications will likely continue to be prescribed for years to come.

Even if more complete information does become available on the Web, the question remains as to how useful it will all be to consumers: How likely will they be to access
CAREGIVERS (from pg. 1)

“The intervention provided that most scarce of caregiver commodities—time,” wrote the authors, led by Linda Nichols, PhD, of the Memphis VA Medical Center and the University of Tennessee Health Science Center.

“We think the biggest outcome was in the increase in perceived free time of one hour,” added study team member Jennifer Martindale-Adams, EdD. “The extra non-caregiving time could allow the caregivers to do what they wanted.”

Caregivers report better emotional health

Along with the extra time, most of the caregivers involved in the earlier research reported improvements in areas such as caregiver burden, depression and emotional well-being, and social support. They also reported fewer problem behaviors by the older family member with dementia, although nursing-home admissions did not differ between the intervention and control groups.

The six-month intervention that was included in the earlier research and will now be implemented more widely with veterans’ caregivers includes 12 individual sessions in the home and by telephone, complemented by five telephone support groups. Specially trained “interventionists” teach caregivers how to reduce stress, solve problems, and manage difficult behaviors by their family member. They use role-playing and other strategies to build coping skills. The material is tailored to family members based on assessments of where they need the most help. For example, some caregivers might simply need more knowledge about available resources or Alzheimer’s symptoms, while others need to learn how to reframe their emotional responses.

“Risk priority assessment is the most innovative part of REACH and REACH VA,” says Nichols. “Targeting the intervention to the caregiver’s needs and not just to the behavior problems of the patient helps to individualize the program and to focus on high-risk areas first.”

That the program can deliver benefits relatively cheaply is another important feature, says Martindale-Adams, who works with VA and the department of preventive medicine at the University of Tennessee. “The cost-analysis is helpful to show that you can do behavioral interventions. There are a lot of people who have said they won’t work due to cost.”

Dementia in the VA population

A study published in 2005 by Dr. Mark Kunik and colleagues at the Houston VA found that among VA patients age 65 and older, about 7 percent overall had a diagnosis of dementia, with Alzheimer’s disease being the most common type. The prevalence of dementia among African American veterans, however, was 50 percent higher.

‘Experimental Therapeutics’ award to Alzheimer’s researcher

Jerry Buccafusco, PhD, director of the Neuropharmacology Lab at the VA Medical Center in Augusta, Ga., and the Alzheimer’s Research Center at the Medical College of Georgia, is the 2008 recipient of the Award for Experimental Therapeutics from the Pharmacia-American Society for Pharmacology and Experimental Therapeutics.

Buccafusco studies potential drug therapies to treat Alzheimer’s disease, substance abuse, and cognitive problems due to exposure to neurotoxins. His research, in partnership with colleagues in VA, academia and private industry, has yielded multiple compounds that are moving toward clinical trials. His team was the first to show that very low doses of nicotine increase cognition in monkeys, and they have since shown that a nicotine byproduct called cotiline may exert similar effects.
Recent publications and presentations by VA investigators

Below is a brief sampling of recent publications and presentations by VA investigators, based on notifications received by R&D Communications (see reporting requirements at www.research.va.gov/resources/policies/pub_notice.cfm.) Every attempt is made to present a cross section of investigators, topics and medical centers. Only VA-affiliated authors are listed here, due to space constraints.


“Association of Suboptimal Prescribing and Change in Lower Extremity Physical Function over Time.” Mary Jo V. Pugh, PhD, RN; Michael E. Parchman, MD, MPH; Eric Mortensen, MD, MSc. San Antonio. Gerontology, Feb. 29, 2008.


“Human Subject Protection issues in QUERI Implementation Research.” Edmund Chaney, PhD; Laura G. Rabuck, MPIA; Jane Ulman, MPH; Deborah C. Mitterman, MS; Carol Simons, BA; Barbara F. Simon, MA; Mona Ritchie, MSW; Marisue Cody, PhD; Lisa V. Rubenstein, MD, MPH. Seattle, Little Rock, Sepulveda. Implementation Science. Feb. 15, 2008.


“Inflammation, Statin Therapy, and Risk of Stroke after an Acute Coronary Syndrome in the MIRACL Study.” Scott Kinlay, MBBS, PhD; Gregory G. Schwartz, MD, PhD. West Roxbury, Denver. Arteriosclerosis, Thrombosis and Vascular Biology, Jan. 1, 2008.


“Prescription Medication Misuse and Substance Use Disorder in VA Primary Care Patients with Chronic Pain.” Benjamin J. Morasco, PhD; Steven Dobbsa, MD. Portland. General Hospital Psychiatry, March-April 2008.


Impaired sense of smell may be key part of early detection for Parkinson’s disease

Validating the results of some earlier studies, a team led by researchers at the Honolulu VA has shown that an impaired sense of smell—long established as an early symptom of Parkinson’s disease—may also precede key symptoms of the disease by at least four years, and thus could help enable early detection and treatment. The team reported their findings in the Feb. 2008 Annals of Neurology.

Led by G. Webster Ross, MD, a neurologist with the VA Pacific Islands Health Care System, the study included 2,267 men from the Honolulu-Asia Aging Study who received olfactory testing at least once, either between 1991 and 1993 or between 1994 and 1996. To conduct the smell test, the researchers used a booklet containing scratch-and-sniff samples of familiar odors. The volunteers would have to identify, for example, whether an odor was banana, garlic, cherry or motor oil.

The men were followed for up to eight years to find out if they developed Parkinson’s. During the course of follow-up, 35 men developed the disease. The researchers determined that difficulty identifying odors can predate the development of Parkinson’s by at least four years, although it was not a strong predictor beyond this time period.

Decreased odor identification was associated with older age, smoking, increased coffee consumption, less frequent bowel movements, lower cognitive function and excessive daytime sleepiness. But even after adjusting for these factors, the researchers found that those with the lowest olfactory scores—the poorest odor identification—had a greater risk of developing the disease.

Olfactory trouble known to accompany other brain conditions

Ross acknowledges that olfactory testing by itself may not be adequate to identify early-stage Parkinson’s, mainly because there are other neurological conditions linked to impaired sense of smell in the elderly—for example, Alzheimer’s disease and cognitive decline in general. However, Ross does envision “olfactory testing used with a battery that includes assessment of other early symptoms such as constipation, sleep disturbances and others to identify individuals at high risk for developing Parkinson’s.”

Findings from earlier studies suggest that olfactory impairment begins between two and seven years prior to diagnosis, and estimates from neuroimaging and pathological studies suggest that five to seven years can elapse between the onset of nerve loss in an area of the brain affected by Parkinson’s and diagnosis of the disease. Scientists don’t know for sure how Parkinson’s affects smelling ability, but nerve loss and the formation of Lewy bodies—abnormal clumps of proteins inside nerves cells, thought to be a marker of Parkinson’s—are known to take place in the olfactory structures within the brain of patients with the disease.

According to Ross, there are no proven therapies to prevent or slow the progression of Parkinson’s, but early detection would be valuable nonetheless. “The benefit now would be to identify a group of individuals at high risk for developing Parkinson’s who could participate in clinical trials designed to prevent or slow the disease.”

BIAS (from pg. 2)

the information, and will they be able to make sense of it? According to Turner, even physicians, because of time constraints, may need to turn elsewhere for the bottom line on how well a drug really works.

“Perhaps the doctors will rely on another layer of people doing meta-analyses—taking the full complement of the data that’s out there, and giving them an idea of what the real efficacy is.”

Turner now hopes to be funded to study other drug classes, which he said are likely to reflect similar patterns of publication bias.
Lead author Roy M. Soetikno, MD, MS, says the new study suggests that flat or depressed growths—known as nonpolypoid colorectal neoplasms, or NP-CRNs—may account for many of the lesions that are overlooked during colonoscopies in the U.S. and later develop into cancer. Colorectal cancer, one of the deadliest forms of cancer, kills more than 55,000 Americans each year. Experts believe many cases involve patients who fail to undergo recommended screenings. But studies also show that .3 to .9 percent of patients who undergo a colonoscopy and have all their intestinal polyps removed will nonetheless develop invasive cancer within three years.

**Findings likely to have impact on colorectal-cancer screening**

Colonoscopy, considered the gold standard for screening and early detection of colorectal cancer, uses a long, flexible tube fitted with a miniature video camera and cutting tools. Gastroenterologists use the procedure to hunt for polyps. These small outgrowths from the intestinal or rectal wall are generally removed and biopsied because they often contain cancer cells, or are likely to develop into cancer.

Until now, non-polyp growths—also linked to cancer—have been considered rare outside Japan. But a few recent studies show that people in places like Europe and North America may also be affected. The new VA study, according to the authors, is the “largest cohort of patients in which NP-CRNs have been formally evaluated in a non-Asian population.”

David Lieberman, MD, of the Portland VA and Oregon Health and Science University, widely known for his research on colonoscopy and cancer detection, wrote an accompanying editorial in which he said, “It is now clear that both Asian and Western populations may develop NP-CRNs.” He told the Associated Press, “This paper will have a big impact on gastroenterology. It will heighten people’s awareness that, yes, these are found in the United States.”

The study included 1,819 male veterans, mostly white, who underwent a colonoscopy in 2003 or 2004. About a third of the procedures were for routine screening. The rest were because of symptoms such as rectal bleeding or diarrhea, or because of a family or personal history of colon polyps or cancer. Most of the lesions found were polyps: 594 men had only polyps, 89 had only NP-CRNs, and 81 had a combination. But the presence of NP-CRNs in 170 of the men, for a prevalence of 9.35 percent, suggests the problem is far more widespread among Americans than previously thought. And even though the flat or depressed growths represented only about 15 percent of the lesions found, they proved nearly 10 times more likely to harbor cancer, accounting for more than half the malignant tumors found.

**Learning from Japanese doctors**

Through a faculty-exchange program with Japanese endoscopy centers, Soetikno’s team developed expertise in detecting the NP-CRNs, which are harder to spot than their raised counterparts, the polyps. “They look like a pancake just lying on the floor,” said Soetikno. The physician-researchers studied colonoscopy videos showing flattish or depressed growths and learned how to spray a reddish dye inside the colon to highlight their subtly abnormal texture. The specialized methods have been used at the Palo Alto VA since 2000, and Soetikno and his colleagues expect they will now become more widespread in VA and other medical centers.
physically fit group, however, the risk of death was about one third that of the "low fit" group. Over the 22-year study period, the death rates were, respectively, 44, 30, 15, and 8 percent. Men in the two fittest groups were, respectively, 50 and 70 percent less likely to die than those in the lowest group.

The study’s take-home message, according to lead author Peter Kokkinos, PhD, is, “Get out and walk!” He says the peak exercise workload achieved by the “highly fit” men was twice that of the “low fit” group and could be achieved by a brisk walk of about 30 minutes a day, five or six days a week. “Walking is the safest and most practical exercise one can do,” says Kokkinos, who conducts research on cardiovascular disease at the VA Medical Center in Washington, DC, and Georgetown University School of Medicine.

He adds that people should always check with their physician before starting any exercise program. The caution sounds familiar, but the words take on a certain gravitas coming from Kokkinos: He has carefully watched thousands of men huff and puff their way through a stress test, their bare chests taped with electrodes and biceps fitted with blood-pressure cuffs, as he monitors their pressure and checks the EKG on the computer screen for signs of blockages in blood flow to the heart, or abnormal rhythms.

“Exercise represents a stressful condition for the body—in fact, it is this stress that provides the impetus for favorable adaptations by the body,” notes the researcher. “However, the stress imposed by exercise must not exceed the capacity of the system—in this case, the body. Although humans have a great capacity to tolerate work, when this capacity is compromised by heart disease, inappropriate exercise can cause harm.”

Though the results are not surprising, the study is the largest to date to link longevity with higher aerobic capacity—as measured with an actual exercise test, as opposed to a questionnaire. Moreover, it is the first large study to evaluate the effects of fitness in African American men, who are more at risk for hypertension and other diseases that could conceivably offset the benefits of exercise.

Kokkinos emphasizes that it isn’t necessary to run marathons to benefit from physical activity—only to exercise moderately—and that it’s never too late to start. He adds that if 30 minutes of walking is too much to start with, the routine can be split into 10- or 15-minute sessions in the morning and evening, and the overall benefits would be the same.
VA’s Magnuson Award to director of Seattle-based prosthetics and limb-loss-prevention center

Bruce J. Sangeorzan, MD, an orthopedic surgeon, researcher, and director of the Center of Excellence for Limb Loss Prevention and Prosthetic Engineering, part of the VA Puget Sound Health Care System, is the recipient of the 2007 Magnuson Award, the agency’s highest honor for rehabilitation investigators.

Sangeorzan’s expertise in foot mechanics and abnormalities has helped establish his center as a leading site for research on amputation prevention and care, particularly in connection with diabetes and peripheral vascular disease. The program’s basic and clinical research is focused on preserving the lower limb and its function and better understanding the deformities that lead to foot ulcers. Another major goal is examining the role of protective footwear and preventive correction of deformities. Researchers at the site also assess the benefits of limb salvage versus amputation and the quality of life of veterans who undergo amputation.

Under Sangeorzan’s leadership, the center, which recently expanded to incorporate a motion-analysis lab, is also working to improve the design of artificial legs by comparing suspension systems and measuring the effect of impact-absorbing prosthetic shanks in below-knee prostheses.

The Magnuson Award is named for Paul B. Magnuson, a bone and joint surgeon and chief medical director for VA in the years after World War II. The award, which includes $5,000 in cash, a plaque, and $50,000 a year for three years to supplement ongoing peer-reviewed research, is given annually to VA rehabilitation investigators who display entrepreneurship, humanitarianism and dedication to veterans, in the spirit of Magnuson. Known for his pursuit of creative, individualized solutions for meeting the needs of disabled veterans, Magnuson is quoted as saying, “People are no more alike in the shape and functional movements of their bodies and limbs than they are in their faces.”