MOVING CLOSER TO EFFECTIVE TREATMENTS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

U-M trials seek participants

Fernando J. Martinez, M.D.
director of U-M Pulmonary Diagnostic Services and professor of internal medicine

Chronic obstructive pulmonary disease, or COPD, affects more than 12 million Americans and is currently the fourth leading cause of death in the United States. Of the top 10 causes of death, it is the only one that continues to increase, even though the smoking rate has declined.

COPD mortality rates are rising in part because emphysema and chronic bronchitis typically get diagnosed in people age 40 years and older, a fast-growing segment of the U.S. population. Nearly all people diagnosed with COPD have emphysema or chronic bronchitis or, most commonly, both conditions.

Fernando J. Martinez, M.D., director of Pulmonary Diagnostic Services at U-M and professor of internal medicine, notes that U-M currently has two major COPD clinical trials open, with more slated to open in the next few months.

Martinez and his team hope that community physicians who are managing COPD patients in their practices will consider informing those patients about the opportunity to assist in research that seeks to answer important questions in COPD treatment.

The Long-term Oxygen Treatment Trial, funded by the National Heart, Lung and Blood Institute and the Centers for Medicare and Medicaid Services, aims to accrue thousands of participants at U-M and 13 other regional health centers nationwide.

The trial may change the way oxygen therapy is prescribed over the next 20 years, says Martinez.

The study is badly needed, he says. Billions of dollars are spent each year on oxygen therapy, based on data from only a few hundred subjects from two decades ago. There are also uncertainties regarding the specifics for the duration and timing of oxygen use.

continued on back page
Now that living kidney donation has become a standard approach, the transplant community finds itself with a new issue to tackle: Willing healthy living donors who are incompatible with the loved one in renal failure they want to donate to.

A new option called kidney paired donation provides additional opportunity for some of those patients and donors to find a match.

“We have a solution for many patients who have a donor who isn’t compatible with them,” says Alan Leichtman, M.D., medical director of the Kidney Paired Donation Transplant Program at the University of Michigan.

“U-M is distinguished in two ways. One way is that we are the largest single center pool, and the second is that our matching program is very efficient. It’s designed to find kidneys for these people who are the most difficult to find kidney transplants for. Consequently, we are effective in transplanting those people who are the hardest to transplant.”

Since July 2008, the U-M Paired Kidney Donation program has given an additional opportunity for transplantation to people who need a kidney transplant and who have a willing but incompatible donor. The program also can match altruistic donors — people willing to donate without a recipient in mind — to potential recipients; thus creating a chain of transplants potentially involving numerous recipients and donors.

The need for kidney transplantation has grown significantly over the past
decade with over 83,000 patients currently waiting for a kidney transplant. In 2009, only 14,059 kidney transplants were performed in the United States, and 3,577 people died waiting for a transplant. In Michigan, the wait for a kidney from a deceased donor is currently about five years.

Leichtman encourages physicians who are caring for renal failure patients with willing, but incompatible, donors to explore the possibility of enrolling them in the U-M database.

**The Paired Kidney Donation Program at work**

Although strangers before they met in July, two married couples already shared a profound bond because they had surgically swapped kidneys after being matched by U-M’s software.

Both of the women needed a new kidney. Their husbands were willing to donate one of theirs, but neither man could give a kidney to his own wife due to tissue incompatibilities.

After the software match was identified, the U-M transplant team determined that Dave Hedberg, of Alto, Mich., could give a kidney to Lyn McKiernan-Karsten, of Allegan, Mich., and Brian Karsten could give one to Dave’s wife, Marilyn Hedberg.

“Dave is so generous to give a part of himself to someone he doesn’t know. It’s amazing that there are people out there who are so generous,” McKiernan-Karsten says of her donor. “I was extremely ill before the surgery. Afterwards, it’s like a whole new life. I have some more energy and I’m able to do things I couldn’t do before. It’s incredible.”

“There’s not that many of these programs out there,” says Marilyn Hedberg. “They are such a life saver for people because you know a lot of people who don’t make it on the waiting list. So this is a real blessing.”

**FOR MORE INFORMATION**
call M-LINE at 800-962-3555.

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In December, the University of Michigan performed its 5,000th kidney transplant since U-M teams began transplanting organs in 1964. As of Jan. 20, there have been 5,028 kidney transplants performed. Although the paired donation program accounts for a small number thus far, the number will increase as the database of willing donors and potential recipients grows.

**LEARN MORE ON THE WEB**

U-M Transplant Center
visit www.med.umich.edu/trans/public.

U-M Paired Kidney Donation Program
visit www.michigantransplant.org/kidney/paired.htm.

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(L) Dave Hedberg and Marilyn Hedberg
(R) Lyn McKiernan-Karsten and Brian Karsten

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The study showed that even small defects and divots in the humeral head can affect stability. Because standard procedures meant to stabilize the joint do not address bone defects, a new technique was developed.

To sculpt the new joint, surgeons take cadaver cartilage and bone from the glenoid and the humeral head. "We transfer and transplant the tissue by matching it with X-rays to make sure the sizes are appropriate. Then in surgery we actually shape it to be the same shape and consistency as the patient, and then secure it and let it heal," says Sekiya. “We’ve been able to stabilize shoulders that have failed one, two, sometimes three surgical procedures that did not address the bone and cartilage damage.”

Sekiya practices at MedSport, the University of Michigan Health System’s sports medicine clinic.

FOR MORE INFORMATION

FOR MORE ON THE WEB
Online video with Jon Sekiya, M.D. as he explains using cadaver cartilage to sculpt new shoulder joint, visit www.med.umich.edu/medsport.

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CONCUSSION CONNECTION: U-M NEUROLOGIST PUTS FOCUS ON ATHLETES’ BRAINS

Jeffrey S. Kutcher, M.D.
Assistant professor of U-M neurology and Director of Michigan NeuroSport

After the kickoff on any football Sunday, hundreds of bone-jarring collisions rattle the athletes of the National Football League. U-M’s Jeffrey S. Kutcher, M.D., is leading the charge to determine what those crushing blows can do to the brains of those players — and those of athletes down to the littlest hockey defensemen or soccer goalie.

Kutcher is assistant professor of neurology at the University of Michigan Medical School and director of Michigan NeuroSport, a U-M Health System clinic where he leads a team that works with and treats athletes from a variety of sports — including soccer, ice hockey and wrestling — at all levels from youth to professional leagues.

Many physicians — especially in primary care and neurology — find themselves treating the after-effects of concussion and other neurological sports injuries in their patients. But the topic doesn’t get much attention in medical school.

“When I first found myself on the sidelines of a football game as a team physician, I remember thinking that I might as well have been on Mars for as much as my residency training prepared me for that environment,” Kutcher says. “But now I feel almost comfortable, or at least as comfortable as one can get doing a hyper-focused neurological examination with a marching band directly behind you, fans on top of you — sometimes heckling! — and coaches wondering what’s taking so long because you’ve had your 30 seconds.”

Kutcher is the team neurologist for the University of Michigan and Eastern Michigan University athletic programs and a neurological consultant for several high schools and the USA Hockey Development Program. He was recently named to the NFL’s concussion committee and testified in January before a Congressional committee on the issues related to football head injuries.

He was also influential in getting the American Academy of Neurology to establish a division of sports neurology. And he now serves as the first chair for that new section.

“We’re not taught about taking care of athletes in neurology training,” says Kutcher. “Caring for athletes requires a different kind of approach.”

Kutcher says at Michigan NeuroSport, the staff is ready to deal with the special set of challenges associated with athletes, including different patient expectations and unusual practice environments.

Athletes often suffer from the kinds of problems that require a neurologist’s expertise: concussions, peripheral nerve injuries, migraine headaches or sleep disorders.

The perspective for an athlete can also be very different from the typical patient that neurologists are trained to treat, Kutcher adds. Athletes are concerned about returning to an exceptionally high level of physical and mental function that they consider normal. They are also looking to get back in the game as quickly as possible.

One of Kutcher’s goals is to increase the neurological care of athletes at every age and skill level by encouraging more neurologists to get directly involved in athletic programs and improving understanding of neurological concepts and their application to athletic injuries.

“For a lot of neurologists, when it comes to athletes, some of the finer points are a mystery. We weren’t taught about it, and our field has not recognized that this population, and the neurological problems they experience, are unique,” Kutcher says.

FOR MORE INFORMATION
Michigan Neurosport, visit www2.med.umich.edu/departments/neurosport.
American Academy of Neurology Sports Neurology section, visit www.aan.com/go/about/sections/sports.
Initial surgery for papillary thyroid carcinoma should include prophylactic removal of cervical lymph nodes to reduce risk of recurrence, according to the American Thyroid Association’s recently revised treatment guidelines.

Although this approach has been somewhat controversial, the benefits outweigh the potential risks of more thorough surgery, said Gerard M. Doherty, M.D., an endocrine surgeon who helped write the guidelines and chief of general surgery at the University of Michigan health System.

“A more thorough operation only makes sense if it can be done well,” Doherty said. “The key is to choose a surgeon who performs this procedure frequently. The emphasis here is on expertise.”

By removing level six lymph nodes in the central neck, the likelihood of recurrence is substantially reduced, Doherty said. Because lymph node metastases cannot be reliably detected using ultrasound or intraoperative examination, traces of the disease can be left behind if the lymph nodes are not removed. A recent study in Sweden showed that lymph node metastases were associated with diminished survival even when adjusted for disease staging.

Furthermore, patients who have more thorough surgery may not have to undergo treatment with radioactive iodine, Doherty said, which can cause side effects such as dry mouth and dry eyes.

Surgical risks of the more extensive procedure — such as laryngeal nerve injury and permanent hypoparathyroidism — can be limited if a patient’s surgeon has extensive experience in performing the procedure, he said.

Last year at the University of Michigan Comprehensive Cancer Center, four endocrine surgeons performed 401 thyroidectomies, 301 parathyroidectomies and 65 reoperative lymph node dissections for thyroid cancer, Doherty said.

Nationally, 50 percent of thyroid operations are performed by surgeons who perform five or fewer annually, according to a U-M study published in Surgery.

As an alternative for those who do not have access to a more experienced endocrine surgeon, the guidelines recommend removal of the tumor followed by radioactive iodine.

About 38,000 people are diagnosed with thyroid cancer annually. Papillary thyroid cancer, the most common form of the disease, is highly treatable; if detected early, most people can be cured.
SUBTLE SIGNS: DETECTING ADRENAL CANCER

Diagnosing adrenal cancer is a challenge. Consider: The disease often causes no symptoms. If it does, the symptoms may include weight gain, hypertension and diabetes — very common disorders. Add to this that there are only about 600 new cases of adrenal cancer diagnosed each year in the United States, a number so small that many physicians will never encounter a case in their entire careers. On the contrary, up to 7 percent of Americans have benign adrenal tumors, Hammer said. So, adrenal cancer is both a difficult disease to detect or diagnose early — and it is deadly.

“A lot of adrenal tumors are ‘silent.’ They’re found incidentally when someone gets a CT scan for something completely unrelated,” said Gary D. Hammer, M.D., Ph.D, director of the University of Michigan Comprehensive Cancer Center’s Endocrine Oncology Program and the Millie Schembechler Professor of Adrenal Cancer.

The types of tumors and related symptoms include:

- **Adrenocortical tumor** (both benign and malignant pheochromocytoma): A tumor that grows in the adrenal gland’s outer cortex, which produces aldosterone, cortisol and sex steroid precursors. Signs can include:
  - An increase in the production of aldosterone, which may cause hypertension that may be difficult to control and low potassium.
  - An increase in the production of cortisol, which may cause hypoglycemia, diabetes, central obesity (weight gain in the trunk), purple stretch marks, and weakness of limbs.
  - An increase in the production of sex steroid precursors, which may cause breast growth and erectile dysfunction in men or a deepening of the voice, bulky musculature, facial hair and irregular menstruation in women.

 “Because hypertension, obesity and diabetes are prevalent today but most often not caused by an adrenal tumor or hormone excess, the key to diagnosing excessive hormone production is severity and duration,” Hammer said. “How fast did the symptoms come on? How difficult are they to treat? For example, a marathon runner who has gained 50 pounds, has new hypertension and has developed diabetes should raise a red flag about the possibility of cortisol excess.”

Additionally, radiologic scans help assess whether an adrenal tumor is benign or malignant, he said.

Under Hammer’s direction, the U-M Cancer Center treats about 200 new cases of adrenal cancer each year in the Endocrine Oncology Multidisciplinary clinic. It also provides consults to patients who have adrenal tumors with an unclear diagnoses or with difficult-to-manage adrenal hormone excess syndromes.

In addition to 16 clinical faculty members who provide patient care, a team of researchers is studying the genetics and stem-cell biology of adrenal cancer to identify novel genetic mutations and signaling pathways that could lead to targeted therapies. A clinical trial evaluating the effectiveness of IMC-A12 (a human antibody that may counteract the effects of genetic alterations in the IGF signaling pathway linked to adrenal cancer) is now open.

FOR MORE INFORMATION

call M-LINE at 800-962-3555.
“We may be overusing oxygen in a negative way,” Martinez explains.

There are clearly patients who benefit from continuous oxygen therapy, he says. The trial should shed light on which patients benefit and should receive it.

While smoking is the leading cause of COPD, only 25 percent of smokers develop the disease, suggesting a genetic involvement in vulnerability to the disease. For the COPDGene clinical trial, U-M is one of 21 leading medical centers in a study that collectively will enroll more than 12,000 people across the United States.

COPD Gene is funded by the National Heart, Lung, and Blood Institute (NHLBI) and National Jewish Health.

“Unlocking the keys to the genetic disposition of COPD and the efficacy of oxygen therapy can go far in making life better for the millions affected by COPD,” says Martinez, principal investigator for both trials.

U-M has been involved in every National Institutes of Health initiative on COPD for the past 10 years, Martinez says.

In addition to the growing list of trials, U-M Pulmonary and Critical Care Medicine researchers are actively involved in studies such as the following one, which may make it possible to detect COPD early, when treatments can be more effective.

U-M researchers recently linked changes in immune dendritic cells to worsening COPD in a study published in the December 15 issue of the American Journal of Respiratory and Critical Care Medicine. The research adds to growing awareness of the immune system’s role in COPD.

“We found that dendritic cells, which initiate immune responses, are in the lung interacting with lymphocytes, and that these dendritic cells seem to get more active as the disease goes on. If we could alter or stop their action, perhaps we could stop the disease from progressing,” says the study’s senior author Jeffrey L. Curtis, M.D., professor of internal medicine at U-M and chief of the pulmonary and critical care medicine section at the VA Ann Arbor Healthcare System.

FOR MORE INFORMATION on both COPD trials, visit www.umengage.org or email copdresearch@umich.edu.

FIND MORE ON THE WEB:
LOTT Trial on ClinicalTrials.gov visit http://clinicaltrials.gov/ct2/show/NCT00692198.
COPD Gene Trial site visit www.copdgene.org.

RESOURCES
U-M Division of Pulmonary and Critical Care Medicine visit www.med.umich.edu/intmed/pulmonary.
COPD Foundation visit www.copdfoundation.org.